Malignant catarrhal fever (MCF)

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INTRODUCTION

Malignant catarrhal fever (MCF) is a multisystemic viral disease with a high case fatality rate particularly in cattle, but also a variety of other ruminants including captive and farmed species of antelope, deer, and bison (Bison bison), water buffalo (Bubalus bubalis), African buffalo (Syncerus caffer) and occasionally of domestic pigs. The clinical course of MCF in individual animals is varied and may be peracute, with few overt signs prior to death, acute, chronic or mild. In the acute disease, the clinical signs are usually severe and are characterized by high fever and severe inflammation of the mucosae of the respiratory and alimentary tracts and conjunctivae, and the eyes and skin. These lesions are often accompanied by profuse mucoid to mucopurulent nasal and ocular discharges and, in some cases, signs of meningoencephalitis. The disease in susceptible animals tends to appear sporadically although, on occasion, relatively large numbers of animals may be affected.

Malignant catarrhal fever is caused by infection with either the gammaherpesvirus of blue, white-bearded, and black wildebeest (Connochaetes taurinus taurinus, C. t. albojubatus and C. gnou, respectively), i.e. alcelaphine herpesvirus 1 (AlHV-1), or that of domestic sheep, i.e. ovine herpesvirus 2 (OvHV-2). Neither of these viruses causes clinical disease in their respective natural hosts. There is evidence that substantiates the existence of an extensive group of related gammaherpesviruses in four subfamilies of Bovidae that may cause MCF following experimental transmission to certain animal species other than their natural hosts which themselves exhibit no clinical signs following infection.

No vaccine is available to protect animals and, as transmission to MCF-susceptible species tends to be erratic and eradication is usually impractical if it does not involve the elimination of carrier species (wildebeest and sheep), control is difficult and generally relies on segregating carrier species from susceptible animals. Infectious virus is only excreted by the natural hosts, wildebeest and sheep respectively, and no transmission occurs from MCF-susceptible species except by experimental inoculation.

EPIDEMIOLOGY

Only AlHV-1 has been isolated and characterized; OvHV-2 has consistently proved impossible to isolate using conventional methodologies and has only been identified by applying molecular techniques to detect the viral DNA.

It was not until 1960 that the causal virus of the wildebeest-associated disease was identified by Plowright and co-workers as a herpesvirus that could be isolated in cell culture provided that infected intact cells were included in the inoculum.

The genome of AlHV-1 is characteristic of the gammaherpesviruses, and consists of a 130 kb unique region together with 25 to 30 kb multiple direct repeats of approximately 1 kb each located terminally. The cloning and structural analysis of the complete genome of the virulent isolate C500 was completed in 1997.
The aetiological agent of the sheep-associated form of MCF has remained elusive. Despite several reports to the contrary, no aetiological virus has ever been isolated either from cases of this form of MCF or from sheep. Evidence for the existence of a virus antigenically related to AlHV-1 that infects sheep was based on the detection of antibody that reacted with AlHV-1 in an indirect immunofluorescence antibody (IFA) test in virtually every sheep serum examined, as well as on the detection of antibody in sheep sera which reacted with the major structural proteins of AlHV-1 in immunoblots. In addition, hamsters experimentally infected with tissues from cattle and deer that had contracted this form of MCF were found to develop antibody to AlHV-1.

Despite consistent failure to isolate an aetiological virus from cases of the sheep-associated form of MCF, it has been possible to generate lymphoblastoid cell lines originating from cattle and deer suffering from this form of the disease. The DNA from such cell lines was found to hybridize with a number of DNA clones of the unique region of the AlHV-1 molecule and subsequent screening of a genomic library from these cells enabled the identification of several viral clones which were established to be OvHV-2. Sequence data from one of these clones has formed the basis of a polymerase chain reaction (PCR) specific for OvHV-2 which allows the detection of the virus both in sheep and MCF-affected cattle, domestic pigs, several species of farmed deer, bison, water buffalo, African buffalo as well as a number of exotic hoofstock in zoological collections.

The disease occurs worldwide but its importance varies as it is markedly dependent on both the source of virus and the species affected. The two blue wildebeest subspecies and the black wildebeest may be a source of AlHV-1. This form of MCF occurs throughout the natural distribution of these antelope in Africa, as well as in zoological collections when mixed populations of members of the Artiodactyla (hoofstock), including wildebeest, are kept. In the latter instance a variety of susceptible species may be affected.

