Lumpy skin disease

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INTRODUCTION

Lumpy skin disease (LSD) is a pox viral disease of cattle with a major socio-economic impact. The disease is characterized by fever, multiple firm, circumscribed skin nodules, and necrotic plaques in the mucous membranes (chiefly of the upper respiratory tract and oral cavity), mastitis, orchitis and swelling of the peripheral lymph nodes. The disease is caused by a capripox virus of which the prototype strain, "Neethling" was first isolated in South Africa. Clinically, the skin lesions of LSD closely resemble those of pseudo-lumpy skin disease caused by the Allerton strain of bovid herpesvirus 2 (BHV-2).

Lumpy skin disease was recognized as an infectious disease in 1943 when an outbreak occurred in Ngami land in the northern part of Botswana. Towards the end of 1944 it was reported for the first time in South Africa and spread rapidly throughout the country, despite enforced control measures. The disease appeared to be confined to southern Africa until 1956 when it was encountered in Central and East Africa and since then has been reported in most countries in Africa and Madagascar. Apart from Madagascar the disease was recorded for the first time in 1989 outside Africa, in southern Israel. Since 2000, LSD outbreaks have been reported across the Middle East and it is highly likely the disease will become endemic at least in parts of the Region. Incursion of LSD was reported for the first time in Turkey and Iraq in 2013, indicating that the disease has a potential for further spread to the European Union and Caucasus Region, as well as to Asia.

EPIDEMIOLOGY

Available evidence suggests that there is only one immunological type of LSDV: virus isolates collected over an extended period from a large number of natural cases originating from outbreaks of the disease in South Africa, Kenya and Malawi showed complete cross-neutralization with the prototype “Neethling” strain.

Cross-protection between LSDV and sheep- or goat pox viruses has been exploited by the use of sheeppox virus for the immunization of cattle against LSD in Kenya and in the Middle East.

Lumpy skin disease virus is remarkably stable. It can be recovered from skin nodules kept at –80 °C for ten years and from infected tissue culture fluid stored at 4 °C for six months. The virus can persist in necrotic skin nodules for up to 39 days but this period may be much longer.

Periodic epidemics occur in most African countries, particularly in those of the sub-Saharan region.

Imported *Bos taurus* breeds with thin skins, such as Friesland cattle, usually show more severe signs of the disease than thick-skinned indigenous breeds including the Afrikaner and Afrikaner cross-breeds. Similarly, all age-groups are susceptible. Cows in the peak of lactation as well as young animals show usually more severe clinical disease.

Very little is known about the susceptibility of wild ruminants to LSDV. Using novel molecular diagnostic techniques and sequencing, clinical LSD has been confirmed in springbok in South Africa.
Clinical disease suspected to be LSD has been described in five Asian water buffalo (*Bubalus bubalis*) in Egypt and in an Arabian Oryx (*Oryx leucoryx*) in Saudi Arabia, springbok (*Antidorcas marsupialis*) in Namibia and oryx (*Oryx gazella*) in South Africa. Giraffe (*Giraffa camelopardalis*) and impala (*Aepyceros melampus*) are highly susceptible to experimental infection, whereas two young African buffalos (*Syncerus caffer*) did not develop clinical signs or seroconverted. A random sample of 440 sera taken from culled buffalo in the Kruger National Park in South Africa between the ages of one and 20 years were all negative for serum-virus neutralizing antibody to the prototype Neethling strain. From the clinical trial, and the failure to detect antibody in a random sample of sera, it was concluded that the African buffalo is not susceptible to the virus or only slightly so. More recently, LSDV DNA was detected in samples collected from naturally-infected water buffaloes in Egypt. However, the PCR method used in this study was not able to differentiate between LSDV and sheep- and goat pox viruses.

The mode of transmission of LSD has not been established fully, although circumstantial evidence suggests that biting insects play a role in the dissemination of infection. It is usually more prevalent during the wet summer and autumn months, particularly in low-lying areas and along water courses, but outbreaks may also occur during the dry season and winter months.

