



E-ISSN: 2320-7078

P-ISSN: 2349-6800

JEZS 2019; 7(3): 26-32

© 2019 JEZS

Received: 15-03-2019

Accepted: 18-04-2019

Barkha Sharma

Assistant Professor,

Department of Epidemiology
and Preventive Medicine, C.V.
Sc. & A.H., DUVASU, Mathura,
Uttar Pradesh, India

Singh Parul

Assistant Professor, Department
of Veterinary Public Health,
C.V. Sc. & A.H., DUVASU,
Mathura, Uttar Pradesh, India

Gourab Basak

M.V.Sc. Scholar, Department of
Veterinary Public Health, C.V.
Sc. & A.H., DUVASU, Mathura,
Uttar Pradesh, India

Raghendra Mishra

Ph.D., Scholar, Department of
Veterinary Public Health, C.V.
Sc. & A.H., DUVASU, Mathura,
Uttar Pradesh, India

Correspondence

Barkha Sharma

Assistant Professor,

Department of Epidemiology
and Preventive Medicine, C.V.
Sc. & A.H., DUVASU, Mathura,
Uttar Pradesh, India

Malignant catarrhal fever (MCF): An emerging threat

Barkha Sharma, Singh Parul, Gourab Basak and Raghendra Mishra

Abstract

Malignant Catarrhal fever is a highly infectious and often fatal viral disease of animals of family Bovidae and Cervidae in the order Artiodactyla. MCFV is group of at least 10 gamma herpesviruses belonging to Genus Macavirus in the subfamily Gammaherpesvirinae, of which two viruses *viz.*, Alcelaphine Herpesvirus -1 (AIHV-1) causing Wildebeest associated MCF (WA-MCF) and Ovine Herpes Virus -2 (OvHV-2) causing Sheep associated MCF (SA-MCF) are potentially pathogenic. These viruses remain asymptomatic in their natural Hosts wildebeests and sheep, respectively, but cause severe clinical disease in susceptible animals which are terminal/dead end hosts. MCFV is found worldwide wherever clinically susceptible hosts are found in the vicinity of inapparent wildlife carriers. The WA-MCF is a problem in African countries, threatening the conservation of dwindling wildebeest populations in these countries along with a major cause of tremendous economic losses to the livestock farmers in terms of increased veterinary cost, deaths and income lost due to annual migration of cattle during the breeding season of wildebeests to avoid the disease. SA-MCF is mainly an emerging disease of domestic animals, captive ruminants and wildlife outside Africa including India. Till now, clinical findings in susceptible species and histopathology was the main stay for the diagnosis but now serology is the method of choice. Competitive ELISA is a preferred test for the screening of infection in susceptible animals. Several multiplex PCRs have been validated to simultaneously detect and differentiate MCFVs OvHV-2, CpHV-2, MCFV-WTD, MCFV-ibex and AIHV-1 with high sensitivity. Various vaccine candidates for AIHV-1 have been tested upon for last sixty years but hitherto, no effective commercial vaccine is available. As the disease is continuously spreading, a lot still needs to be understood regarding its transmission, epidemiology and ecology. Thus, there is a lot of scope for detailed studies and improved methods for better and prompt diagnostic methods, control and prevention.

Keywords: Malignant catarrhal fever, AIHV-1, OvHV-2, African wildebeests, WA-MCF, SA-MCF

Introduction

Malignant catarrhal fever (MCF) is a sporadic but fatal disease of many species of Bovidae and Cervidae family, especially ruminants though pigs are also affected [1]. Of all gammaherpesviruses implicated in the etiology of MCF, alcelaphineherpesvirus 1 (AIHV-1) and ovine herpesvirus 2 (OvHV-2) are the main [2]. It is a Lymphoproliferative disease characterised by lymphoid cell accumulation in non-lymphoid organs, vasculitis and the T-lymphocyte hyperplasia in the lymphoid organs. The complex epidemiology and the pathogenesis of the disease is a challenging aspect making the understanding of disease incomplete. The present review is an attempt to bring forth recent studies undertaken on various aspects of epidemiology, transmission, pathogenesis and diagnosis of the MCF in a precise way.

Etiology of MCF

Malignant Catarrhal Fever is caused by several gamma herpesviruses in the MCF virus (MCFV) group of genus Macavirus (previously classified as Rhadinovirus) [3] in the subfamily Gammaherpesvirinae [4]. The causative agent or virus was first isolated from blue wildebeest previously known as Bovid herpesvirus 3 [5]. The disease is now considered as one the most economically important diseases of ruminants [6]. Hitherto, atleast 10 MCF viruses have been recognized out of which six cause disease while others are considered to be species-adapted variants of the same virus existing only in asymptomatic carriers [7]. The most important ones are the viruses carried by sheep and wildebeest *viz.*, Alcelaphine Herpes virus-1 (AIHV-1) and ovine herpes virus-2 (OvHV-2) [8]. The AIHV-1 causes the wildebeest associated (WA-MCF) or wildebeest derived MCF (WD-MCF).

