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A Comprehensive Review on Lumpy Skin Disease

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ABSTRACT

The poxvirus lumpy skin disease virus (LSDV) infection is the primary cause of the high-consequence disease lumpy skin disease in cattle. The virus is a rising hazard to cattle populations in Europe and Asia and is endemic in the majority of African nations. It is crucial for animal carers to quickly identify disease indications as LSDV expands to new areas. This study describes the overall, microscopic, and ultrastructural alterations in cattle exposed to LSDV throughout time. Four calves received a wild-type LSDV inoculation and were watched for 19 to 21 days. Two of the four calves displayed multifocal cutaneous nodules that were indicative of LSD 7 days after the injection. Targetoid-like lesions could be seen in some cases. Histologically, the epidermis displayed intercellular and intracellular edema.

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INTRODUCTION

Lumpy skin disease (LSD) is an infectious disease in cattle by a virus of the family Poxviridae called lumpy skin disease virus also known as the needling virus. [1] The disease primarily affects cattle, both Bos taurus and Bos indicus cattle breeds are susceptible. Thin-skinned, high-producing B. Taurus bovines are generally more severely affected than the zebu-type or cross-bred cattle. LSDV affects domestic buffaloes but this species seems to show limited susceptibility to LSD. The disease is characterized by fever, enlarged superficial lymph nodes, and multiple nodules on the skin and mucous membrane including respiratory and GIT tracks. Lumpy skin disease is not zoonotic. Infected cattle also may develop oedematous swelling in their limbs and exhibit lameness. [2] Termination of seroprevalence of LSD has a time limitation for the presence of detectable antibodies in the serum for more than seven months of post-infection. Serological tests such as virus neutralization are less sensitive and time-consuming to detect the low-level antibody titers following the infection of the animals.[3] The virus causes raised, wart-like skin lesions, leading to disfigurement and a reduction in the value of affected cattle. Additionally, the disease causes significant reductions in milk production, fertility, and weight gain. The virus has important economic implications since affected animal tends to have permanent damage to their skin, lowering the commercial value of their hide.[4] Large-scale vaccination combined with other appropriate control measures is the most effective way of limiting the spread and economic impact of lumpy skin disease. This review is designed to provide, the latest information on the biology of lumpy skin disease virus, the mechanism of spread, and clinical and pathological features of lumpy skin disease. [5]

HISTORY OF LDS

The first description of the clinical sign of LSD was in 1929 in Zambia (formerly Northern Rhodesia) (Morris 1931).In the beginning, LSD signs were considered to be the consequence either of poisoning or a hypersensitivity to insect bites.[6]After fourteen years, in October 1943, another outbreak of the disease occurred in Botswana and was named provisionally “Ngamiland cattle disease” as the case occurred for the first time in Ngamiland. Whether these new foci of disease were the result of spread from the original foci in Zambia or whether LSD had hitherto, not been recognized in these two countries is not clear. The suggestion is that LSD spread from the original foci in Zambia.[7] The same clinical signs occurred in Botswana, Zimbabwe, and the Republic of South Africa between 1943 and 1945,

where the infectious nature of the disease was recognized in these outbreaks. One of the recent outbreaks of LSD in the African continent occurred in central Ethiopia from 2007 to 2011. These outbreaks were described as active. A total of 1,675 outbreaks were reported over 5 years period from 2007 to 2011, with 62,176 cases and 4,372 deaths.[6] LSD was introduced in Bangladesh, China, and India, beginning in July 2019. In 2019, LSD reached some of the major cattle-producing and trading countries across Asia, for example, India, Bangladesh, and the Republic of China. In 2020 the disease then spread to other parts of China and India as well as Nepal and Bhutan.[8] In 2020, LSD was reported in Bhutan, Hong Kong, Myanmar, Nepal, Sri Lanka, Taiwan and Vietnam. Most recently, in 2021, the disease was reported in Cambodia, Malaysia, the Lao People's Democratic Republic, and Mongolia (OIE WAHIS). The American continent and Oceania are still free of LSDV. The disease will likely continue to spread. [7]

