



Caprine Arthritis-Encephalitis: A Holistic Review of Disease

Burhan Nabi¹, Sanobar Rasool², Simran Jeet Singh^{1*}, Divyam Chaoudhary¹ and Abha Tikoo³

¹Department of Veterinary Medicine, Khalsa College of Veterinary and Animal Sciences, Amritsar, Punjab-143002

ABSTRACT

Caprine Arthritis Encephalitis Virus (CAEV) is a monocyte/macrophage-tropic virus generally infects dairy goats and categorized as list B disease as per OIE. It poses huge economic losses by decreasing productivity and delayed maturity. Main mode of transmission of the disease is considered as colostrum and milk of infected dams. CAEV is found all over the world, with the largest prevalence of infected goats in developed countries such as the United States, Canada, France, Norway, and Switzerland and in India reported cases of CAE infection are from Uttar Pradesh, Rajasthan, Andhra Pradesh. Infected goats show clinical indications in about 30% of cases. Nearly 20% of CAE virus-infected goats manifest clinical signs during their lifetime. Regular foot trimming, the use of soft additional bedding, and the administration of NSAIDs are commonest treatment regimen used after infection of CAE in an individual animal or herds. There is no current vaccine available against CAE virus but once the arrays of pathogenesis are known, then a suitable vaccine or drug can be formulated against the CAEV and animals can be safeguarded against this disease.

Key words: Colostrum, Delayed Maturity, Foot-trimming, Monocyte.

INTRODUCTION

Caprine Arthritis Encephalitis Virus (CAEV) is a monocyte/macrophage-tropic virus that is not associated with immunodeficiency, generally infects dairy goats and was first reported as a retrovirus in 1980, described previously as unreported nervous disease of goats supposed to be caused by a virus and was named Viral Leukoencephalomyelitis of Goats (VLG), followed by a report of an arthritic disease in goats likely caused by the same agent. Later on the viral cause of these conditions was confirmed and the virus was characterized. When it became apparent same viral infection could also result arthritis in affected animals, the name of the disease was reformed to Caprine Arthritis Encephalitis Syndrome (CAE). It is now evident that the virus also produces pathological changes in the lung and udder also (Murphy *et al*, 2021). The name CAE however still remains in place (Bulgin 1990). According to OIE, categorized as list B disease is a chronic progressive infectious disease that leads to economic losses to the goat industry by decreasing productivity and delayed maturity and life-long multi-tissue inflammation is the usual features of

this disease (Konishi *et al*, 2015, Lofstedt 2016, Fu *et al*, 2020).

Main mode of transmission of the disease was considered as colostrum and milk of infected dams and raising kids in isolation proved to be main method of maintaining virus free herds (Bulgin, 1990; Rowe and East, 1997). The aim of this article is to summarize the current state of many facets of CAE in goats and to urge efforts to avoid the introduction of positive reactors into the local goat population for genetic improvement and rural development projects.

Etiology

The CAE virus is a single stranded, icosahedral, RNA virus, of the family retroviridae and sub-family lentiivirinae (ungulate Lentivirus) (Gendelman *et al*, 1997). The virus is a magnesium dependent and has RNA dependent-DNA polymerase (Reverse transcriptase), (Knowles 1997, Knight and Jokinen 1982, Pugh, 2002, Radostitis, 2003). There are numerous, genetically distinct isolates of the virus that vary in virulence (Lofstedt 2016). CAEV is contained within in the group of small ruminant lentiviruses

*Corresponding Author's Email - simranjeets140@gmail.com

¹Department of Veterinary Medicine, Khalsa College of Veterinary and Animal Sciences, Amritsar, Punjab-143002

²Department of Veterinary & Animal Husbandry Extension Education, Khalsa College of Veterinary and Animal Sciences, Amritsar, Punjab-143002