Transmission of AlHV-1 in free-living populations of wildebeest is extraordinarily efficient with all calves becoming infected within the first few months of life. Following the isolation of the virus from wildebeest calves in East Africa in 1960, Plowright et al embarked on an exhaustive study of transmission in free-living C. t. albojubatus. These studies established that all adults had neutralizing antibody to the virus and that virus could be recovered from a proportion of their foetuses. Furthermore, sera from wildebeest calves examined for antibody to the virus were usually positive. These data suggest that most calves receive colostral antibody and are infected either in utero or during the first few months of life when maternal antibody is still present. Virus has been recovered from nasal or ocular secretions of wildebeest calves aged six to eight weeks suggesting that the respiratory tract is the likely route of contagious spread. Thus, in free-living wildebeest, a proportion of foetuses are infected in utero which is followed by intense transmission within the population during which all calves become infected in the first few months of life.

Following infection, AlHV-1 establishes a latent infection with virus only on occasion being detectable. The work of Plowright suggested that wildebeest cows may become viraemic in the late stages of pregnancy, while a study by Rweyemamu et al. in 1974 found that reactivation with excretion of virus occurred in captured adult wildebeest at the time of confinement following abrupt changes in diet and following betamethasone (corticosteroid) treatment at the dosage rate of 40 mg daily for seven days.
In all the numerous studies of AlHV-1 infection in wildebeest, no evidence of clinical disease or pathological lesions has been reported.

Direct transmission of AlHV-1 to MCF-susceptible indicator hosts only occurs from wildebeest; all reports consistently confirm the observation that horizontal spread does not take place from MCF-affected animals or from the few that survive the disease, although vertical (transplacental) transmission in cattle has been described.

Although the actual method of transmission has not been fully established, it is noteworthy that an outbreak of MCF in cattle has been described in the USA where wildebeest situated a substantial distance away were almost certainly the source of AlHV-1. In South Africa, too, there are reports of MCF occurring in cattle separated from wildebeest by up to 800 metres. This has led to speculation that spread by arthropod vectors may occur. However, the known physical characteristics of the herpesviruses, the extraordinarily efficient spread amongst wildebeest calves, and observations on the transmission of the closely related OvHV-2 support the view that natural spread is generally, if not exclusively, by aerosol with many of the apparent anomalies being explained by prolonged incubation periods occurring in some animals.

In the Maasai areas of East Africa, the seasonal occurrence of MCF in cattle which is predominantly in March and April in northern Tanzania and from April to July in southern Kenya, has been associated with blue wildebeest (*C. t. albojubatus*) calving seasons. Therefore, the disease is more common in cattle in these areas when the wildebeest calves are two to three-months-old. In South Africa, blue wildebeest (*C. t. taurinus*)-associated MCF occurs regularly in provinces where free-living or semi-captive wildebeest are present. However, the majority of cases occur in the Limpopo and North-West Provinces where ecotourism has expanded and the number of game farms increased significantly during the 1990s. Two peaks in the prevalence of the disease are encountered; one in January to May (with the highest number of cases occurring in early April) following the wildebeest calving season in December, January and February, and a second, in which the prevalence is higher, from September to November (the highest number of cases being in mid-September) when the wildebeest calves are nine to 11 months old. The disease is rare in the summer months of December, January and February, as well as in mid-winter. The ages of cattle (excluding congenital cases) that develop clinical signs vary from 4.5 months to a few years with the majority being between eight and 18 months old.

South Africa is the only natural habitat of the black wildebeest. Although the blue wildebeest has thus far been regarded as the most important carrier of AlHV-1, indications are that black wildebeest are equally important transmitters of MCF virus. This increase can be ascribed to the increase in the number of farms on which black wildebeest are kept. Whereas the black wildebeest was a few decades ago regarded as a threatened species, its area of distribution is now even bigger than that of the blue wildebeest. All black wildebeest herds tested thus far in South Africa were serologically positive for antibodies against AlHV-1.

As with AlHV-1 infection amongst wildebeest, OvHV-2 is transmitted to a proportion of lambs *in utero* and this is followed by an intense transmission in the periparturient flock with all becoming infected.
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within three months of birth. However, more recent research has shown that lambs do not shed virus occurs until after 5 months of age.

The sheep form of the disease occurs wherever domestic sheep are kept, including African countries, although the susceptibility of recipient animal species varies considerably. Cattle (Bos taurus and B. indicus) are relatively resistant to infection with OvHV-2 and cases of MCF usually occurs only sporadically although outbreaks affecting many animals have been recorded. Other species, such as Bali cattle of Indonesia (Bos javanicus) and Père David's deer (Elaphurus davidianus), are extremely susceptible to infection and must be kept well separated from sheep if heavy mortality is to be avoided. Other species of deer and the water buffalo have an intermediate susceptibility between cattle and the extremely susceptible hosts. The disease has also been described in zoological collections affecting a variety of species belonging to the subfamilies Bovinae and Tragelaphinae as well as in giraffe, although the identity of the causal virus has not always been established. With the increasing interest in the farming of bison in North America, the sheep-associated form of MCF is proving to be a common cause of mortality in them.