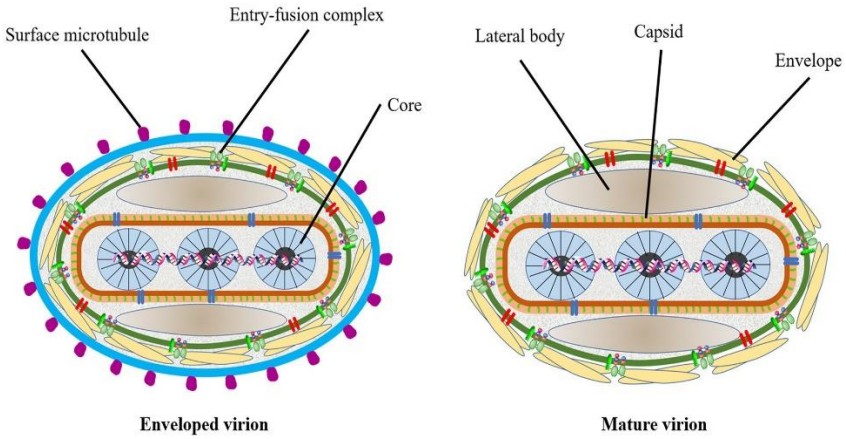
BIOLOGY OF LDS

The family Poxviridae contains the largest viruses which can cause disease naturally in most domestic animals, except in dogs. It is divided into two subfamilies, Chordopoxvirinae, the poxviruses of vertebrates, and Entomopoxvirinae, the poxviruses of insects.[9] The family Poxviridae is featured by its large and complex genome consisting of a single, linear molecule of double-stranded DNA (ds DNA) approximately coding for 200 proteins. The ends are ligated to each other so the DNA molecule is continuous, without free ends. Poxviruses are the only DNA viruses known to complete their replication cycle in the cytoplasm. [10]

Lumpy skin disease virus classification [2] (unranked):

Realm	: Varidnaviria
Kingdom	: Bamfordvirae
Phylum	: Nucleocytoviricota
Class	: Pokkesviricetes
Order	: Chitovirales
Family	: Poxviridae
Virus Genus	: Capripoxvirus
Species	: Lumpy skin disease virus

It is stable in the environment and may remain viable for up to three months in dry scabs on the skin, at least six months in dirty, shaded pens and infected tissue culture fluid stored at 4°C. Infected animals shed scabs from skin lesions and inside the scabs, the virus may remain infectious for several months.[2] LSDV survives in necrotic skin nodules for at least 39 days even dried out prior to sequestration and in air-dried hides at room temperature for at least 18 days.There are no studies published that identify how long it takes for LSDV to lose infectivity in different environments. LSDV survives well within the pH range 6.3-8.3. It is highly susceptible to sunlight, and high alkaline or acid pH; can be inactivated at 55º C for 2 h, 60º C for 1 h or 65º C for 30 minutes.[8]Under an electron microscope, the structure of LSDV closely resembles that of the vaccinia virus, displaying a characteristic dumbbell-shaped core with lateral bodies[11] The causal virus is related to that of sheep pox. Lumpy skin disease appears epidemically or sporadically. Frequently, new foci of infection appear in areas far removed from the initial outbreak. [12]



MAJOR SIGNS & SYMPTOMS

The clinical representation of LSDV infections shows a remarkable variation, including short- and long-term subclinical infections, and even death.[13]Infected cattle develop fever, lacrimation, nasal discharge, and hypersalivation, followed by characteristic eruptions on the skin and other parts of the body in ~50% of susceptible cattle.[14] The clinical signs of LSD include two febrile phase (biphasic fever), which appear after variant incubation period 4-12 days (usually 7 days).The temperature of the infected animals rises to 40-41.5°C, which may persist for 6-72 h or more and may rarely be up to10 days. The infected animals also show lacrimation, increased nasal and pharyngeal secretions, anorexia, dysgalactia, general depression and a disinclination to move. Skin nodules with 5-50 mm size (with a round shape, rising above the skin) usually appear 2 days after the start of fever, on the skin of the

head, neck, udder, genitalia, perineum, and limbs. The nodules can cover the entire body or only a few can appear.[15] The nodules on the mucous membranes of the eyes, nose, mouth, rectum, udder, and genitalia begin to ulcerate, the virus is present in all secretions, including saliva, ocular and nasal discharge, and the nodules on the genitalia. Many cattle suffer severe emaciation and loss of production for several months. The skin lesions cause permanent damage to the hides. The disease is of economic importance as it can cause a temporary reduction in milk production, temporary or permanent sterility in bulls, damage to hides, and, occasionally, death.[16]The serum may have leaked at first, followed by a distinctive inverted greyish-pink conical zone of necrosis from LSD skin nodules. Congestion, hemorrhages, and edema are present in adjacent tissue. Secondary bacterial infections are prevalent in necrotic cores, as are enlarged lymph nodes.[14]Painful genitalia in bulls can prevent from serving for long periods. Foetus born to infected cows may show skin lesions at birth presumably acquired through intra-uterine infection.[17]