The OvHV-2 or sheep-associated agent (ShAA) causes sheep associated (SA-MCF) or non wildebeest-associated form (NWA-MCF) with domestic and wild sheep (*Ovis aries*) as the reservoir. Apart from these, caprine herpesvirus-2 (CPHV-2) affects goats [9] and wild animals like sika deer (*Cervus nippon*) [10]. MCFVs of unknown origin are known to cause disease in white-tailed deer (MCFV-WTD) [11], Ibex MCFV (MCFV-ibex) [12] and Jackson hartebeest [13]. The remaining 4 supposedly non pathogenic viruses are carried by Roan antelope [14], Oryx, Muskox [15] and aoudad [10], respectively. Natural hosts of WA-MCF are two inapparently infected wildebeest species, namely the blue or white bearded wildebeest (*Connochaetes taurinus*) and the black or white tailed wildebeest (*C.gnou*) [16]. The viruses cause subclinical infection in their respective natural hosts but frank clinical disease in susceptible hosts like cattle, deer, bison and pigs. MCFV has an icosahedral symmetry and a large double stranded DNA genome encoding 100-200 genes. The capsid is embedded in tegument, a complex amorphous multiprotein layer which is further enclosed by a glycoprotein containing lipid envelope [17]. Sequencing of the genomes of both AIHV-1 and OvHV-2 has revealed a high degree of similarity [18]. Of the 10 unique genes in AIHV-1 (A1-A10) [19], 8 are homologous to OvHV-1 except A1 and A4. OvHV-2 has a few unique genes Ov2.5, Ov3.5, Ov4.5 and Ov8.5 [20] and a comparison of the genomes of both of these viruses showed 62 open reading frames (ORFs) conserved with other gammaherpesvirus, ten ORFs present only in these two viruses, two ORFs unique to AIHV-1, and three ORFs unique to OvHV-2 [21]. These viruses are also closely related to a recently identified virus, porcine lymphotropic herpesvirus 1 (PLHV-1), that causes post-transplant lymphoproliferative disease in pigs [22].

Table 1: MCFVs Classification Genus Macavirus Subfamily Gamma herpesvirinae

Alcelaphine/ Hippotraginae group	Caprinae group
AIHV-1	OvHV-2
AIHV-2	CpHV-2
Hippotragin HV-1 (HiHV-1)	MCFV-WTD (White Tailed Deer)
MCF carried by Oryx	MCFV carried by ibex, muskox and aoudad

Epidemiology

MCFV is found worldwide wherever clinically susceptible hosts are found in the vicinity of inapparent wildlife carriers. European and African Form of MCF were originally described. WA-MCF is mainly reported from Sub-Saharan African countries like Kenya, Tanzania, South Africa where wildebeests are keystone wildlife species, especially in specific geographical zones and private conservatories [23]. The annual migration of wildebeests across the Maasai Mara-Serengeti corridor is a global tourism attraction often termed as 8th wonder of the world. It threatens the cattle around the area and cause loss of around 10% of cattle herds per year due to WA-MCF [24] in Kenya. In South Africa, cases of WA-MCF have been reported with increasing frequency as a result of growth in game ranching, wildlife and the tourism industry [25].

The European form or the sheep associated MCF (SA-MCF) caused by OvHV-2 is mainly found in domestic animals, captive ruminants and wildlife outside Africa. The disease is quite prevalent in Europe, North and South America, Europe,

Middle East, Asia, Africa and New Zealand as sporadic outbreaks and is a serious concern in countries with bison and cervid farms. SA-MCF has shown its presence in Indian cattle and sheep after first report from Punjab in 1975 [26] and is classified as an emerging disease [27] in India.

Transmission

Transmission is facilitated where reservoir and susceptible animals form close interspecies interaction owing to similar nutritional requirements [28]. A lifelong latent infection is established in natural hosts very early in life. Susceptible host (cattle, bison, deer and pig) acquire the infection either by inhalation or ingestion of cell free virus shed in mucosal secretions of the reservoir host (wildebeest or sheep) in sufficient doses. The disease doesn't get transmitted from MCF-susceptible animals to other animals or even among themselves as these are terminal/dead end hosts and shed extremely fragile cell associated virus in their nasal and ocular secretions [29]. Thus sick animals need not be segregated from the herd [30]. The AIHV-1 has been seen to cross placenta in cows thus congenital transmission may be possible [31].

Transmission of AIHV-1 from wildebeest to cattle has been speculated to occur via infected secretion of respiratory tract during close contact or from pastures contaminated with their secretions aided by close contact and a cool, moist environment. However long distance transmission upto 1 km or more has been seen [32]. Almost 100% of wildebeests are asymptomatic carriers of AIHV-1 and secrete low levels of virus in cell-free and cell associated form in their ocular and nasal secretions [33]. Shedding may increase during the periods of stress or parturition thus occurrence of WA-MCF peaks seasonally with wildebeest calving. Virus is present in placenta and fetal material of calving wildebeest and spleen and blood of wildebeest fetus and less than one week old calves [34]. Within the wildebeest population, all the calves are infected either prenatally in-utero [35] or perinatally via direct contact or aerosol within first few months of life and remain carriers for life. The wildebeest calves are most infectious, shedding a lot of virus during first 90 days of life which declines dramatically thereafter and is rare beyond 6 months due to formation of neutralizing antibodies [36]. Transmission has been seen to have occurred in absence of wildebeest calves giving rise to speculation of involvement of vector or intermediate host but there is no evidence to substantiate this hypothesis.

Infectious OvHV-2 is shed in large amounts for a short time in ovine nasal secretions [37] especially of 6-9 months old lambs. Transmission increases during spring lambing season because of improved virus survival at cool temperature. Aerosol transmission upto 5 km have been documented with maximum probability of spread within 1 km [38]. A dose of 10^3 - 10^5 genome copies of OvHV-2 intranasally can induce disease in sheep and bison but cattle may not acquire the infection even at 1000 fold higher dose [39]. Possibility of vertical transmission of OvHV-2 is suggested by the presence of virus-infected cells in colostrum and milk and also through placenta [40]. Viral DNA has also been reported in the semen of rams, alimentary, respiratory and urogenital tracts [41]. Majority of lambs are infected with OvHV-2 after the age of two months from contact with infected sheep. This delayed infection is due to viral dose at first exposure rather than age related susceptibility or passive-immune protection. There is no evidence of the disease being zoonotic.