Another anomaly for which no satisfactory explanation has been forthcoming is the relatively common occurrence of SA-MCF in domestic pigs in Norway, although it has also been reported in Finland, Sweden, Germany and Switzerland. The occurrence of the disease in pigs does not appear to be determined by the breed of pigs or sheep involved, and the amplicon derived by PCR from pigs had a nucleotide sequence identical to that obtained from other sources. Incidents tend to occur in small holdings where sheep and pigs are housed in the same air space and generally several pigs become affected over a few days. However, no feature of the management could be identified to explain why disease in pigs should be so restricted to these countries. Malignant catarrhal fever has not been reported in pigs in Africa.

As with animals suffering from MCF following infection with AlHV-1, horizontal spread from animals with SA-MCF does not occur. Transmission is thus only from sheep to the susceptible host, but the factors playing a role in this phenomenon are poorly understood and there are many irreconcilable features that cannot yet be explained.

The sheep-associated disease in domestic cattle occurs sporadically usually affecting only one or a few animals. This may occur following intimate contact with sheep and personnel or fomites that have had contact with sheep, as well as where no obvious contact with sheep can be established. Infection, however, can result in outbreaks in which substantial losses may occur over weeks or months while on occasion the disease recurs annually when several animals are affected during the course of several years. This is associated with certain groups of sheep becoming more efficient in transmitting the infection to cattle.

PATHOGENESIS

Despite the severe pathological changes that occur in animals affected by MCF the pathogenesis remains to be fully elucidated. What is certain, however, is that the lesions do not arise through direct
virus-induced cytopathology as there is no evidence of herpesvirus cytopathic effects and very little
evidence of viral antigen or nucleic acid can be found in them. Consequently, numerous authors have
suggested a variety of immunopathological mechanisms to explain the pathogenesis of the lesions,
one of which is entirely satisfactory.

The pathology of MCF consists of three components:

- T-lymphocyte hyperplasia in lymphoid organs and accumulation of these cells in non-
  lymphoid tissues,
- Epithelial degeneration/necrosis and hyperkeratosis, and
- Vasculitis.

In an explanation of these lesions, Plowright was the first to suggest that immune mechanisms were
responsible for their development which involved a hypersensitivity to viral or viral-induced antigens.
Explanations from other researchers include suggestions that that the different lesions resembled
both an Arthus (Type III) response and a cell-mediated (Type IV) response, or that they arose through
immune-complex formation. None of these suggestions is compatible with the nature of the lesions or
with the lack of identifiable viral antigens in affected tissues. Another observation was that there was a
strong histological resemblance of the disease to that seen in graft-versus-host reactions and it was
speculated that this could result from virus infection of lymphocytes causing activation of
autoaggressive T-lymphocytes, either directly through clonal stimulation or by depression of specific
suppressor cell populations. This concept was further developed when the surface markers, cytokine
expression, and cultural characteristics of virus infected lymphoblastoid cell lines derived from cattle
naturally infected with OvHV-2 and from experimentally infected rabbits were characterized. It was
concluded that the cell lines most closely resembled anergic T-cell clones. Such cell lines can
regularly be derived from animals affected with MCF induced by either AlHV-1 or OvHV-2, the cells
morphologically resembling large granular lymphocytes that function as indiscriminate killer cells.
Such cells most closely resemble lymphokine-activated killer cells.

There is evidence that viral DNA is present in episomal form and only limited viral transcription occurs
in the cells with no intact virions being detectable. It is concluded that only early transcripts of virus
replication are present, probably the latency-associated virus products. In the natural host, OvHV-2 is
present in B-lymphocytes, presumably as a latent infection. Thus it is tempting to propose that these
same virus transcripts expressed in the T-lymphocytes of MCF susceptible animals drives an
immunological response that precipitates the reaction characteristic of MCF.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

While a diagnosis on clinical and gross post-mortem examination may be possible in acute and more
protracted cases presenting with the typical clinical signs of the disease, the wide spectrum of clinical
manifestations that can develop frequently requires laboratory examination to establish a definitive
diagnosis. Historically, the principle method for confirming a diagnosis was the detection of the
characteristic histological changes of vasculitis, hyperplasia of lymphoid tissues and accumulations of
lymphoid cells in non-lymphoid organs. The detection of these lesions in a variety of tissues particularly the brain, kidneys and liver provided a basis for reaching a diagnosis. However, with the development of molecular biological methodologies ante-mortem confirmation is now possible as is the identification of non-fatal infections. A history of contact with sheep or wildebeest or with pasture recently grazed by either of these species will generally support the diagnosis, but the possibilities of prolonged incubation periods and of transmission by aerosol or by fomite may make it difficult to establish this contact.