³Division of Veterinary Medicine, F.V. Sc & A.H., SKUAST-Jammu-181102

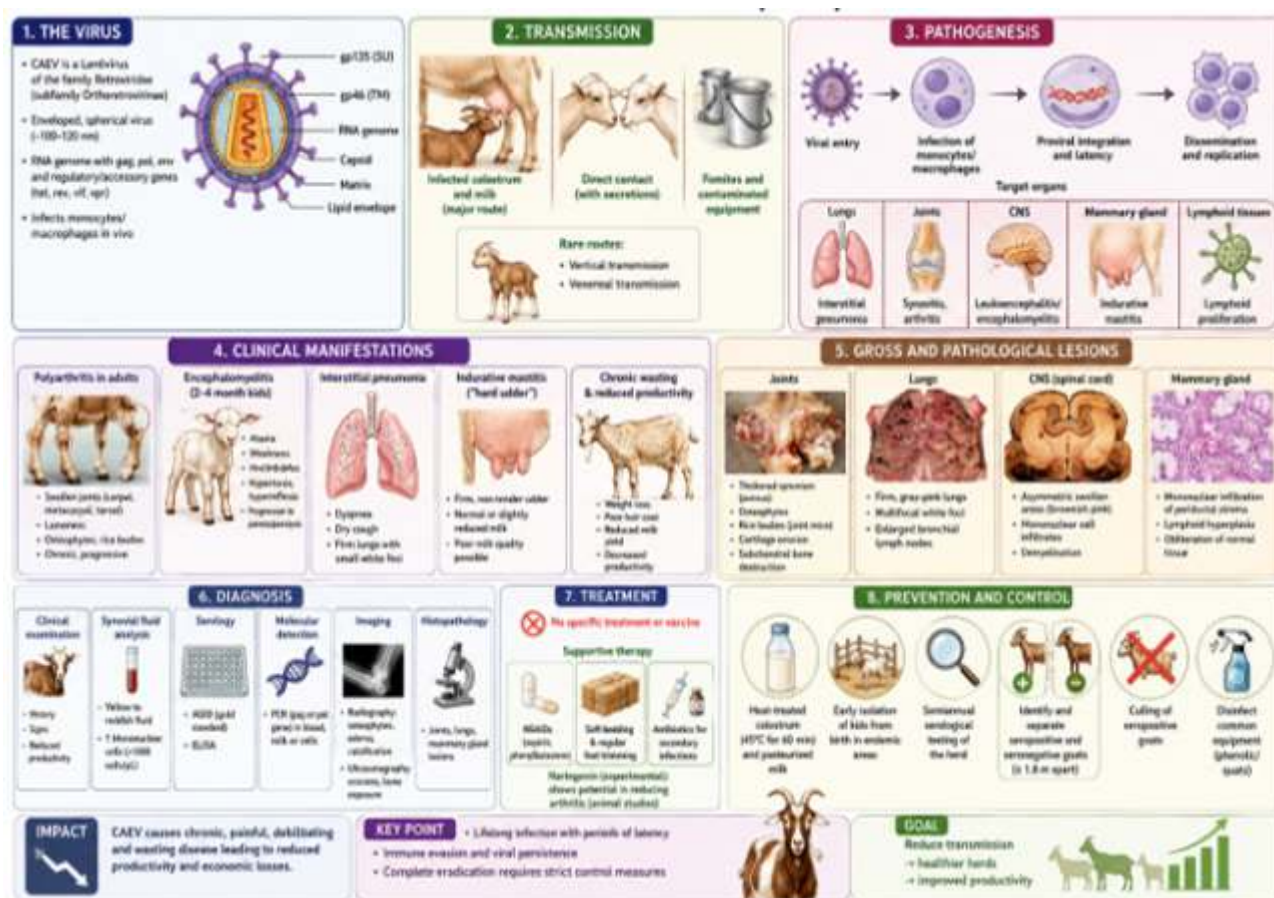


Fig. 1. Pictorial Summary of the CAE

(SRLVs) that comprise of ovine progressive pneumonia virus (OPPV), and visna-maedi virus (VISNA) (Smith and Sherman, 2009). The CAE virus infects mono nuclear cells specially tissue macrophages of the central nervous system, synovium and mammary gland. CAE virus is one of only two Lentiviruses that at present are known to infect sheep and goats and there is a high degree of similarity between viruses associated with maedi-visna and ovine progressive pneumonia in sheep (Knowles Jr, 1997, Rowe and East, 1997, Pugh 2002).