The virus has been recovered from *Stomoxys* spp. and *Musca confiscate* and mechanical transmission of LSDV has been demonstrated by *Aedes egypti* mosquito. The three common African hard tick species, namely, brown tick (*Rhipicephalus appendiculatus*), the bont tick (*Amblyomma hebraeum*) and the African blue tick (*Rhipicephalus (Boophilus) decoloratus*), have recently been incriminated in the transmission and epidemiology of LSD. *R. appendiculatus* and *A. hebraeum* males were able to transmit the virus mechanically and successful transovarial transmission of LSDV by *R. decoloratus* species was demonstrated. *A. hebraeum* ticks over-winter as nymphal stage and *R. decoloratus* in gravid females and eggs. Therefore, the survival of the virus in *R. decoloratus* eggs and larvae and *A. hebraeum* nymphs/adults may at least in part explain how LSD overwinter during inter-epidemic periods.

Some scientists are of the opinion that the low titre of LSDV present in the blood of infected animals during the viraemic stage is not sufficient for mechanical transmission to occur by biting flies feeding on blood alone and that biting flies have to feed on skin lesions to obtain enough virus for transmission to take place. The virus may remain viable in scab or tissue fragments for several months.

Direct transmission by contact between animals is inefficient. However, transmission did occur when common drinking troughs were used, thus confirming the suspicion that infected saliva might contribute towards the spread of the disease. The disease is transmissible to suckling calves through infected milk.

Lumpy skin disease virus has been demonstrated to persist in bovine semen for up to 42 days post-infections (dpi) and viral DNA was detected until 159 dpi. The virus was isolated from the semen of bulls with inapparent disease.
PATHOGENESIS

Subcutaneous or intradermal inoculation of cattle with LSDV results in the development of a localized swelling at the site of inoculation after four to seven days and enlargement of the regional lymph nodes while generalized eruption of skin nodules usually occurs seven to 19 days after inoculation.

In experimentally infected cattle LSDV was demonstrated in saliva at least for 11 days after the development of fever, in semen for 42 days and in skin nodules for 39 days. Viraemia occurred after the initial febrile reaction and persisted for two weeks.

Viral replication in pericytes, endothelial cells and probably other cells in blood vessel and lymph vessel walls causes vasculitis and lymphagitis in some vessels in affected areas. In severe cases infarction may result.

Immunity after recovery from natural infection is life-long in most cattle; calves of immune cows acquire maternal antibody and are resistant to clinical disease for about six months.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Clinical signs and pathology

A morbidity rate of five to 45 per cent on affected farms is usual. The mortality rate may be as high as ten per cent, even among indigenous cattle.

Typically, cattle develop a biphasic febrile response two to four weeks after exposure to the virus. Animals remain febrile for four to fourteen days, during which time they may develop salivation, lachrymation and a mucoid or mucopurulent nasal discharge. Lachrymation may be followed by conjunctivitis, corneal opacity and blindness in some cases. In the majority of animals the superficial lymph nodes are enlarged.

Skin nodules, the characteristic feature of the disease, appear before or during the second rise in body temperature, four to ten days after the initial febrile response.
Lumpy skin disease: randomly distributed nodules in the skin

The nodules, which are randomly distributed and range in diameter from 10 to 20 mm, involve both the skin and subcutaneous tissues and sometimes even the underlying musculature. The size of the nodules is usually fairly uniform but several nodules may fuse to form large, irregularly circumscribed plaques. The number of nodules may range from a few to several thousand in severely affected animals. The nodules are well-circumscribed, firm, round and raised and are particularly conspicuous in short-haired animals.
In long-haired cattle the nodules are often only recognized when the skin is palpated or moistened. In most cases the nodules are particularly noticeable in the perineum and on the vulva. Skin lesions resolve, become indurated (in which case they persist as hard lumps or “sitfasts” for 12 months or longer) or sequestrated to leave deep ulcers partly filled with granulation tissue that often suppurates.
In severely acutely affected animals the ventral parts of the body, for example the dewlap and the legs may be slightly oedematous one to two days before the appearance of the nodules. In these acute cases the oedema of particularly the legs may become very severe following the development of the nodules.