Clinical signs and pathology

The clinical and pathological changes associated with MCF resulting from infection with either AlHV-1 or OvHV-2 in susceptible animal species are similar and cannot be reliably differentiated.

The duration of the natural incubation period is often difficult to establish as the time of infection cannot be identified although there is good evidence that it can be very variable, ranging from two weeks to nine months. The course of the disease is also highly variable and ranges in individual animals from peracute or acute to chronic with more florid clinical signs developing in the more protracted cases which may die nine to ten days after the first clinical signs are noticed. In general, the disease in the more susceptible species follows an acute or peracute course. The peracute disease is characterized by rapid onset of depression and high fever followed by the development of diarrhoea, which in some cases may be haemorrhagic, with death occurring 12 to 24 hours after its onset. In all forms of the disease, the onset of signs is generally associated with the development of fever (rectal temperature of < 42 °C), inappetence, photophobia, lachrymation and a serous nasal exudate.
Epiphora and mucopurulent discharges from the eyes and nasal cavities

Blockage of the nares as a result of nasal exudate

The latter two progress to become profuse mucopurulent discharges. The ocular discharge may matt the hair on the face while the nasal exudate may, in time, result in blockage of the nares and difficult breathing. In lactating animals the milk yield drops. Characteristically, bilateral corneal opacity develops progressively from the periphery often to involve the whole cornea which may become oedematous and is accompanied by blindness. Corneal ulceration and hypopyon may be present.

Peripheral keratitis

Advanced keratitis with hypopyon

Salivation with hyperaemia of the oral epithelium may be an early sign. Erosions develop in the mucosa of the ventral surface of the tongue, hard palate, gums and, characteristically, the tips of the buccal papillae. In some cases skin lesions may develop but are often overlooked. These manifest as exanthema, exudation and encrustation of the areas concerned which are often restricted to the perineum, udder, teats, interdigital spaces and skin at the base of the horns and hooves.
Erosive and ulcerative interdigital dermatitis

Affected unpigmented skin is hyperaemic. Not infrequently the epithelium of the muzzle becomes severely encrusted, necrotic and may slough. The superficial lymph nodes are usually enlarged.

Visibly swollen pre-femoral lymph node

Neck extension to relieve discomfort associated with swollen lymph glands in the oro-pharyngeal region, blocked nares and conjunctival inflammation

Nervous signs such as hyperaesthesia, incoordination, nystagmus, behavioural changes and head pressing may be present in the absence of other clinical signs or as part of a more typical clinical picture. Some affected animals become aggressive.
Usually the outcome of MCF is fatal; however, mild cases of the SA-MCF were described. The latter observation was for a long time treated with scepticism but studies of some multiple case outbreaks using serological testing and PCR for OvHV-2 DNA have confirmed that such cases do occur. Recovery or mild disease may also occasionally occur in those animals in which the disease is caused by AlHV-1. However, the frequency with which this occurs is at present not clear.

The macroscopical and microscopical lesions caused by both AlHV-1 and OvHV-2 in all susceptible animal species are similar. They are generally widespread and may involve most organ systems. In animals in which the course of the disease was protracted, the carcass is emaciated and dehydrated. Apart from the lesions of the eyes, muzzle, external nasal orifices and skin which are clinically discernible, the mucous membranes of the upper and lower respiratory tract are congested and sometimes oedematous, may contain small haemorrhages, multiple foci of epithelial necrosis, erosions and ulcerations, as well as evidence of mucopurulent inflammation and pseudomembrane formation. The nasal passages, particularly between the turbinates may be partially blocked by exudate. A patchy bronchopneumonia may be present in animals which suffered from the more protracted disease.

The mucosa of the mouth may be hyperaemic and contain petechiae and ecchymoses and foci of epithelial necrosis, erosions and, in some, diphtheritic deposits.