TRANSMISSION

The most important source of infection to healthy animals is considered to be skin lesions or nodules since the virus persists in the lesions or scabs for long periods and has strong tropism. Flying insects are the main mode of transmission. LSDV has been isolated in the mosquito genera Aedes and Culex. Flies, such as Stomoxys calcitrans and Biomyia fasciata, in South Africa, along with other insects, like ticks (Ixodid, Amblyomma hebraeum, and Rhipicep appendiculatus), may be other mechanical vectors.[18] Sheep and goats do not become infected during outbreaks of LSD even when held in close contact with infected cattle. African buffaloes (Syncerus caffer) and Asian water buffaloes (Bubalus bubalis) do not show lesions in the field during epizootics of LSD but both buffalo types may suffer an unapparent infection and seroconvert.[17]The virus is mainly mechanically transmitted by insect vectors (mosquitoes, flies, ticks, etc.) or by contaminated needles.[19]LSDV is thought to be transmitted primarily by arthropod vectors. Mosquitoes, biting flies (e.g., Stomoxys calcitrans, Biomyia fasciata), Culicoides midges and hard ticks (e.g., Amblyomma hebraeum, Rhipicephalus spp.) are currently thought to be mechanical vectors. Ticks probably play little or no role when LSDV is spreading rapidly during epizootics; however, they might be involved in transmission and maintenance in endemic regions. [20].LSD is transmitted primarily by blood-feeding insects. Other routes of spread are iatrogenic, direct or indirect contact and artificial insemination. Various flying and non-flying blood-feeding insects can

transmit LSDV mechanically and play a major role in within-herd as well as between-herd transmission. Direct contact seems to be a minor source of infection. Early studies suggested that transmission between animals was inefficient in insect-free environments, although some cattle became infected when they were allowed to share a water through with severely affected animals.[21]. It is transmitted by arthropod vectors like flies, beating midgets, ticks, mites, bugs, and ticks, by direct contact with cattle, through contaminated food & and drinking water, infected needles and medical equipment, also transmitted through nasal discharge & and direct contact.LSDV can be transmitted by various blood-feeding arthropods but is not known to replicate in vectors. Therefore, transmission is mechanical but not biological in nature. [22]

Potential vectors studied to date Aedes aegypti, Anopheles stephensi, Culex quinquefasciatus (Mosquitos); Stomoxys calcitrans, Haematobia irritans, Prostomoxys sp., Haematopota spp., Biomyia fascinate (Flies); Culicoides tuberculosis (Midges), Rhipicephalus appendiculatus, Rhipicephalus decoloratus, Amblyomma (Ticks)**.**[18]

Non-vector transmission

Although ineffective, non-vectored LSD transmission happens when clinically afflicted animals come into contact with contaminated materials, without the need of biological or mechanical vectors. Infectious LSDV is excreted in saliva, nasal and ocular discharges, contaminating communal eating and drinking areas and spreading the disease. [23]

Morbidity and Mortality rate

LSD can occur in sporadic cases or in epizootics. The incidence of disease is highest in wet, warm weather, and decreases during the dry season. New foci of disease can appear at distant sites; in these cases, the virus is thought to be carried by insects. The morbidity rate varies widely, depending on the presence of insect vectors and host susceptibility, and ranges from 3% to 85%. [24] Although the morbidity rate varies between 5% and 45% (sometimes up to 100%), the mortality rate is usually under 10% (sometimes up to 40%) [25] the morbidity and mortality rates of outbreaks were reported as 8.7% and 0.4%, respectively, in Greece [26] and 12.3% and 6.4%, in Turkey. [27]

