INTRODUCTION

Members of the genus *Parapoxvirus* include the ORF virus (ORFV), pseudocowpox virus, and bovine papular stomatitis virus and a parapoxvirus of deer. Infection of sheep and goats by ORFV, results in a contagious disease, clinically characterized by the presence of vesicles, pustules and scabs, particularly around the mouth known as orf, contagious ecthyma, contagious pustular dermatitis, scabby mouth or sore mouth.

The morbidity rate may be as high as 100 per cent in yearling sheep and goats. Mortality rate can be greater than 10 per cent in some outbreaks and usually when associated with secondary bacterial infections and complications such as fly strike. Secondary bacterial mastitis and lameness are common consequences. The disease tends to have a seasonal appearance, being particularly destructive when it appears around lambing. This disease occurs worldwide and is of great economic importance to small stock farming and infectious to humans. Some wild ruminants may be affected.

EPIDEMIOLOGY

ORFV infections are distributed worldwide being everywhere in sheep- and goat-raising countries. Outbreaks of ORF had been reported in many countries with most recent reports from Greece, Korea, Brazil, India, Taiwan and Japan. Clinical disease has a considerable economic impact on small stock farming being regarded as one of the most important diseases affecting the welfare of farmed sheep and goats in developed countries. Despite this
many ORF outbreaks go unreported due to the low mortality rate and low incidence of infections in humans and as it is not a notifiable disease.

All sheep and goats are susceptible to infection and, although all ages are susceptible, infection is mainly seen in young animals. Wild sheep and goats may also become infected. Spread may also occur from wild ruminants sharing common pasture.

Natural transmission of the virus occurs by either direct contact or indirectly from the environment or fomites. Scabs contain high titres of stable virus which sustain annual outbreaks of the disease. This virus is relatively stable and may still remain infective after exposure for 30 minutes to temperatures of 55°C. If dry scab material is stored in the dark at 70°C it may remain infective for many years. Infection may also be established and maintained by chronically infected animals which then spread virus over long periods of time. Exposure to sunlight and temperate environmental conditions may result in scabs material losing its infectivity in a few weeks. Detergents containing lipid solvents, may destroy the virus membrane.

Abrasions in the skin or mucosa are the common portals of entry. The buccal mucosa may be damaged by rough or sharp plant material, and skin is softened by damp and muddy conditions. Skin damage following shearing or rough handling, Vitamin A deficiency, bacterial and/or other viral infections which compromise the mucosal integrity can also predispose to ORFV infection. Concomitant poor hygiene, particularly in hand-milked flocks or herds, may greatly aid in the rapid spread of the virus. Transmission between ewes and suckling lambs is common. This may result in the greatest losses, and is often associated with an inability of lambs to feed due to the presence of labial and or buccal lesions and secondary mastitis in the ewes.

There are few examples in the literature of epidemiological investigations of ORF infections worldwide. Some recent articles were published on the findings of investigations in China, Korea, India, Brazil and Japan. There is also a very recent study into the epidemiology of ORF in South Africa and we will focus on the findings of this study.

In the latter study 54 outbreaks were reported over a period of seven months (September 2009 to March 2010). Of these 44 occurred in rural areas and the rest on commercial farms. Findings confirmed that sheep and goats were all affected with ORF but also that goats are far more commonly affected than sheep, and the largest number of affected animals were Boer goats. Observations also indicate that Boer goats appear to be more prone to developing severe ORF. It was observed that ORFV infections have a higher incidence during summer (the rainy season) which differs from experiences in other countries, where the highest incidence has been reported in the dry season. The latter coincides with the consumption of dried, fibrous grass which in turn contributes to oral lesions and virus penetration. Lesion distribution was recorded and the face was as the most frequent site (61.9%) affected. This was often associated with lesion at other sites as well, such as the ears (14.9%), the legs (10.7%) and the udder (6.7%).

Many plant species belonging to the Acacia genus were associated with the incidence of ORF. These species are dominant woody plants with spikes or hooked thorns, in the bushveld areas, and they produce tender, succulent leaves early in the rainy season. The thorns most probably causes micro-lesions around the lips and faces of browsing goats allowing the virus
to enter through the damaged mucosa. Scabs of infected animal may remain on the thorns, in turn infecting other animals.

Employing PCR phylogenetic clustering linked to the geographical origin has been excluded. Strains SA52, SA90 and SA142 collected from the North West, Western Cape and Mpumalanga provinces clustered together. These strains were also found to be identical to the ORFV strain contained in the locally produced vaccine.