Nodular skin lesions may extend into underlying tissue such as tendons and tendon sheaths resulting in lameness in one or more legs. Most affected animals have multifocal, roughly circular, necrotic areas on the muzzle and in the respiratory tract (nasal cavity, larynx, trachea and bronchi), and buccal cavity (the inside of the lips, gingivae and dental pad), but these lesions may also be present in the fore stomachs, abomasum, uterus, vagina, teats, udder, and testes. Generalized lymphadenopathy comprising lymphoid hyperplasia and oedema is a regular finding.
If extensive necrosis occurs in the upper respiratory tract, secondarily infected necrotic tissue may be inhaled resulting in pneumonia. Stenosis of the trachea following healing of lesions with scar tissue formation some weeks or months after infection has been described.

Circumscribed necrotic areas in the trachea

In bulls, lesions may occur on the scrotum, preputial mucosa, the glans penis and in the parenchyma of the testes. Acute orchitis may progress to fibrosis and atrophy of the testes resulting in temporary or permanent infertility or more rarely, sterility. Similarly, lesions in the reproductive tract of cows may result in infertility.

Necrotic lesions in the testis of a bull
Nodules may form in the skin of the udder and teats, and when the parenchyma of the udder is involved, as it frequently is, the gland is swollen and tender as a result of mastitis. Secondary bacterial mastitis may be severe and complicate the udder lesions. Occasionally, parts of the gland may become sequestrated and slough. Involution of the udder as a result of mastitis often causes severe economic losses on dairy farms. Lesions on and in the teats may cause distortions of the teat canal leading to ascending bacterial infections.

Microscopically the lesions vary considerably depending on the stage of development. In the acute stage of the disease vaculitis is sometimes accompanied by thrombosis, and infarction, as well as perivascular fibroplasia and infiltration of macrophages and some lymphocytes and eosinophils in particularly the dermis and subcutis. During the acute and subacute stages of the disease eosinophilic intracytoplasmic inclusions may be present particularly in macrophages and keratinocytes in the skin. Mature viral particles are randomly distributed in the cytoplasm of affected cells.

Numerous viral particles in the cytoplasm of a macrophage

**Laboratory confirmation**

A presumptive diagnosis of the disease can be made on the clinical signs. The diagnosis can be confirmed within a few hours of receipt of specimens by transmission electron microscopic demonstration of virus in negatively-stained preparations of biopsy specimens taken from affected skin or mucous membranes. Immunohistochemical methods, for example immunoperoxidase staining of tissue sections, can also be used to demonstrate the virus in acute and chronic skin lesions.

Mature capripox virions have a more oval profile and larger lateral bodies than orthopox virions. Their average size is 320 x 260 nm.
Lumpy skin disease virus (LSDV) grows to high titre in a wide variety of cell cultures (e.g. primary lamb testis and bovine dermis cells). Capripoxvirus grows slowly in tissue cultures and may require several passages. The development of cytopathic effects may take up to 14 days during primary isolation. Replication is accompanied by the formation of intracytoplasmic inclusion bodies similar to those which occur in skin lesions of affected cattle. The virus also multiplies in chick embryos and on the chorio-allantoic membrane of embryonated hens’ eggs.

Bacterial and fungal contaminations are frequently encountered in skin biopsy samples.

Several conventional and real-time polymerase chain reaction (PCR) methods are available for the detection of three members of the genus *Capripoxvirus*.

The interpretation of serological results may sometimes be difficult due to low antibody titres in vaccinated animals and some individuals following mild infection. The virus neutralization test is considered to be the most reliable serological test although it is not suitable for large-scale testing. Several ELISAs for the detection of capripoxvirus antigen or antibody have been published but currently none of them is commercially available. In addition, an indirect antibody ELISA based on inactivated sheeppox virus has been developed.