Disinfection and Survivability of MCFV

The MCF virus is very labile and gets inactivated quickly by sunlight. The optimum pH needed for the virus survival is 5.5- 8.5. Cell-associated AIHV-1 is very fragile and infectivity disappears after 72 hours in the environment, but in humid conditions, it has been seen to survive more than 13 days. The virus is susceptible to common disinfectants like 3% sodium hypochlorite in the presence of heavy organic debris (recommended by the OIE).

Host Range

Members of order Artiodactyla subfamily Bovinae (Cattle, Bison, water buffalo and exotic ruminants as antelope, gaur, banteng), family Cervidae (deer, reindeer, moose), giraffe and pigs are susceptible hosts. Blue and black wildebeests (*Connochaetes spp.*) are the carriers and reservoir hosts for AIHV-1. Black wildebeest (*C. gnou*) is only found in South Africa. It is a particular problem with Bali cattle in Indonesia, bison in the US and in pastoralist herds in Eastern and Southern Africa.

OvHV-2 is the major cause of MCF in domesticated animals outside Africa and domestic sheep being the reservoir hosts. Disease course tends to be shorter in highly susceptible species like Père David's deer (*Elaphurus davidianus*), white-tailed deer (*Odocoileus virginianus*), axis deer (*Axis axis*), Bali cattle (*Bos javanicus*) and Asian water buffalo (*Bubalus bubalis*), pigs^[42] and domestic goats and horses^[43]. Clinical disease has been observed in Stone's sheep (*Ovis dallistonei*) and Barbary sheep (*Ammotragus lervia*)^[44]. This virus has also been reported from exotic animals like antelopes, elephant seals, giraffes, American elk and buffalos. A variety of ungulates, hamsters and rabbits have been infected experimentally with OvHV-2 and AIHV-1, developing clinical disease similar to that seen in susceptible animals^[45]. American bison (*Bison bison*) are approximately 1,000 times more susceptible to clinical disease than domestic cattle (*Bos taurus* and *Bos indicus*) which are quite resistant and may not become sick on being exposed to OvHV-2^[38]. Water buffalo is also more susceptible to OvHV-2 than cattle.

CpHV-2 associated disease has been seen in cervids including moose (*Alces alces*), roe deer (*Capreolus capreolus*), sika deer (*Cervus nippon*), white-tailed deer and pronghorn antelope (*Antilocapra americana*), as well as in water buffalo. MCFV-WTD has been found in sick white-tailed deer. The ibex-associated MCF virus has caused disease in several bongo antelopes (*Tragelaphus euryceros*) and an anoa. A virus resembling AIHV-2- was found in sick Barbary red deer (*Cervuselaphus barbarus*)^[13].

Pathogenesis

Most gamma viruses establish latency very early in infection in lymphoid tissues causing subclinical or latent infection in wide range of ruminant species. Exact Incubation period is quite broad varying from 14 days in rabbits to 21-90 days in rodents^[46] and 16-29 days in cattle. IP thus is a function of virus titre upon infection, host immunity, route of inoculation etc. Around 95-100% of affected cattle die within 4-7 days of onset of clinical signs. Disease induced by AIHV-1 induces similar disease in rabbits as that observed in the naturally susceptible species, and has helped in understanding the pathogenesis of MCF. WD-MCF is characterized by a combination of lymph proliferation and degenerative lesions caused by unknown mechanisms^[47]. There is progressive T cell hyperplasia with local proliferation and infiltration of

both lymphoid and non-lymphoid organs along with extensive lymphoproliferative vasculitis and tissue destruction and epithelial necrosis caused by dysregulated cytotoxic lymphocytes^[48].

Infection, Disease and clinical signs

The disease occurs in variety of intensities viz peracute, head and eye form, alimentary, neurological and cutaneous^[6]. In susceptible species like bison and many cervids, the clinical course is shorter than in cattle and sudden death may ensue. These species likely mask the clinical signs until terminal signs supervene. Highly susceptible species suffer with peracute form of the disease. The disease progresses rapidly with few clinical signs observed before death. Some animals may show depression, weakness, diarrhea or dysentery.

In cattle the disease is usually acute with the head and eye form being most common, although almost any organ can be affected. A spectrum of symptoms are seen including fever, inappetance, bilateral corneal opacity beginning at corneoscleral junction and progressing inward which is characteristic for the disease. There is profuse serous ocular and nasal discharge which later becomes purulent. Muzzle and nares are encrusted with hardened scabs on the perineum, udder and teat. Dyspnoea, open mouthed breathing and excessive salivation, hyperemic oral mucosa with diffuse multifocal areas of necrosis along with erosions of tongue, hard palate, gums and characteristically, the tips of buccal papillae is the usual sign. Diarrhea, hemorrhagic gastroenteritis or hematuria, enlarged lymph nodes, fever and anorexia are also observed. Limb joints may be swollen and milk yield falls considerably. Some animals show nervous signs terminally like hyperaesthesia, incoordination, nystagmus and head pressing alone or with other signs. Around 25% of cattle suffer with chronic disease and mortality rate in affected animals generally reach upto 95%. A few infected animals may recover following mild or even severe clinical reaction.