Similar lesions may be found in the oesophagus, particularly its more cranial part, forestomachs and abomasum. In the latter organ, erosions and/or ulcers are frequently present particularly on the margins of the mucosal folds.
Ulcerations in the wall of the rumen

Erosions and ulcerations on the internal surface of the oesophagus

The small and large intestines may exhibit a catarrhal to haemorrhagic enteritis with their contents, particularly in the more acute cases, watery and blood-stained. Similar erosions or ulcerations to those in the abomasum may be present along the ridges of the mucosal rugae of the ileoceleval valve, caecum, colon and rectum. The intestinal lesions are generally more severe and widespread in deer.

The majority of lymph and haemolymph nodes are enlarged as a result of lymphoid hyperplasia, oedema and, in some, congestion. Some, particularly the submandibular and retropharyngeal, may
show foci of necrosis and haemorrhage. Slight splenomegaly may or may not be present. On cross section of the spleen, the white pulp is generally prominent.

The liver is usually slightly enlarged with diffuse greyish-yellow mottling. The wall of the gall bladder may be oedematous and contain petechiae and ecchymoses, and its mucosa a few small erosions.

In many cases the kidneys present characteristic changes. These are manifested by varying numbers of greyish-white foci one to five mm in diameter in the cortices, some of which may project above the renal surface and in some cases the presence of small scattered haemorrhages.

Multifocal lymphoid infiltration in the renal cortex

The mucosa and wall of the urinary bladder in most cases is oedematous and contains petechiae and ecchymoses in the mucosa and serosa and, occasionally, mucosal erosions or ulcers. Haematuria may be present.

The histopathological lesions, which have long formed the basis for confirming cases of MCF, are basically those of lymphoid hyperplasia, and vascular and epithelial lesions, the latter being associated with the infiltration or accumulation of cells mostly of the lymphocytic series, particularly lymphoblasts, into subepithelial tissues.

Segmental fibrinoid necrosis and lymphocyte infiltration in the wall of an artery
There is marked hyperplasia of lymphoblasts and reticuloendothelial cells in pre-existing lymphoid tissues as well as widespread interstitial accumulations of these cells in nonlymphoid organs such as kidneys, liver and lungs. The severity of the epithelial changes seems to correlate with that of the cellular infiltrations or accumulations in mucosae or dermis. The epithelial lesions may be present in all epithelial tissues and are characterized by inflammation, and erosion and/or ulcer development. Those in stratified squamous surfaces are also accompanied by acanthosis, parakeratosis and hyperkeratosis, vasculitis and haemorrhage.

The arterial and venous lesions are, characteristically, a fibrinoid vasculitis accompanied by the infiltration of lymphoblasts, lymphocytes and macrophages into the walls and adventitia of the vessels and perivascular spaces. Endothelial swelling may be present, and in the lumens there may be pavementing by lymphoid cells. Thrombosis is rare. The vascular lesions may be focal or segmental, and involve the full thickness of the wall of the vessel or be confined to one of the layers. They may occur throughout the body but are most prominent in the brain, meninges, carotid rete, liver, kidneys, lungs, and capsule and medulla of the adrenals as well as in those areas of the skin and alimentary tract which are grossly affected.

Marked hyperplasia of lymphoblasts occurs in the T cell-dependent areas of the interfollicular cortical and paracortical zones of lymph nodes. Evidence of necrosis of individual mature lymphocytes is usually present. Oedema, haemorrhages, focal areas of necrosis and vasculitis may be evident in the cortex and medulla. In the spleen, there is lymphoid cell hyperplasia and a depletion in the number of lymphocytes.

The mottling of the liver and the greyish-white foci in the cortices of the kidneys noted macroscopically are due to the accumulation of large numbers of lymphoid cells, mainly lymphoblasts and some macrophages in the portal tracts of the liver and interstitium of the kidneys, respectively. In the kidneys of some cases, thrombosis of arcuate or interlobular arteries gives rise to small infarcts.

In the brain, there may be a non-suppurative meningoencephalitis with perivascular lymphoid cuffing and a marked increase in the cellularity of the cerebrospinal fluid.

Consistent ocular findings include keratitis, uveitis, iridocyclitis, hypopyon, and vasculitis in most structures of the eye. Oedema, neovascularization, and mononuclear cell infiltration of the cornea arise at the limbus and spread centripetally. Erosion of the cornea may occur. The uveitis is frequently accompanied by the accumulation of fibrin, neutrophils and mononuclear cells in the anterior chamber of the eye and vitreous body.

