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Malignant Catarrhal Fever (MCF)

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George C. Russell BSc, PhD
Moredun Research Institute
Pentlands Science Park
Bush Loan
Penicuik
Midlothian EH26 0PZ

Highlights

- Malignant Catarrhal Fever (MCF) is a generally fatal disease of cattle, deer, bison and certain other hoofed animals.
- MCF is the most serious viral disease of farmed deer and bison worldwide.
- In the UK, MCF in cattle is caused by Ovine herpesvirus-2 (OvHV-2). The clinical signs of disease in cattle are similar to mucosal disease, foot-and-mouth disease (FMD), bluetongue disease (BTD), papular stomatitis and vesicular stomatitis.
- The commonest clinical signs include high fever, enlarged lymph nodes, discharge from eyes & nose, lesions in the mouth and muzzle, inflammation and cloudiness of the eyes and sometimes diarrhoea.
- MCF cases are sporadic. The disease usually affects small numbers of animals, but occasional outbreaks can affect up to 50% of a herd. The reasons for this are not clear.
- OvHV-2 also infects most sheep throughout their lives without causing clinical disease. Sheep are therefore considered to be the reservoir species for OvHV-2.
- The virus is occasionally shed in the nasal secretions of infected sheep. These periods of shedding normally last less than 24 hours in the adult animal. Lambs become infected in the first few months of life and during this initial infection can shed the virus for days or even weeks until the immune response controls the infection.
- The likely routes of infection are by aerosol, by contact and by ingestion of contaminated feed, water and bedding.
- Cattle or deer can become infected when kept in close contact with sheep or lambs: shared grazing, housing, feeding troughs or water supplies may all contribute to the likelihood of infection.
- Stressful situations, such as transportation, shearing or lambing, may increase the shedding of virus by sheep and therefore increase the risk of transmission to cattle.
- Cattle can only get MCF through contact with sheep; infected cattle cannot pass the disease on to other animals.
- There is no treatment or vaccine for MCF and the disease is almost always fatal.
- The best method of control is to keep sheep separate from susceptible species such as cattle and deer. To help reduce the risk of transmission avoid shared grazing, housing and the sharing of food and water troughs.

Introduction

Malignant catarrhal fever (MCF) is a dramatic, fatal disease of cattle and other hoofed animals, including deer, bison and pigs. This disease is sporadic in nature and probably affects several hundred cattle each year in the UK. However the fatal nature of the disease and occasional outbreaks that can affect up to 40% of a herd mean that the effects on individual farms can be serious.

Most cases of MCF in deer and cattle in the UK are caused by ovine herpesvirus-2 (OvHV-2) caught through contact with infected sheep or lambs. The disease is characterised by fever, loss of appetite, inflammation and discharge from the eyes & nose. In deer and bison, death can occur within a few days while cattle may survive for several weeks after the onset of clinical signs. The reasons for this difference are not clear. OvHV-2 is present in most sheep and although causes no disease in sheep, is a known cause of sheep-associated MCF (SA-MCF) in susceptible species. The disease was initially observed in Europe but is found worldwide wherever sheep and cattle (or other MCF-susceptible species) are kept together.

Worldwide, MCF is caused by a group of related herpesviruses that infect a range of reservoir species (Table 1). In addition to OvHV-2 which is carried by sheep, these include caprine herpesvirus-2 (CpHV-2), carried by goats and alcelaphine herpesvirus-1 (AlHV-1), carried by wildebeest. In South Africa, the wildebeest-associated disease of cattle called 'Snotsiekte' was recognised in the 19th century. During the 1930s it was recognised that Snotsiekte was analogous to European SA-MCF. All of these viruses appear to cause similar forms of MCF in the same susceptible species – varieties of cattle, deer and bison.