In deer and bison, severe eye lesions like panophthalmia, hypopyon etc. are more frequent than hemorrhagic enteritis and cystitis. They may also suffer with haemorrhagic diarrhea, dysuria, bloody urine and corneal opacity before death. There is severe depression, separation from herd, dehydration and weight loss. Animal may become very aggressive and charge at the attendants. Seizures may develop during latter stages and death normally ensues after 5-10 days of the onset of clinical signs. Although deer may die within 48 hours of getting ill, bison generally dies within three days and cattle may survive one week or so [49]. On average, European cattle breeds survives longer than deer, bison, water buffalo and Bali cattle.

Diagnosis

Earlier, the disease was confirmed by characteristic histopathological changes of vasculitis, hyperplasia of lymphoid tissues and accumulation of lymphoid cells in non-lymphoid organs in brain, kidney, and liver. A history of contact with sheep or wildebeest or with pasture recently grazed by either of these species generally confirm the diagnosis but prolonged incubation period may make the correlation quite difficult to reach any conclusion.

Samples to be collected

As the virus is inactivated quickly in dead animals, the most useful samples are collected immediately after death. For

histopathology, in cattle, the tissue samples to be collected are lung, liver, lymph nodes, skin, kidney, adrenal gland, eye, oral epithelium, esophagus, urinary bladder, thyroid, heart muscles, carotid rete and brain. In bison, urogenital and intestinal tissues are important [49]. For virus isolation, anticoagulated blood (10-20 ml in EDTA) in live animals or a portion of spleen, lung, lymph node, adrenals, intestinal wall, brain etc. after death, may be collected. PCR can be readily done to detect viral DNA in peripheral blood leukocytes or affected tissues as the full sequence of AIHV-1 genome has been published. For serology, paired serum samples (5ml) collected 3-4weeks apart are ideal.

Gross lesions and Histopathological findings

Histopathology has long been recognized by World Organization for Animal Health (OIE) for definitive diagnosis for MCF [50]. The pathological features resemble those in graft-host reactions and suggest that virus infection of lymphocytes may cause activation of auto-aggressive T-lymphocytes, either directly through clonal stimulation or by depressing specific suppressor cell populations.

The lesions basically consists of three components-

- T lymphocyte (predominantly CD8+ T lymphocyte, with very few CD+4 lymphocytes) hyperplasia in lymphoid organs and accumulation of these cells in non-lymphoid tissues [51].
- Epithelial degeneration/necrosis and hyperkeratosis
- Macrophage driven rather than lymphoproliferative vasculitis [52].

Liver is slightly enlarged with diffuse grayish-yellow mottling. Petechial hemorrhages may be present on the tongue, buccal mucosa and in the gastro-intestinal along with catarrhal exudates, erosions and diphtheritic membranes in respiratory tract. Urinary bladder has characteristic ecchymotic haemorrhages of epithelial lining, especially in bison. Punctate or larger ulcers may be present on gums, palate, esophagus, abomasums, rumen and intestine. Purulent inflammation of entire eye with vasculitis in medium caliber arteries and veins, diffuse infiltration of all the skin layers by lymphoid cells leading to oedema, vasculitis, hemorrhages, and necrosis of epithelial cells, exudation and erosions along with hyperkeratosis, acanthosis and parakeratosis are usual findings.

There is marked hyperplasia of lymphoblasts and reticuloendothelial cells in pre-existing lymphoid tissues causing their epithelial degeneration, hyperplasia and necrosis. Interstitial accumulation of these cells as multiple, pale, raised foci of 1-5mm in diameter on the surface of kidney extending to cortex, non-lymphoid organs and periportal areas of liver and lungs are important findings. These lymphoblasts, lymphocytes and macrophages also infiltrate into the walls and adventitia of the blood vessels and perivascular spaces causing fibrinoid vasculitis and necrosis. Vascular lesions are most prominently present in liver, brain, meninges, carotid rete, kidneys, lungs and capsule and medulla of the adrenals etc. In brain, there may be non-suppurative meningencephalitis with perivascular lymphoid cuffing and increased cellular components in cerebrospinal fluid [6]. Accumulation of fibrin, neutrophils and mononuclear cells in anterior chamber of eye and vitreous body are prominent ocular findings. When the disease was experimentally produced in rabbits, considerable difference was found in the disease caused by AIHV-1 and OvHV-2 as

infection by latter causes more necrosis [45]. In natural host, OvHV-2 causes latent infection in B-lymphocytes.

Serology

Serology should be used along with histopathology and clinical findings in susceptible species for the diagnosis of AIHV-1. Most of the animals die before initiating an effective immune response. The common serological tests employed are immunoblotting, cELISA and immunofluorescence. These tests are best used for detecting seropositive asymptomatic carriers and reservoir hosts of the virus, but do not differentiate MCFVs. Competitive ELISA is a preferred test for the screening of infection in susceptible animals. A positive serological test is indicative of infection but not of clinical disease. A competitive inhibition (CI)-ELISA using a glycoprotein antigen has been developed as an OvHV-2 – specific assay [53]. ELISA, IFA and IPT can suffer from non-specificity because of sharing of antigens between different herpesvirus as BHV 1 and 4 [54]. MAB based cELISA using antibody against an epitope conserved among all MCFVs is specific, rapid, economical and currently preferred for detecting antiMCF viral antibodies. VNT specifically detects neutralizing antibodies in animals infected with AIHV-1 or other related viruses in Alcelaphine/Hippotraginae group, but is of very limited use in detecting antibody against OvHV-2 or other related viruses in the Caprinae group due to low or no cross-reactivity of OvHV-2 neutralizing antibodies to AIHV-1 [55].