The histopathological changes in the macroscopically-affected parts of the skin are characterized by a diffuse infiltration of all its layers by cells of the lymphoid series, oedema, vasculitis, haemorrhage, necrosis of epithelial cells, exudation and erosions, as well as hyperkeratosis, acanthosis and parakeratosis.
Laboratory confirmation

A variety of serological tests for detection of antibody in animals has been described, while recovery of virus in cell culture or identification of viral DNA by PCR amplification may be used to identify the virus. As most cattle infected with AlHV-1 die, the detection of antibody in clinically affected animals provides good supportive evidence. Antibody detection by neutralization assays using the cell-free WCII strain of virus is highly specific while assays, such as the IIFA test, are more rapid but cross reaction with antibody to bovine herpesvirus 4 (BHV-4) may confuse their interpretation.

Virus recovery of AlHV-1 in cell culture is achieved by co-cultivating either peripheral blood leukocytes or disaggregated cells from affected tissues with monolayer cell cultures of bovine or ovine origin. As virus can only be recovered from viable cells, tissue samples for virus isolation must be obtained either before or shortly after the death of the animal. These must be kept cool until processed in the laboratory. Virus cannot be recovered from frozen material.

The full sequence of the AlHV-1 genome has been published; thus primers for PCR can readily be designed for detecting viral DNA in peripheral blood leukocytes or affected tissues.

OvHV-2 has not been isolated, thus prior to the cloning and sequencing of a segment of viral DNA which allowed the design of an OvHV-2 specific PCR, confirmation of a diagnosis relied on histopathological examination or on the detection of antibody that cross reacted with AlHV-1. A CI-ELISA has been developed using a monoclonal antibody to AlHV-1 and has good specificity.

The PCR for OvHV-2 has been assessed as a diagnostic tool in several European countries, North America, Australia, New Zealand, Africa and Indonesia and has proved to be a robust, sensitive and specific indicator of infection. As viral DNA can be extracted from peripheral blood leukocytes confirmation of clinical cases is now possible. The application of the test to cattle involved in multiple case outbreaks has confirmed that up to 20 per cent of cases do recover and that mild, or even inapparent infections, may also occur in up to ten per cent of those at risk. There is increasing evidence that the epidemiology of MCF is complex and is only now starting to be understood through the application of molecular techniques.

Differential diagnosis

The sporadic occurrence in cattle with signs and lesions typical of MCF and with identifiable contact with sheep or wildebeest is sufficient to reach a presumptive diagnosis. However, outbreaks affecting several animals do occur and the wide spectrum of clinical signs that may develop complicates the differential diagnosis.

Clinical signs similar to MCF may occur in many other conditions including mucosal disease, foot-and-mouth disease, lumpy skin disease and infectious bovine rhinotracheitis. In the more acute forms, in which diarrhoea is a prominent clinical sign, particularly in deer, yersiniosis presents a similar picture although, in general, this condition only affects animals under one year of age. In South Africa, severe disease associated with lachrymation, stomatitis, coronitis, sloughing of the skin of the teats and muzzle and, on occasion, diarrhoea has been recorded in cattle following infection with bluetongue...
virus and epizootic haemorrhagic disease virus. Therefore recourse to laboratory confirmation is generally required to reach a definitive diagnosis.

CONTROL / PREVENTION

In the absence of a vaccine, the only effective strategy is to limit contact between MCF-susceptible species and the natural hosts of the viruses. In the case of free-living wildebeest, the advice to remove cattle from the areas where wildebeest are present, particularly during the calving period of the latter, is becoming increasingly difficult to follow due to encroachment into and settlement of traditional wildlife areas. Similarly, where mixed animal species are kept on ranches or in zoological collections, effective separation may not be practical.

The unpredictability of the occurrence of SA-MCF makes it particularly difficult to establish rational control strategies. Usually sheep and cattle co-habit in the absence of disease but occasionally catastrophic outbreaks occur. As yet the precipitating factor(s) of such epidemics is unclear although it has been observed that the sheep flocks involved may continue to cause substantial losses over several years. It may thus be appropriate to dispose of such flocks preferably by slaughter.

With the more susceptible species segregation from sheep is imperative and it is important to minimize contact either directly or through personnel or fomites. With highly susceptible species, such as Bali cattle strict, segregation from sheep is essential; in Indonesia the keeping of small ruminants on some of the islands on which Bali cattle are raised is illegal.

While studies in East Africa indicated that wildebeest older than three months of age are unlikely to be a source of infection, evidence from South Africa suggests that older calves may also be a source of infection. Similarly, disease induced by OvHV-2 can occur following the lambing period but this is by no means always the case. It would be prudent to regard both wildebeest and sheep of any age as potential sources of infection.

In view of the fact that epidemiological observations indicate that aerosol transmission does occur, the distance of separation between both sheep and wildebeest from susceptible species should be as great as possible and should be at least 1000 metres if not further. As the causal viruses are gammaherpesviruses their survival period outside the host is likely to be short and thus infectivity on pasture or in buildings will only survive for a short period, and will not be present after 48 hours of destocking.