Epidemiology

CAE virus infection is common in dairy goat breeds, but not so much in meat and fibre goats. Genetics, management tactics such as providing colostrum and milk from a single dam to many kids, and industrialized farming practices have all been blamed for transmission of this disease. Infection prevalence rises with age but is unaffected by gender. Most goats become infected at a young age, stay virus positive for the rest of their lives, and eventually develop sickness months or years later (Lofstedt, 2016).

CAEV is found all over the world, with the largest prevalence of infected goats in developed countries such as the United States, Canada, France, Norway, and Switzerland. The geographical distribution of prevalence of CAE infection in many places is listed in below given table 1.

Host Susceptibility

Infection occurs in all breeds and throughout every age group, but increasing seroprevalence is seen in older ones. The apparent differences in breed and age susceptibility to the disease, could be owing to management factors such as colostrum and milk feeding techniques, or genetic susceptibility variances and these discrepancies are most likely due to changes in herd management as well as differences in the relative relevance of transmission mechanisms between herds.

Morbidity and Mortality

Infected goats show clinical indications in about 30% of cases. Once encephalomyelitis or polyarthritis emerge, they are progressive and

Caprine Arthritis-Encephalitis: A Holistic Review of Disease.

Table :1 Geographical distribution of prevalence of CAE Infection

S. No.	Geographical Area	Percentage Prevalence (%)	Reference
1.	Iran	15.7	Kojouri <i>et al</i> , 2014
2.	Mexico	3.6	
3.	Italy	4.0	
4.	United Kingdom	10.1	
5.	United States	73.0	
6.	Norway	86.0	
7.	Hungary	30.0	Kusza <i>et al</i> , 2004
8.	Thai	12.4 (in adults)	Ratanapob <i>et al</i> , 2009
9.	Brazil	8.2	Al-Qudah <i>et al</i> , 2006
10.	Mexico	3.6	
11.	Australia	82.0	
12.	Jordan	23.2	
13.	Sudan	5.8	Elfahal <i>et al</i> , 2013
14.	Thailand	31	Ghanem <i>et al</i> , 2005
15.	Lebanon	51.67	Tabet <i>et al</i> , 2015
16.	Uttar Pradesh (India)	7.3	De Groot <i>et al</i> , 1993, Singh <i>et al</i> , 1997, Waseem <i>et al</i> , 2015
17.	Rajasthan (India)	19	
18.	Mathura (India)	3.33	
19.	Andhra Pradesh (India)	4.5	Didugu <i>et al</i> , 2016

incurable. The majority of affected goats are culled for welfare and/or economic reasons, or they die of secondary causes. Management techniques can have an impact on the prevalence of infection and, as a result, disease frequency. Clinical symptoms are rarely seen in herds with a low infection incidence (OIE, 2017).

Incubation Period

The incubation period is highly variable. Most goats become infected when they are very young, and develop disease months or years later. Encephalitis usually occurs in kids 2 to 6 months of age, but it has been reported in a one-month-old kid, and in older goats. Polyarthritis is generally seen only in adults (OIE, 2017). The time interval between infection and seroconversion varies among animals, ranging from weeks to months or even years, with the probability of seroconversion making it even further difficult to control the disease (de Galiza *et al*, 2020).

Modes of Transmission

The risk of CAE spreading is through the importation of live diseased animals. Inadvertent carriers from infested areas are especially dangerous (Lofstedt, 2016).

The most common way for CAE to spread is for kids to consume virus-infected goat colostrum or milk (pooled or unpooled, Fig.1). Other common

modes of transmission of the virus includes direct contact, exposure to fomites at feed bunks and waterers, consumption of infected milk in milking parlours, or serial use of blood-stained needles or equipment (Radostitis *et al*, 2003; Bulgin, 1990)

Perinatal transmission of CAEV occurs in-utero, through exposure to respiratory and salivary secretions during neonate licking after birth or during birth direct vaginal contact, accidental ingestion of infected dam's colostrum, or infection through breeding or embryo transfer, all of which are unusual methods of transmission (Lofstedt, 2016; Paul *et al*, 2021; Radostitis *et al*, 2003; Robinson and Ellis, 1986). Other uncommon route of transmission could be use of infected semen as suggested by findings that the virus can be transferred by artificial insemination with contaminated sperm. As a result, the venereal pathway is a possible infection route (de Souza *et al*, 2013).