Virus Isolation

AIHV-1 can be isolated in bovine thyroid turbinate cell line or other cell lines, co-cultivated with peripheral blood leukocytes or disaggregated cells from affected tissues with monolayer cell culture of bovine/ovine origin and identified by immunofluorescence or immunocytochemistry. The characteristic cytopathological effects (Cowdry type A intranuclear inclusion bodies) may develop after several passages with fresh susceptible cells. Samples should not be frozen and collected immediately after death as virus loses its infectivity in an animal which is dead for more than one hour. In a recent study, MDBK cell lines were found best suitable for growth of AIHV-1 virus with cytopathic effects consisting of syncytium formation and destruction of monolayers 2-3 days after the virus isolation. The size of syncytia seemed to be influenced by the animal species from which the virus was isolated [56].

OvHV-2 and CpHV-2 cannot be isolated in cell culture but it has been possible to generate lymphoblastoid cell lines from infected cattle and deer. Thus the diagnosis of OvHV-1 infection has been hitherto based on histopathological examination or detecting antibodies that cross react with AIHV-1 by using tests like immunofluorescence assay, ELISA or immunoblotting.

PCR assays

PCR using fresh and frozen tissues has proven to be a reliable method of diagnosing MCFV infection. Low amount of viral DNA in samples from subclinically infected animals however can lead to false negative results. A nested PCR targeting DNA fragment in the ORF 75 of OvHV-2 encoding viral tegument protein has given good results in infected sheep as well as animals having clinical disease and is an OIE approved diagnostic test for detection of OvHV-2 infection. This nested PCR is considered a gold standard [57] but may

suffer with contamination of amplicons leading to false positive cases. Multiplex quantitative real time PCR, targeting the same ORF75 gene is highly reliable, rapid and sensitive method to diagnose OvHV-2 induced MCF in mixed species samples from clinically infected animals ^[59], currently used in many European countries, North America, New Zealand, Africa and Indonesia. Multiplex PCRs have been validated to simultaneously detect and differentiate MCF viruses OvHV-2, CpHV-2, MCFV-WTD, MCFV-ibex and AIHV-1 with high sensitivity.

Differential Diagnosis

Sporadic occurrence in cattle, slow spread within the herd and sign and lesions typical of MCF and history of contact with sheep or wildebeest is sufficient to reach a presumptive diagnosis. Wide spectrum of clinical signs may complicate the differential diagnosis which has to be made with Bovine Viral Diarrhea-Mucosal Disease, Foot and mouth Disease, lumpy skin disease and Infectious Bovine Rhinotracheitis. In deer, when diarrhea is the main sign, yersiniosis may be the cause but it usually affects the animals under one year of age. Differential diagnosis should also be made from cattle suffering with Blue tongue as disease is also quite rampant in South Africa and Northern Europe ^[61]. In both the diseases, lachrymation, stomatitis, coronitis, sloughing of skin of teats and muzzle and diarrhea may be seen, therefore laboratory confirmation is generally required to reach a definitive diagnosis.

Treatment and Control

The treatment is entirely symptomatic and involves supportive care with fluids, anti inflammatory steroids and antibiotics ^[61]. Some animals might recover after receiving treatment but whether recovery actually occurs due to treatment is still not established. No effective vaccine is yet available commercially although various vaccine candidates for AIHV-1 have been checked upon since last sixty years. Attempts have been made using inactivated AIHV-1 virus ^[62], inactivated cell cultures of AIHV-1 (WCII strain in Freund's Complete Adjuvant (FCA), inactivated cell free AIHV-1 virus in FCA ^[63] and most recently inactivated virus strain C500 from serially passaged cell culture with emulgisen adjuvant and CpG oligodeoxy nucleotides (TLR9 agonist) ^[64]. A promising recombinant vaccine candidate tested in rabbits but not validated in cattle is AIHV-1 ORF73 null mutants lacking expression of latency-associated nuclear antigen (LANA) ^[65]. A vaccine field trial involving an attenuated AIHV-1 virus vaccine has shown to reduce infection rates by 56% in cattle exposed to wildebeests ^[66].

Conclusion

Since an effective treatment against MCF is not available, the disease management entirely depends upon prevention and control. The only effective strategy is to limit contact between MCF-susceptible species and natural hosts of the viruses which is being made almost impossible by encroachment and settlement of wildlife areas. A three pronged approach for integrated control of WA-MCF might include vaccine development, efficient and prompt confirmatory diagnosis and genetic studies of WA-MCF. Numerous knowledge gaps exist. Both wildebeest and sheep of any age should be considered to be potential source of infection. For generations, Maasai communities in East Africa has been plagued by WA-MCF and annually suffer from huge

economic losses by having to move cattle to less productive grazing areas to avoid wildebeest during calving season when forage quality is critical [67]. A strong vaccine candidate with potential to reduce the transmission of MCFV to cattle from wildebeests will reduce this cost considerably. In case of SA-MCF, the unpredictable pattern makes the control particularly difficult. Although mode of transmission is not yet fully understood, still it is advisable to minimize contact either directly or through personnel or fomites. In case of highly susceptible species like Bali cattle, strict separation from sheep is essential. Infact, in Indonesia, keeping small ruminants and Bali cattle on the same islands is illegal. Evidences suggest that airborne transmission can occur so distance of separation between both sheep and wildebeest from susceptible species should be not less than 1000 meters. Virus is not able to survive for long outside the host so a 48 hour of destocking is enough to ensure infectivity is lost. In India, most recent case of SA-MCF was recorded in 2012 in a captive female bison from Bengaluru [68]. There is high chance of exposure of susceptible hosts to the MCFV present in the sheep due to practice of mixed farming. Thus it is a matter of no time that the disease will become endemic in India if appropriate control strategies are not put in place in time. Systematic and regular monitoring and surveillance targeting small ruminants is needed. Available diagnostic tests are lengthy, need expertise and not suitable to support active field surveillance especially in hot-spots. Sensitive and speedy detection methods under field conditions are necessary, as most of the affected animals die within two weeks leaving no time for lengthy diagnostic tests.