MARKETING AND TRADE / SOCIO-ECONOMICS

Legislation to control MCF transmitted by wildebeest was enacted in 1984 in South Africa under the Animal Diseases Act. The disease was declared a controlled disease and every outbreak and number of deaths due to it were required to be reported. Farmers were given authorization up to 1987 to
register their properties for keeping wildebeest although subsequent registration was only possible if several strict requirements enforced by the Regional State Directorate of Animal Health were complied with including agreement from all owners of contiguous properties. Further methods to control the disease included restriction of the movement of wildebeest controlled by the institution of a movement permit system, and the removal of wildebeest from unregistered properties.

Game ranchers and groups involved in ecotourism formed a strong lobby to convince the responsible government minister that, notwithstanding all measures being implemented to regulate the distribution of wildebeest, MCF had not been significantly controlled. The appeal by these interest groups was based inter alia on the importance of wildebeest to the agricultural economy and game ranching and the discriminatory and prescriptive legislation regulating the free trade and movement of wildebeest. In addition, the importance of game ranching for land-use in semi-arid regions and the possible role of sheep in the dissemination of the disease were accentuated. The appeals were successful, and the control measures for MCF were lifted in April 1993. The lifting of control measures for MCF heralded a period of unrestricted movement of wildebeest into especially the Limpopo and North-West Provinces of South Africa. This was accompanied by a concomitant increase in cases of MCF in cattle in these areas.

Many farmers have opted to substitute cattle farming for game ranching, both from the perspective of reducing losses from MCF and the more lucrative nature of the latter. A situation may thus develop in the future where the prevalence of the disease will diminish in some areas as a result of the decline in the cattle population.

During the past two decades disease-free buffaloes (buffaloes free from bovine tuberculosis, foot-and-mouth disease, theileriosis and brucellosis) became widely distributed throughout South Africa. This translocation has resulted in African buffaloes being exposed to sheep which otherwise may never have occurred (except in zoological gardens). These developments in the management of African buffaloes translocated from their traditional habitats have likely contributed to the identification during the past decade of another susceptible host in the subfamily Bovinae.

### IMPORTANT OUTBREAKS

While outbreaks of CSF are always important to the victims, they assume a particular importance when they occur in countries that are considered to be free of CSF. Most countries in Western Europe had eradicated CSF by the 1980s and had ceased vaccination. Small outbreaks sporadically occurred in countries like Germany and Italy where the wild boar population was known to be infected and unsafe practices resulted in domestic pigs becoming infected. However, in 1997 an outbreak of CSF occurred in the Netherlands in areas of dense pig farming that resulted in the loss of 11 million pigs and cost $2.3 billion to eradicate. Although the outbreak originated in Germany and was believed to have been introduced into The Netherlands by a contaminated truck used for transporting pigs, molecular genetic studies of the German and Netherlands outbreak viruses demonstrated that it differed at group level from the viruses circulating in European wild boar populations and most likely came from in Asia. In 2001 the United Kingdom suffered an outbreak and although the origin was not
traced with certainty, the first confirmed case occurred in outdoor pigs and the virus was again of the Asian type.

An outbreak of CSF was documented in South Africa in 1900 in the Western Cape that spread and was only eradicated in 1918, three years before African swine fever was described for the first time as a different disease. Apart from Madagascar, where CSF was introduced during the colonial period and became endemic, CSF was not reported from Africa again until 2000, when the island of Mauritius suffered an outbreak apparently due to an introduction from Madagascar. Eradication was accomplished by 2002 with the help of vaccination. In 2005 CSF was reported from South Africa, first in the Western Cape and then in the Eastern Cape. Although only a few commercial farms were infected, the disease spread rapidly among pigs in the smallholder sectors. In the Western Cape smallholder pig farmers were just recovering from a devastating outbreak of porcine reproductive and respiratory syndrome (PRRS) when once again all their pigs had to be culled to control CSF. In the Eastern Cape, as indicated above, almost half a million pigs belonging to nearly as many households were culled, an operation that continued until 2007.

FAQs

1. **MCF was diagnosed in my cattle herd and 7 pregnant cows were lost during the outbreak. All 11 wildebeest on the farm were shot. How long can the virus survive in the environment and is there a chance that more cattle will become sick?** Some sources of information say that once the wildebeest are gone the risk would likewise disappear. Others say it can take up to 7 months. Must we translocate our cattle to another farm? The wildebeest have been gone for more than 3 weeks. Is the threat gone or can we still expect mortalities?