Table 1. The major MCF viruses, their reservoir species and susceptible species

MCF Virus	**Reservoir species** (i.e. animals which naturally carry the virus but do not show clinical signs of MCF)	**Susceptible species** (i.e. Animals which can become ill with MCF)
OvHV-2	Sheep and goats	Cattle, deer, bison, pigs
CpHV-2	Goats	Mainly deer
AlHV-1	Wildebeest	Mainly cattle

One interesting feature is that the reservoir species for MCF viruses (e.g. sheep for OvHV-2) do not exhibit any clinical signs of infection, whereas the disease is dramatic and usually fatal in MCF-susceptible species, like cattle and deer. In addition, infection of MCF-susceptible species appears to be less efficient than infection of the reservoir species, leading to sporadic outbreaks with one or a few susceptible animals being affected. This may suggest that susceptible species are less easily infected than the reservoir species. However, occasionally there are more serious outbreaks of MCF in cattle and bison that can affect up to 40% of a herd. The reasons for this are not currently known.

Even among the MCF-susceptible species, some animals seem to be more susceptible to MCF than others. For example, deer and bison appear to be much more susceptible to MCF than cattle, with death rapidly following the onset of clinical signs and with more animals being affected when there are outbreaks. In cattle, a very small number of cases of recovery from MCF have been recorded.

Each year, scientists at Moredun Research Institute diagnose over 100 cases of MCF, mainly in cattle samples from the UK, but scientists believe that many more cases may occur that are not submitted for testing. The number of samples submitted for MCF testing has increased in recent years, possibly because the symptoms of MCF are similar to FMD and BTD (in particular, the presence of lesions in the mouth).

MCF Viruses

MCF viruses belong to the herpesvirus family. This means that in their reservoir species the viruses cause a lifelong infection in which the virus lies dormant most of the time, only re-appearing occasionally in response to stressful situations (e.g. transportation, disease, lambing/calving). It is very unusual for the MCF viruses to cause disease in their own reservoir species. Studies in sheep show that they shed the OvHV-2 virus only occasionally and when adults shed OvHV-2, virus is released for less than 24 hours. In contrast, wildebeest appear to shed AlHV-1 virus more often and in greater quantities.

The infection of MCF susceptible species appears to be of a different nature. No virus is shed by the infected animals at any point and infected cells are not readily detectable until the later stages of the infection when clinical signs are seen. At this stage of the disease, virus-infected cells can be detected in the blood and in many tissues but the relationship between the virus infection and the clinical disease is still unclear.

MCF has been directly associated with infection by only four viruses (OvHV-2, AlHV-1, CpHV-2, and the MCF virus of white-tailed deer, which hasn't been formally named because its' reservoir species has not been identified). Most MCF cases worldwide are caused by OvHV-2 infection but AlHV-1, whose reservoir species is the wildebeest, causes considerable MCF in cattle in areas of Africa where pastoralist cattle grazing coincides with the wildebeest migration routes and calving areas. In addition, CpHV-2 and the MCF virus of white-tailed deer have been detected in a few MCF cases, mainly in deer. Interestingly, while goats appear to be able to act as reservoir species for both OvHV-2 and CpHV-2, some cases of MCF in goats have been reported. It's therefore possible that different goat breeds may act as either reservoir or susceptible species.

The MCF viruses form a group of ruminant herpesviruses that are closely related, according to studies of their DNA sequences and of the antibody response in infected animals. About 10 members of the MCF virus family have now been recognized.

Most research on MCF has been done using OvHV-2 and AlHV-1. OvHV-2 is studied because it causes the largest number of MCF cases but this virus cannot be grown in the laboratory. MCF cases caused by AlHV-1 are restricted to mainly African cattle, but because AlHV-1 can be grown in the laboratory, research on this virus is much more feasible. The disease caused by both viruses is very similar and their genome sequences reveal that they are highly related viruses. Thus genetic features common to both viruses may play important roles in MCF disease.

MCF clinical signs

The clinical signs commonly seen in cattle with MCF make it an important differential diagnosis for other diseases that produce lesions in the mouth including FMD, BTD, bovine papular stomatitis and vesicular stomatitis, although the most common challenge for diagnosis is with mucosal disease caused by bovine viral diarrhoea virus.