References

1. Constable PD, Hinchcliff KW, Done SH, Grunberg W. Veterinary Medicine: A textbook of the diseases of Cattle, Horses, Sheep, Pigs and Goats. Edn Elsevier Publication, Missouri, 2017, 11(1).
2. OIE, World Organization for Animal Health. 2013a. Manual of Diagnostic Tests and Vaccines for Terrestrial Animals [online]. Paris: OIE; 2013a. Malignant catarrhal fever. Available at: http://www.oie.int/fileadmin/Home/fr/Health_standards/tahm/2.04.15_MCF.pdf.
3. Russell GC, Stewart JP, Haig DM. Malignant catarrhal fever: a review. *Vet J.* 2009; 179:324-35.
4. Roizman B. The family herpesviridae: general description, taxonomy, and classification. In *The Herpesviruses* (Edited by Roizman B.), Plenum Press, New York. 1982; 1:1-23.
5. Plowright W, Ferris RD, Scott GR. Blue Wildebeest and the aetiological agent of bovine malignant catarrhal fever virus. *Nature.* 1960; 188:1167-1169.
6. Li H, Cunha CW, Taus NS, Knowles DP. Malignant Catarrhal Fever: Inching Towards Understanding. *Annu. Rev. Anim. Bio sci.* 2014; 2:209-33.
7. Li H, Gailbreath K, Flach EJ, Taus NS, Cooley J, Keller J *et al.* A novel subgroup of rhadinoviruses in ruminants. *J Gen. Virol.* 2005; 86:3021-3026.
8. O'Toole D, Li H. The pathology of malignant catarrhal fever, with an emphasis on ovine herpesvirus 2. *Vet Pathol.* 2014; 51(2):437-52.
9. Chmielewicz B, Goltz M, Ehlers B. Detection and multigenic characterization of a novel gammaherpesvirus in goats. *Virus Res.*, 2001; 75:87-94.
10. Zhu H, Huang Q, Hu X, Chu W, Zhang J, Jiang L *et al.*