   The virus does not survive in the farm and there is no chance that other cattle can become sick as a result of virus in the environment. If no more wildebeest are present nearby, the threat has disappeared, even after one day following their removal. Some of the remaining cattle can still become sick because the incubation period varies between 3-8 weeks and in rare instances several months. This however, occurs independently of the absence of the wildebeest. That is why some sources mention that it may take 7 months before reasonable certainty that more cases will not occur. It will not be advisable to translocate the cattle to another farm. The reason being that with newer knowledge it is now accepted that when MCF breaks out on a farm, large numbers of cattle may become infected, but only a small number become sick and die. Animals that did not become sick remain persistently infected but are not able to transmit the virus to susceptible cattle. Only wildebeest can transmit the virus. However, when those cattle are exposed to stress such as movement to another farm, the disease can appear among them. This is not a common phenomenon and farmers must not have the impression that in the event of an outbreak, most of their animals represent a risk for further outbreaks. Recrudescence (re-appearance of clinical signs) remains a rare occurrence of which one must only take notice. It does however, explain some outbreaks that occurred without the presence of wildebeest.

2. **Does a positive PCR test result for MCF nucleic acid confirm the cause of death?**
No. Several animals in a herd can become infected subclinically during an outbreak of MCF. Those animals will remain persistently infected and will yield positive PCR test results. If later in life an animal dies of a disease other than MCF but which resembles the latter in terms of clinical signs and post-mortem lesions, a positive PCR test result will represent a false positive result. Confirmation of the diagnosis in a dead animal (especially for legal purposes) therefore requires both a histopathological examination and PCR result.

3. What is the main mode of viral transmission?

Although the exact mode of transmission has not been established, the predominant mode for transmission is regarded as shedding of virus in nasal secretions. Eloquent studies in the USA employing experimental aerosol infection of sheep, cattle and bison and real-time PCR provided support for the theory that reservoir ruminant species experienced short-lived peaks of viral DNA in their nasal secretions. These episodes occur sporadically and infrequently. Viral infectivity in nasal secretions was also demonstrated by aerosolization of the secretions into virus-negative sheep, calves and bison.

4. Do other wild antelope species transmit MCF-causing viruses?

Except for AlHV-1 and OvHV-2, none of the gammaherpesviruses that have been detected in a range of wild ruminant species has been reported to cause clinical disease in nature, nor with experimental infections.

5. What is the ideal distance of separation to avoid outbreaks of the disease?

The risk for development of wildebeest-associated MCF (and likely also sheep-derived MCF) diminishes exponentially as the distance of separation increases. If we regard the risk for transmission between wildebeest and cattle in close association as 99%, then separating them for example by a distance of 200-300 metres may diminish the risk to 50% or less. Separation by 500 metres may diminish the risk to 10% and for 1 km to less than 1%.

6. Are there subclinical MCF virus infections?

Yes, several studies have been documented where healthy animals from herds that previously experienced outbreaks of MCF were tested several years later and found to be positive with PCR assays.

7. Are there cases of MCF that recover?

MCF is traditionally regarded as a disease with a short clinical course, low morbidity and high case fatality rate. However, several publications have described both recovery and chronic disease, albeit it very rare. The large majority of these documented cases were the result of infection with OvHV-2, and recovery from cases of wildebeest-associated virus infection remains anecdotal. Such cattle remain persistently infected with the causative virus, similar to cattle that develop subclinical infections.

8. Do subclinical/recovered cases become carriers?
Yes, subclinical/recovered cases remain persistently infected.

9. Do carrier cattle represent a risk for susceptible cattle?

It is not known if latent infection in healthy cattle may be reactivated during periods of stress. Even if this is the case, it is unlikely that that persistently infected cattle represent a source of virus for horizontal transmission, as cattle with acute overt MCF do not transmit virus to susceptible cattle. In addition, it has been reported that on farms with known recovered animals, MCF did not occur within a period of at least 2 years subsequent to an outbreak.

10. Can carriers experience recrudescence (re-appearance of clinical signs)?

Recrudescence of a latent infection in cattle has been described. An example is the fact that healthy cattle from a farm where reservoir ruminant species were present were transported to a different farm and experienced an outbreak of MCF a while later without any reservoir ruminant species being present at the new destination. The stress of traveling and introduction to a new environment is postulated to have triggered recrudescence.

11. Why do outbreaks sometimes occur in the absence of reservoir ruminant species?

Some of the explanations include the long incubation period of several months that can occur in some cases of MCF and recrudescence in previously infected cattle that experienced a stressful incident.

REFERENCES