The clinical signs and lesions in mild cases of LSD can easily be confused with pseudo-lumpy skin disease (BHV-2 infection). Generally, BHV-2 infection causes more superficial skin lesions, has a
shorter course and is a milder disease than LSD. In addition, the presence of histopathologically
demonstrable intranuclear inclusion bodies in BHV-2 infection as opposed to intracytoplasmic
inclusions in LSD, are characteristic. In contrast to LSD the detection of BHV-2 in negatively-stained
biopsy specimens by electron microscopy or the isolation of the virus is only possible approximately
one week after the development of skin lesions. Skin lesions caused by insect bites, *Demodex*
infection, bovine dermatophilosis, onchocerciosis and besnoitiosis should be differentiated from those
associated with LSD.

**CONTROL / PREVENTION**

As biting flies and certain tick species are most probably the most important method of transmission
of the disease, control by quarantine and movement control is generally not very effective. In endemic
areas control is therefore essentially confined to immunoprophylaxis.

Two approaches to immunization against LSD have been followed. In South Africa the Neethling
strain of LSD was attenuated by 20 passages on the chorio-allantoic membranes of hens' eggs, but
the vaccine virus is now propagated in cell culture. In Kenya the vaccine produced from sheep- or
goatpox viruses produces a solid immunity in cattle to LSD. However, it is important to notice that the
recent molecular and phylogenetic studies have confirmed the virus in the Kenyan sheep and goatpox
O-240 and O-180 strain vaccines is actually a LSDV and the level of attenuation required for a safe
use in sheep and goats is not sufficient for cattle and may cause the clinical disease in vaccinated
animals. Other sheeppox vaccines used against LSDV are Yugoslavian RM-65 strain and Romanian
sheeppox strains. The sheeppox vaccines against LSDV have the disadvantage that they can only be
used in countries where sheeppox or goatpox is endemic as the live vaccines could otherwise provide
a source of infection for the susceptible sheep and goat populations.
Susceptible adult cattle should be vaccinated annually to ensure adequate protection against LSD. Approximately 50 per cent of cattle develop a swelling ten to 20 mm in diameter at the point of inoculation and this may be accompanied by a temporary drop in milk yield in dairy cows. The swelling disappear within a few weeks. Animals younger than six months of age whose dams were either naturally infected or immunized should not be vaccinated, in order to preclude interference from maternal antibody. However, calves born to susceptible cows are themselves very susceptible and should be vaccinated as soon as possible in the face of an outbreak.

MARKETING AND TRADE / SOCIO-ECONOMICS

Although LSD does not have a high mortality rate, it is of economic importance because of permanent damage to hides, the prolonged debilitating effect it may have on severely affected animals with consequent losses resulting from reduced weight gain, temporary or permanent cessation of milk production as a result of mastitis, temporary or permanent infertility or even sterility in bulls as a consequence of orchitis, and abortion in approximately ten per cent of pregnant cows.

Morbidity rates generally varied between one and 20 per cent, but in a few instances reached more than 50 per cent. The mortality rates were usually less than ten per cent. Abortions in cows occurred in one to seven per cent of cases. Severe economic losses, mostly as a result of mastitis, were suffered by a number of dairy farmers.

The World Organization for Animal Health (OIE) categorizes LSD as a notifiable disease and sets standards for safe international trade of live animals and animal products.

IMPORTANT OUTBREAKS

The epidemics of 1989/90 and 2000/01 in South Africa and most other countries of southern Africa were particularly severe affecting large numbers of cattle. Unfortunately, there are no accurate statistics on these epidemics. Currently there are only four countries in Africa (Morocco, Tunisia, Algeria and Libya) that has newer reported LSD.

Lumpy skin has been reported by the most of the countries in the Middle East and it’s highly likely that it is endemic in the Region. Outbreaks in Israel (2012), the West Bank (2013), Lebanon (2013), Jordan (2013) were followed by outbreaks of the disease in Turkey and Iraq in 2013. It is likely that LSD may spread and pose a threat to Greece, Bulgaria and the Caucasus Region, as well as Iran and Syria.