- BMC Vet Res. 2018; 14: 38.
11. Kleiboeker SB, Miller MA, Schommer SK, Ramos-Vara JA, Boucher M, Turnquist SE. Detection and multigenic characterization of a herpesvirus associated with malignant catarrhal fever in white-tailed deer (*Odocoileus virginianus*) from Missouri. *J Clin. Microbiol.* 2002; 40:1311-1318.
 12. Li H, Gailbreath K, Bender LC, West K, Keller J, Crawford TB. Evidence of three new members of malignant catarrhal fever virus group in muskox (*Ovibos moschatus*), Nubian ibex (*Capra nubiana*), and gemsbok (*Oryx gazella*). *J Wildl. Dis.* 2003; 39:875-880.
 13. Klieforth R, Maalouf G, Stalis I, Terio K, Janssen D, Schrenzel M. Malignant catarrhal fever-like disease in Barbary red deer (*Cervus elaphus barbarus*) naturally infected with a virus resembling alcelaphine herpesvirus 2. *J Clin. Microbiol.* 2002; 40:3381-3390.
 14. Reid HW, Bridgen A. Recovery of a herpesvirus from a roan antelope (*Hippotragus equinus*). *Vet. Microbiol.* 1991; 28:269-278.
 15. Seal BS, Heuschele WP, Klieforth RB. Prevalence of antibodies to alcelaphine herpesvirus-I and nucleic acid hybridization analysis of viruses isolated from captive exotic ruminants. *Am. J vet. Res.* 1989; 50:1447-1453.
 16. McGeoch DJ, Rixon FJ, Davison AJ. Topics in herpesvirus genomics and evolution. *Virus Res.* 2006; 117:90-104.
 17. Coulter LJ, Wright H, Reid HW. Molecular Genomic Characterization of the Viruses of Malignant Catarrhal Fever. *Journal of Comparative Pathology.* 2001; 124(1):2-19.
 18. Ensser A, Pflanz R, Fleckenstein B. Primary structure of the alcelaphine herpesvirus 1 genome. *J Virol.* 1997; 71(9):6517-6525.
 19. Thonur L, Russell GC, Stewart JP, Haig DM. Differential transcription of ovine herpesvirus 2 genes in lymphocytes from reservoir and susceptible species. *Virus Genes.* 2006; 32:27-35.
 20. Hart J, Ackermann M, Jayawardane G, Russell G, Haig DM, Stewart J. Complete sequence and analysis of the ovine herpesvirus 2 genome. *J Gen Virol.* 2007; 88:28-39.
 21. Russell GC, Todd H, Deane D, Percival A, Dagliesh MP, Haig DM *et al.* A novel spliced gene in alcelaphine herpesvirus 1 encodes a glycoprotein which is secreted *in vitro*. *J Gen Virol.* 2013; 94:2515-2623.
 22. Goltz M, Ericsson T, Patience C, Huang CA, Noack S, Sachs DH *et al.* Sequence analysis of the genome of porcine lymphotropic herpesvirus 1 and gene expression during post-transplant lymphoproliferative disease of pigs. *Virology.* 2002; 294:383-393.
 23. Lankester F, Lugelo A, Mnyambwa N, Ndabigaye A, Keyyu J *et al.* a. Alcelaphine Herpesvirus-1 (Malignant Catarrhal Fever Virus) in Wildebeest Placenta: Genetic Variation of ORF50 and A9.5 Alleles. *PLOS ONE.* 2015; 10(5):e0124121.
 24. Orono SA, Gitao GC, Mpatswenumugabo JP, Chepkwony M, Mutisya C, Okoth E *et al.* Field Validation of clinical and laboratory diagnosis of wildebeest associated malignant catarrhal fever in cattle *BMC Vety Res.* 2019; 15:69.
 25. Reid HW, Van Vuuren M. Bovine malignant catarrhal fever. In: *Infectious diseases of livestock*, 2nd edn. Oxford University Press, Oxford, 2005.
 26. Parihar NS, Rajya BS, Gill BS. Occurrence of malignant catarrhal fever in India. *Ind. Vet J.* 1975; 52:857-9.
 27. Sood R, Hemadri D, Bhatia S. Sheep associated malignant Catarrhal Fever: An emerging Disease of Bovids in India. *Indian J Virol.* 2013; 24(3):321-331.
 28. Ego WK, Mbuvi DM, Kibet PFK. Dietary composition of wildebeest (*Connochaetes taurinus*) kongoni (*Alcephalus buselaphus*) and cattle (*Bos indicus*), grazing on a common ranch in south-central Kenya. *Afr J Ecol.* 2003; 41(1):83-92.
 29. Mushi EZ, Rurangirwa FR. Epidemiology of bovine malignant catarrhal fevers, a review. *Vet Res Commun.* 1981; 5(2):127-142.
 30. Plowright W. Malignant catarrhal fever in East Africa. II. Observations on wildebeest calves at the laboratory and contact transmission of the infection to cattle. *Res. vet. Sci.* 1965; 6:69-83.
 31. Plowright W, Kalunda M, Jessett DM, Herniman KA. Congenital infection of cattle with the herpesvirus causing malignant catarrhal fever. *Res Vet Sci.* 1972; 13(1):37-45.
 32. Li H, Karney G, O'Toole D, Crawford TB. Long distance spread of malignant catarrhal fever virus from feedlot lambs to ranch bison. *Can. Vet. J.* 2008; 49:183-185.
 33. Rweyemamu MM, Karstad L, Mushi EZ, Otema JC, Jessett DM, Rowe L *et al.* Malignant catarrhal fever virus in nasal secretions of wildebeest: a probable mechanism for virus transmission. *J Wildl. Dis.* 1974; 10:478-487.
 34. Barnard BJ, Bengis RG, Griessel MD, de Vos V. Excretion of alcelaphine herpesvirus-1 by captive and free-living wildebeest (*Connochaetes taurinus*). *Onderstepoort J Vet Res.* 1989; 56(2):131-134.
 35. Pretorius JA, Oosthuizen MC, van Vuuren M. Gammaherpesvirus carrier status of black wildebeest (*Connochaetes gnou*) in South Africa. *J S Afr Vet Assoc* 2008; 79(3):136-141.
 36. Hamblin C, Hedger RS. Neutralising antibodies to wildebeest- derived malignant catarrhal fever virus in African wildlife. *Comp Immunol Microbiol Infect Dis* 1984; 7(3, 4):195-199.
 37. Li H, Taus NS, Lewis GS, Kim O, Traul DL, Crawford TB. Shedding of Ovine Herpesvirus 2 in Sheep Nasal Secretions: the Predominant Mode for Transmission. *J Clin Microbiol.* 2004; 42(12):5558-64.
 38. Epp T, Waldner C, Woodbury M. An observational study of mortality on bison farms in Saskatchewan with special emphasis on malignant catarrhal fever. *Canadian Veterinary Journal.* 2016; 57:37-45.
 39. Taus NS, Oaks JL, Gailbreath K, Traul DL, O'Toole D, Li H. Experimental aerosol infection of cattle (*Bos taurus*) with ovine herpesvirus 2 using nasal secretions from infected sheep. *Vet. Microbiol.* 2006; 116:29-36.
 40. Headley SA, Pimentel LA, Oliveira VHS, Toma HS, Alfieri AF, Carvalho AM *et al.* Transplacental Transmission of Ovine Herpesvirus 2 in Cattle with Sheep-associated Malignant Catarrhal Fever. *J Comp Patho.* 2015; 153(4):206-211.
 41. Azevedo Costa É, de Marco Viott A, de Souza Machado G, Quaresma Bomfim MR, Magalhães Coelho F, Portela Lobato ZI *et al.* Transmission of ovine herpesvirus 2 from asymptomatic boars to sows. *Emerg. Infect. Dis.* 2010; 16:2011-12.
 42. Lapp S, Forster C, Kummrow M, Wohlsein P, Haist V. Malignant catarrhal fever in a Vietnamese pot-bellied