The clinical signs of MCF can vary depending on the susceptible species infected, the type of infecting virus, and possibly on genetic features of the virus (i.e. different strains of virus may cause different signs). In cattle, typical signs of MCF include: fever, loss of appetite, discharge from the eyes and/or nose, reddening of the tissues around the eye, opacity (cloudiness) of the eyes, lesions in the mouth, encrustation of the nostrils and muzzle, depression and sometimes diarrhoea. The range of clinical signs and their approximate frequencies are shown in Table 2.

Table 2. Clinical signs of MCF

Clinical signs of MCF	**Frequency symptoms are seen**	**Susceptible species**
Fever	Common	Cattle, deer, bison, pigs
Enlarged lymph nodes	Common	Cattle, deer, bison, pigs
Depression/loss of appetite	Common	Mainly cattle
Discharge from eyes/nose	Common	Mainly cattle
Lesions in/around mouth & muzzle	Common	Mainly cattle
Inflammation (where skin is visible & around eyes)	Sometimes	Mainly cattle
Opacity of one or both eyes	Sometimes	Mainly cattle
Diarrhoea	Sometimes	Deer & sometimes cattle
Other skin lesions	Sometimes	Deer (possibly only due to CpHV-2)
Neurological signs (e.g. spasms, disorientation, tremors)	Rarely	Cattle, deer, bison, pigs

The extent of clinical signs may depend on the length of time animals can survive with MCF; for example, cattle may survive for a week or more and therefore exhibit more clinical signs of infection. Affected bison generally die within 3 days, so have less time to develop clinical signs, and many deer die within 48 hours, following a brief fever or a bout of diarrhoea, often containing blood.

Within infected animals, MCF is characterized by the accumulation of white blood cells in a range of tissues, often associated with inflammation of blood vessels and areas of dead or dying cells.

Gross findings at *post-mortem* examination include inflammation and pinpoint hemorrhages on the tongue, inside the mouth, in the internal organs, gastrointestinal and respiratory tracts and on the urinary bladder. Commonly, there are raised pale spots on the surfaces of the kidneys and these may extend into the cortex. In addition, there is also general enlargement of lymph nodes.

Diagnosis

Diagnosis of MCF depends on a combination of clinical signs, histopathology and detection of virus-specific antibodies in blood, or DNA from blood or tissue samples.

The World Organization for Animal Health (OIE) recognizes histopathology as the definitive diagnostic test for MCF. However, there is currently no 'gold standard' for MCF testing, and diagnostic laboratories worldwide have adopted tests for MCF-specific antibodies and/or viral DNA to help confirm a clinical diagnosis of MCF. These tests add crucial specificity to the observation of MCF-like pathology.

Laboratory confirmation of a clinical diagnosis of MCF is important as the similarity of MCF clinical signs to other mucosal or vesicular diseases, the lack of unique disease-specific clinical diagnostic features and the variability in the presentation of MCF can hinder rapid and accurate diagnosis.

Detection of MCF virus-specific antibodies or DNA in an animal with clinical signs will support a diagnosis of MCF. Diagnosis in MCF-susceptible species has benefited from research in molecular virology that has allowed the development of sensitive DNA-based tests for several MCF viruses. These tests, conducted in laboratories, allow confirmation and identification of MCF viruses in blood samples taken from animals thought to be infected with MCF. Virus DNA may be detected in the blood of MCF cases before the onset of clinical signs and is almost always detectable in blood and tissue samples from fatal MCF cases. These tests may also help scientists understand how these viruses spread and how outbreaks occur.

Epidemiology

The purpose of epidemiology is to help understand how infections spread and to identify the major risks and solutions for disease problems. For MCF, the virus spreads from the reservoir to the susceptible species, so that the extent of infection in reservoir species and the routes of infection from them are the most important concerns. Outbreaks of MCF occur mainly in livestock following contact between the susceptible species and a reservoir species carrying an MCF virus, although a few cases have been reported without direct contact, and there is some evidence of airborne infection of bison.