DIAGNOSIS OF LSD

At present time, no commercial diagnostic test kits for LSD virus detection are available yet and Clinical history, clinical signs, and symptoms of infected animals can be used to make a presumptive LSD diagnosis. During the nodular skin lesion appearance stage, a confirmatory laboratory diagnosis is conducted. There is no diagnostic test tool on the market.[28] The confirmatory tests are mostly in the form of conventional or real-time polymerase chain reaction (PCR) specific for Capripoxvirus. Samples obtained from the skin lesions yield more positive results in PCR than the blood or those collected from septic viscera due to the greater load of viral particles sheltered in the nodule.[29] LSD should be suspected clinically when there are characteristic skin nodules, fever and enlargement of superficial lymph nodes. The lumps on the skin follow within 2 days and may appear anywhere on the body from the nose to the tail. Same characteristic lesions appear in the mucosa of the mouth, vagina and conjunctiva. A purulent nasal and ocular discharge are not rare[30]Additionally, the disease can be detected using serological tests using Enzyme-linked Immunosorbent Assay (ELISA), Indirect Fluorescent Antibody test (IFAT), Indirect Immunofluorescence test, Virus Neutralization Test (VNT) and Serum Neutralization Test (SNT).[31] A fairly new assay called Immuno-peroxidase Monolayer Assay (IPMA) has been identified for potential use in LSD diagnosis. It is a cheap and convenient test, adapted to low biosafety levels, and has higher sensitivity and specificity than VNT and commercial ELISA. [32]

Differential Diagnosis

In animals, LSD is identified by lumpy nodules on the external body coat, mouth, tongue, cornea, oral, and ocular mucus membrane. Almost identical clinical indications have been seen in other disorders, leading to LSD suspicions. Although it has a shorter clinical course, Pseudo-Lumpy Skin Disease, which occurs due to the bovine alpha herpes virus, creates nodule-like skin swellings and can be confused with LSD. [33] Although severe LSD is highly characteristic, milder forms can be confused and misdiagnosed with numerous diseases and infections such as pseudo lumpy skin disease (*Bovine Herpes virus*), *bovine papular stomatitis* (Para poxvirus), *pseudo cowpox* (Para poxvirus), *Vaccinia virus* and *Cowpox virus* (Orthopoxviruses) *infections, dermatophilosis,* insect or tick *bites, besnoitiosis, rinderpest, demodicosis, Hypoderma bovis infection, photosensitisation, urticaria*, cutaneous tuberculosis and *onchocercosis.* [34]

Treatment, Prevention & Control:-

LSD is thought to be transmitted primarily by blood-feeding insects; hence quarantine and movement restriction alone are not very effective to control LSD unless supported by mass vaccination[35] Maternal immunity provides protection from LSD in calves at least for 6 months. Risks of introduction of the disease in to the new areas are by the introduction of infected animals and contaminated materials. [36]Control of Lumpy skin disease by quarantine and movement control is not very effective because biting flies and certain tick species are most probably the most important method of transmission of the disease. LSD control can only be by vaccination or immunoprophylaxis. Live vaccines help control losses from lumpy skin disease in endemic areas. According to OIE, four live attenuated strains of capripoxvirus have been used as vaccines specifically for the control of LSD[37] Anti-inflammatory drugs and intravenous fluid therapy might be administered to upsurge the appetite although it has no prolific feedback. No precise antiviral drugs are available for the treatment of LSD, thus prevention through vaccination is the only effective way of restraining the disease. [38]

Table-1: Therapeutic agents for LSD treatment.

Therapeutic agents	Pharmacological effects	References
Enrofloxacin, Oxytetracycline, Penicillin, Cephalosporin, Tetracycline, Fluoroquinolone	Antibiotic	39
Chlorpheniramine maleate	Antihistamine	40
Meloxicam	Nonsteroidal anti-inflammatory	39,40
Dexamethasone suspension	Steroidal anti-inflammatory	41

The movement of animals infected with LSDV and/or the effects of LSD must be exactingly prohibited to prevent the distribution of the disease to other areas and crossover to non-infected farms. The prevention of transboundary movements and the restriction of animal movement should be strict. Animals with skin lesions should be investigated and should be isolated for assessment.