- pig. A potential threat to pigs in mixed-species exhibits? Tierärztliche Praxis Ausgabe G Grosstiere/Nutztiere. 2015; 43:165-68.
43. Costa EA, Bomfim RQM, daFonseca FG, Drumond BA, Coelho FM, Vasconcelos AC *et al.* Ovine Herpesvirus 2 infection in Foal, Brazil Emerg Infect Dis. 2009; 15(5):844-845.
 44. Himsworth CG, Harms NJ, Wobeser G, Hill J. Bilateral perirenal hemorrhage in two Stone's sheep (*Ovis dalli stonei*): a possible manifestation of malignant catarrhal fever. Journal of Veterinary Diagnostic Investigation 2008; 20:676-78.
 45. Anderson IE, Buxton D, Campbell I, Russell G, Davis WC, Hamilton MJ *et al.* Immuno-histochemical study of experimental malignant catarrhal fever in rabbits. J Comp Pathol. 2007; 136:156-66.
 46. Jacoby RO, Buxton D, Reid HW. The pathology of wildebeest-associated malignant catarrhal fever in hamsters, rats and guinea-pigs. J Comp Pathol. 1988; 98(1):99-109.
 47. Swa S, Wright H, Thomson J, Reid H, Haig D. Constitutive activation of Lck and Fyn tyrosine kinases in large granular lymphocytes infected with the gamma-herpesvirus agents of malignant catarrhal fever. Immunology. 2001; 102:44-52.
 48. Saura H, Al-Saadi M, Stewart JP, Kipar A. New Insights into the Pathogenesis of Vasculitis in Malignant Catarrhal Fever. Journal of Comparative Pathology. 2018; 158:98
 49. O'Toole D, Li H, Sourk C, Montgomery DL, Crawford TB. Malignant catarrhal fever in a bison feedlot, 1994–2000. J Vet. Diagn. Invest. 2002; 14:183-193.
 50. OIE, World Organization for Animal Health OIE Technical Disease Cards: Malignant catarrhal fever, 2013b Available at http://www.oie.int/fileadmin/Home/eng/Animal_Health_in_the_World/docs/pdf/Disease_cards/Malignant_Catharral_fever.pdf.
 51. Dewals B, Boudry C, Farnir F, Drion PV, Vanderplasschen A. Malignant Catarrhal Fever Induced by *Alcelaphine herpesvirus 1* Is Associated with Proliferation of CD8⁺ T Cells Supporting a Latent Infection. PLoS ONE. 2008; 3(2):e1627.
 52. Li H, Cunha CW, Taus NS. Malignant catarrhal fever: understanding molecular diagnostics in context of epidemiology. Int. J Mol Sci. 2011; 12(10):6881-6893.
 53. Alhajri SM, Cunha CW, Knowles DP, Li H, Taus NS. Evaluation of glycoprotein Ov8 as a potential antigen for an OvHV-2-specific diagnostic assay. PLoS ONE. 2018; 13(7):e0200130.
 54. Reid HW. Malignant catarrhal fever. In Manual of Diagnostic Tests and Vaccines for Terrestrial Animals (Mammals, Birds and Bees). 5th edn. Paris, Office Internationale des Epizooties, 2004, 570-578.
 55. Taus NS, Cunha CW, Marquard J, O'Toole D, Li H. Cross-Reactivity of Neutralizing Antibodies among Malignant Catarrhal Fever Viruses. PLoS ONE, 2015, 10(12).
 56. Hristov MV, Peshev RD. Isolation and identification of malignant catarrhal fever virus in cell cultures. Bulg. J Vet. Med., 2016; 19(4):263-273.
 57. Baxter SIF, Pow I, Bridgen A, Reid HW. PCR detection of the sheep-associated agent of malignant catarrhal fever. Arch. Virol. 1993; 132:145-159.
 58. Müller-Doblies UU, Li H, Hauser B, Adler H, Ackermann M. Field validation of laboratory tests for clinical diagnosis of sheep associated malignant catarrhal fever. J Clin Microbiol. 1998; 36:2970-2.
 59. Cunha CW, Otto L, Taus NS, Knowles DP, Li H. Development of a multiplex real-time PCR for detection and differentiation of malignant catarrhal fever viruses in clinical samples. J Clin Microbiol. 2009; 47:2586-9.
 60. Guyot H, Mauroy A, Thiry E, Losson B, Bodmer M, Kirten P *et al.* Fièvre catarrhale ovine chez les ruminants. Description clinique des cas vécus dans le Nord de l'Europe durant l'été et l'automne 2006. Bulletin des Groupements Techniques Vétérinaires. 2007; 39:89-96.
 61. Penny C. Recovery of cattle from malignant catarrhal fever. Vet Rec. 1998; 142:227.
 62. Plowright W, Herniman KA, Jessett DM, Kalunda M, Rampton CS. Immunisation of cattle against the herpesvirus of malignant catarrhal fever: failure of inactivated culture vaccines with adjuvant. Res Vet Sci. 1975; 19(2):159-166.
 63. Edington N, Plowright W. The protection of rabbits against the herpesvirus of malignant catarrhal fever by inactivated vaccines. Res Vet Sci. 1980; 28(3):384-386
 64. Parameswaran N, Russell GC, Bartley K, Grant DM, Deane D, Todd H *et al.* The effect of the TLR9 ligand CpG oligodeoxynucleotide on the protective immune response to alcelaphine herpesvirus-1-mediated malignant catarrhal fever in cattle. Vet Res. 2014; 45(1):59.
 65. Palmeira L, Sorel O, Van Campe W, Boudry C, Roels S, Myster F *et al.* An essential role for c-herpesvirus latency-associated nuclear antigen homolog in an acute lymphoproliferative disease of cattle. Proc. Natl. Acad. Sci. 2013; 110(21):E1933–E1942.
 66. Lankester F, Russell GC, Lugeloe A, Ndabigayec A, Mnyambwac N, Keyyug J *et al.* A field vaccine trial in Tanzania demonstrates partial protection against malignant catarrhal fever in cattle. Vaccine. 2016; 34:831-838.
 67. Lankester F, Lugeloe A, Kazwala R, Keyyu J, Cleaveland S, Yoder J. b the Economic Impact of Malignant Catarrhal Fever on Pastoralist Livelihoods. PLoS ONE 2015; 10(1):e0116059. doi:10.1371/journal.pone.0116059.
 68. Sood R, Kumar M, Bhatia S, Pateriya AK, Khandia R, Siddiqui A *et al.* Transboundary Diseases: ovine herpesvirus type 2 infection in captive bison in India. Vet Rec. 2012; 170:654.