Several studies have used both serological (antibody-based) and DNA-based diagnostic tests to analyse MCF infection of both reservoir and MCF-susceptible species. Over 90% of sheep were found to be OvHV-2 positive in a study using both serology and DNA testing. MCF viruses seem to spread rapidly to uninfected members of the reservoir species probably by contact or aerosol means, so it is reasonable to assume that all members of a reservoir species for MCF viruses will be infected. Most of these animals, therefore, have the potential to shed virus and will therefore present a risk of MCF to in-contact livestock.

Occasional reports have been published of MCF outbreaks in zoological collections where a variety of hoofed species may share grazing or accommodation. There is relatively little information on such collections and on whether exotic livestock species may be susceptible to MCF or present a hazard as carriers of MCF viruses. Studies in animal collections have shown that over 90% of certain species, including sheep, goats, wildebeest and musk ox were MCF antibody-positive, indicating their status as carriers of MCF viruses. In contrast, other species had a lower proportion of MCF antibody positive animals, suggesting that such species do not survive MCF infections and should therefore be considered MCF-susceptible. These species include cattle, bison, deer, caribou, elk and moose. Expanding the analysis of MCF viruses into a wider range of zoological species will help us understand the disease risks associated with keeping groups of diverse animals in close quarters and may increase the number of MCF viruses that have been identified as posing a disease risk.

Vaccine Development

The development of a vaccine for MCF has been a research goal for scientists throughout the world for over fifty years. Initial trials using attenuated viruses (variants of MCF viruses that don't cause disease) or inactivated viruses were unsuccessful and only recently have successful trials taken place at Moredun. The crucial factor in recent developments has been the use of an intra-nasal challenge that mimics the natural infection process better than the previously-used intravenous challenge. Experiments by Moredun scientists to test an attenuated virus vaccine for AlHV-1 (the MCF virus carried by wildebeest) demonstrated significant protection of MCF for the first time. This success not only points the way towards a feasible vaccine for AlHV-1, but may also help identify the virus proteins that are important for protection. The equivalent proteins from OvHV-2 may have potential in the development of a vaccine for sheep-associated MCF.

Preventing the Introduction of Infection

The main method to prevent MCF is to separate MCF reservoir species, such as sheep and goats, from susceptible species, including cattle and deer. Reservoir species can shed MCF viruses occasionally, with the risk of infection to susceptible species. Avoiding shared grazing, housing and especially shared food and water troughs will reduce the risk of virus shed by sheep and goats being passed on to susceptible species. As virus shedding can be increased by stress, it would also be good practice to separate sheep from cattle and deer during and following transportation, shearing, lambing and other stressful events. The increased shedding found during the initial infection of lambs with OvHV-2 also makes them a high risk of passing on MCF to cattle. The co-housing of finishing lambs and calves also presents a high risk of MCF in the calves.

Future Developments

Improvements in diagnostic techniques continue to be made and improved serological assays will help our understanding of the dangers of MCF to livestock and zoological collections. Animal collections, like zoos and wildlife parks, are increasingly being kept in mixed, more natural, conditions that present a risk of MCF being passed from unrecognised reservoir species to susceptible species. Understanding these risks will allow mixing of species in an informed manner and help in the important conservation role that zoological collections now have.

While no vaccine or therapy for OvHV–2 MCF infection in cattle and deer is currently available, the first report of a protective vaccine for the wildebeest-associated form of MCF has been published recently by Moredun scientists. This vaccine may have direct application in sub-Saharan Africa, where wildebeest-associated MCF presents a serious risk to Massai livestock. Current research at Moredun is aimed at defining how this AlHV-1 vaccination approach can be adapted to protect cattle (and other susceptible species) from OvHV-2 sheep-associated MCF and so increase the possibility of developing an MCF vaccine for the UK and world markets.

Produced by: The Moredun Foundation
Pentlands Science Park
Bush Loan
Penicuik
EH26 0PZ
Scotland

Phone: +44 (0)131 445 5111
Fax: +44 (0)131 445 6235
E-mail: info@moredun.org.uk
Website: www.moredun.org.uk