ORFV has been reported in many wild ungulates including musk ox, reindeer, mountain goats, bighorn sheep, chamois, caribou, Dall sheep, buffalo, wild goats and camels. ORFV infection has recently been reported in chamois and red deer in Italy and it appears to be more closely related to the parapoxvirus found in red deer in New Zealand (PVNZ) than to the classical ORFV virus.

ORFV infection in Korean black goats were phylogenetically most closely related to an isolate (ORF/09/Korea) from dairy goats in Korea suggesting that viruses might have been introduced from dairy goats into the Korean black goat population.

An outbreak of vesicular disease affecting dairy cows in midwestern Brazil was also described in which a co-infection with 2 poxviruses-Vaccinia virus (VACV) and a parapoxvirus, most likely ORFV, was demonstrated.

**PATHOGENESIS, CLINICAL SIGNS AND PATHOLOGY**

Primary skin lesions develop two to six days after infection at the portal of entry of the virus to the body and there is no detectable viraemia. Secondary lesions are formed by local extension or implantation of infective material at other sites of the body. Labial, pedal, genital and generalized forms of the disease may occur, but the labial form is the most common.

A macule develops at the site of virus entry usually on the lips, nostrils or udder. This macule enlarges and becomes a papule progressing to a transient vesicle by the fourth to sixth day after infection. This in turn forms a pustule within twenty-four hours which soon ruptures, leaving an ulcer. A brown scab forms which would then be between seven to eleven days after infection. Lesions usually start at the commissure of the lips but are also common in the mouth where it may be seen on the gums, around erupting teeth, and on the dental pad, palate and tongue. The mucosa of the oesophagus and omasum may also become affected in some cases. Skin lesions may also occur elsewhere on the body such as on the inner thigh, axilla, lower limbs, udder, teats, ventral aspect of the tail, and perineum. In the pedal form skin lesions are seen at the coronet and interdigital space, and may even extend up to the carpus and tarsus. This may even result in sloughing of the hooves in severe cases. In uncomplicated cases all evidence of disease may disappear within five weeks.

Depending upon the anatomical location of the lesions, infected animals may be unwilling to nurse, eat, or walk, and in lactating ewes, udder lesions may result in mastitis. Secondary myiasis, bacterial mastitis (staphylococcal) and lameness are the most common consequences. Bacterial mastitis may result in the loss of as much as half of the udder or death of the ewe. Lambs may be unable to or are prevented from feeding, and those with internal lesions may developed a suppurative pleuropneumonia. A further complication of mastitis is that infected lambs or kids may need to be hand-fed, as they can transmit the
disease by suckling other females. Considerable economic losses due to stunted growth or slaughter of the affected animals has been documented.

Histologically lesions associated with ORFV infection are confined to the epithelium. Lesions are characterized by ballooning degeneration and swelling of keratinocytes in the stratum spinosum and reticular degeneration. This all results in marked epidermal proliferation, intraepidermal micro-abscesses, formation of serocellular and scaly crusts, vesicle formation and polymorphonuclear cellular infiltration. Eosinophilic intracytoplasmic inclusions may be seen in the keratinocytes but this finding is only of short duration.

**IMMUNITY**

A large number of in-depth articles have been published on various aspects of the immune responses to ORFV virus infection. A vigorous inflammatory immune response is observed after infection, nevertheless ORFV host animals may be repeatedly infected.

Fribe et al (2013) reports that several immune-escape mechanisms have been identified. A variety of captured cellular genes, e.g. a viral interleukin (IL)-10 homologue, a granulocyte macrophage colony-stimulating factor (GMCSP), an IL-2-inhibiting protein and the vaccinia E3L gene encoding an interferon-resistance factor were all established to be role players. It has been documented that ORFV activates antigen presenting cells (APC) via CD14 and, probably, Toll-like receptor signaling. This triggers the release of IFN-γ which has been recognized as the key mediator of the antiviral activity.

RNA interference (RNAi) pathways are considered important regulators of virus-host cell interactions. Results of a study be Wang G et al (2103) suggest that three siRNAs (named siRNA704, siRNA1017 and siRNA1388) can efficiently inhibit ORFV genome replication and infectious virus production. RNAi targeting of the DNA polymerase gene may therefore be potentially useful for future studies of the replication of ORFV and may also have potential therapeutic applications.

**DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS**

ORF is usually tentatively diagnosed on the strength of the clinical sigs alone. However, confirmation of the diagnosis by demonstration of the typical ORF by means of electron microscopy, culture, PCR and ELISA is conclusive. An ELISA for detection of specific ORF antigen has been developed and virus can be isolated by tissue culture and neutralized by specific antibody. Of these the most convenient, practical and cost effective technique may be PCR.

As is common with most diseases, much of the recent research focusses on the development and optimizing of PCR techniques for the diagnosis, and epidemiological studies of the virus.

As one example Venkatesan G et al (2014) described the development of a rapid and sensitive TaqMan based real-time duplex PCR assay. This assay allows for the simultaneous detection, differentiation and quantification of Capripoxvirus (CaPV) and ORF virus (ORFV) DNA in clinical specimens. They found it to be specific for these viruses as it did not react with buffalopox virus (BPXV), camelpox virus (CMLV) (Orthopoxviruses) and cDNA of Peste des petits ruminants virus and bluetongue virus. It was able to identify mixed infections of CaPV and ORFV in sheep and goats.
The use of antibody serology is of limited use due to the widespread distribution of the virus. ELISA, Western blotting or immunofluorescence can be employed to demonstrate a rising titre in paired serum samples from infected animals.

Differential diagnosis includes sheep and goat pox (capripox), dermatophilosis, bluetongue, foot rot, foot and mouth disease (FMD), papillomatisos, herpes virus infection, staphylococcal infections, actinobacillosis, and ulcerative dermatosis.

**TREATMENT AND PREVENTION**

There is no specific treatment available and treatment may be supportive only. The provision of soft palatable food is recommended and the isolation of infected animals may be beneficial. Commercial vaccines are available but not routinely used, and clinical outbreaks have been reported which were caused by live vaccine viruses. Auto-vaccination is commonly used by many farmers.

In the SA study 61.8% of the respondents treated sick animals during outbreaks, whilst 38.2% did not. Recorded treatment consisted of application of Vaseline® oil or machine oil or less commonly application of copper sulphate and zinc preparations. Rural farmers, reportedly, often scratch open the lesions before treating them with oil when the disease is severe. A minority of farmers use antibiotics or have sought veterinary assistance. In some rural communities (North West province) disease was treated using the root of the plant *Cassia italica* –known as *morototsheishe* or *sebete*. Less than 1% of farmers interviewed made use of commercial vaccine to prevent the disease. The application of auto-vaccination was reported by farmers from the Eastern and Northern Cape provinces.

**ZOO NOTIC DISEASE**

Humans are infected by ORFV following handling of sheep and goats. It is mostly farmers, herders, slaughterers and veterinarians who are occasionally affected. In the United Kingdom it has been identified as the most frequent occupational zoonosis (Buchan 1996) and is also described as common in Australasia.

The lesions seen in these patients are very similar to those of pseudo cowpox or milker’s nodule. Lesions are more proliferative than in sheep. Virus may enter through small abrasions of the skin when people are handling infected animals. Transmission of virus in fomites, sheep harnesses, burrs in sheep wool, and fences is well known. ORF lesions are usually seen on the hands, but unusual locations have also been described which include the nose, scalp, axilla, buttocks, and genitals. Other symptoms which may accompany vesicular or necrotic skin lesions would include pain, pruritus, lymphangitis, axillary lymphadenitis, and rarely fever or malaise.

There are reports of atypical proliferating forms of giant orf in immunocompromised individuals, which may require hospitalisation and complications such as erythema multiform, bullous pemphigoid, swan neck deformity, paresthesia and autoimmune blistering disorders have also been reported.

The danger posed by unpasteurised milk is unknown. However, the Food and Agriculture Organization of the United Nations prescribes that milk from diseased animals must to be discarded. This may have a negative impact on the profitability of dairy farms, particularly in chronic outbreaks.
ORF has been investigated more seriously in recent years owing to its zoonotic importance and ability to infect a variety of other species. Zoonotic disease was recently described in deer hunters in the Eastern USA. Infection was caused by a novel strain of virus clustering with pseudo cowpox virus (PCPV), which could indicate a spill-over from domestic cattle to deer. ORF transmission by cat scratch has also been reported recently.

As this is not a notifiable it could be underdiagnosed, since there are rarely other clinical symptoms, and the skin lesions eventually heal spontaneously

REFERENCES

2. Frandsen J, Enslow M, Bowen AR. ORF parapoxvirus infection from a cat scratch Dermatology Online Journal 17 (4): 9