Vaccines For Lumpy Skin Disease

The immunization of LSD by live attenuated vaccines has been effectively used in endemic areas. Antigenic homology of Carpipoxvirus, including SPPV, GTPV, and LSDV, cross-protection of immune response was beneficial. A live attenuated vaccine is commercially available for LSD eradication. Sheep pox vaccine from SPPV and GTPV is used for control in countries with high LSD outbreaks. Types of LSD vaccines are as follows:[42]Attenuated LSDV vaccines (Neethling vaccines) are the currently effective vaccine to prevent LSD in cattle. The effective control success possibility is 80% in the livestock,[43]Attenuated SPPV vaccines are suitable for the areas where SPPV and LSDV outbreak and[44] Attenuated Gorgan GTPV vaccine is suitable for the areas where outbreaks are a combination of SPPV and LSDV.[42]

Other control techniques

For countries free of the disease, the introduction of the disease can be prevented by restriction of the importation of the animals and their products. In those nations which experience the infection, the spread of LSD can be limited by restriction of the animal movement from one place to another, quarantine or keeping of sick animals well apart from the rest of the herd and such animals must not share drinking or feeding troughs and also by awareness creation of the farmers. [45]Animals older than six months must be vaccinated against LSD during spring. It is safe to vaccinate pregnant cows. All animals must be vaccinated once a year. When vaccinating the animals during a disease outbreak, it is important to use one needle per animal so that the virus is not spread from sick to healthy animals but the practicality and economic feasibility of use of one needle per cattle need to be carefully considered. Professional help and recommendations on vaccines must be carefully followed and practiced. Broad spectrum antibiotics are also given to prevent the secondary bacterial complication as the defence mechanism of the body is weakened which can prolong the complete recovery of the diseased animals. [24]

Economic importance of the disease:-

According to the OIE,(Office International Epizooties)India faced three primary outbreaks of LSD at the Mayurbhanj district in the state of Odisha, followed by one incursion each at four more districts, bringing the total number of outbreaks in the Eastern share of the country. There were 182 clinically affected among 2539 susceptible animals accounting for the

apparent morbidity rate 7.1% with no recorded mortalities. In terms of districts affected, Cuttack displayed the highest morbidity rate of 38.34%, and Kendrapara showed 0.75% [38] The socio-economic impact of LSD can be direct or indirect and has been registered by several major sectors and industries. The sharp drop in milk production is the fast and foremost visible effect directly associated with LSD in the South-Asian region which harbored 21% of the world's dairy farm animals.[45]According to a Turkish investigation, an impacted cow's average milk yield fell by 159L each lactation . However, meat from LSD-infected cattle is not prohibited from entering the food chain, despite the possibility production per annum among local breeds and Friesian cattle was reported in Ethiopia respectively, due to LSDV infection . Besides, any breaches, scars, or lesions in the raw cattle hides or skin may deteriorate the value of leather, as in the case of severely LSD affected animal hides.[46] Bangladeshi leather is highly admired for its good quality and 56% of leather is generated from cattle that contributed 3.5% of the country's annual exports. [47]Pyrexia and lameness hamper the use of animals for draught purposes. LSD can be transmitted to breeding stock through artificial insemination with infected bull semen, resulting in a lower rate of pregnancy. [48]

Recent Outbreak in India:

In three months, over 80,000 bovines had died by September 2022. In July 2022, the outbreak spread in 14 out of 33 districts of Gujarat state of India; by 25 July, more than 37000 cases and 1000 deaths in cattle were reported. As of 1 August, 1200 bovines deaths and more than 25,000 cases were reported in Rajasthan. Inter-state and inter-district movement of bovines in several states has been restricted. Indian Council of Agricultural Research labs have undertaken creation of an indigenous vaccine. A goat pox vaccine is being used, 15 million doses had been administered by September 2022 .vaccine. Institutions with authority to test have been expanded; the Himachal Pradesh Agricultural University has been included.

India is at higher risk because India is the world's largest milk producer at about 210 million tonnes annually. India also has the largest headcount of bovines In Rajasthan, which is witnessing the worst impact of LSD, it has led to reduced milk production, which lessened by about three to six lakh litres a day. Reports indicate that milk production has also gone down in Punjab owing to the spread of the disease. According to FAO, the disease threatens the livelihoods of smaller poultry farmers significantly. Notably, farmers in Uttar Pradesh and

Punjab have incurred losses due to cattle deaths and are seeking compensation from their State governments.

CONCLUSION:-

In this article detailed information on Lumpy Skin Diseases including their history, Sign, symptoms, transmission, diagnosis, physiological study and its treatment. This review article will be helpful for further study on this disease.

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