Zoonotic risk

Antibodies to the CAE virus can develop in people who drink milk from infected animals. There is no evidence that this encounter resulted in a viral infection that lasted longer than a few days. Surface glycoproteins on the CAE virus and the HIV virus have a significant cross reactivity. It's been suggested that some people's false positive HIV tests are caused by earlier exposure to the CAE virus found in goat milk

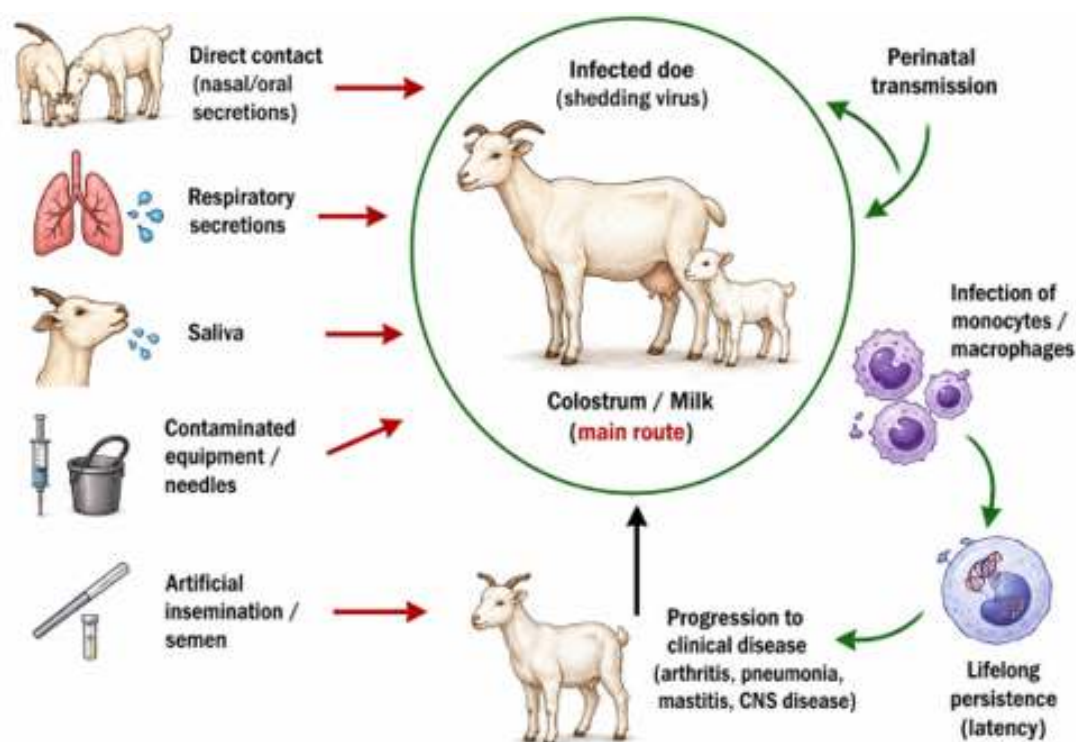


Fig.1. Major Routes of Transmission and epidemiological cycle of CAEV infection

(Diane, 2012). There is no evidence, either serologically or clinically, that humans are vulnerable to CAEV (OIE) and there is no report of this virus having zoonotic potential, including through the intake of milk from an infected goat (Hirata *et al*, 2014).

Determinants to cause the infection in host

Various determinants of the agent which lead to the infection are minimal infectious dose (infectivity of agent) which has been determined as 10^2 TCID₅₀ via the trachea and 10^7 TCID₅₀ via the intranasal route; virulence which can lead to mortality as more as 20-30%, pathogenicity, persistence of agent which can be in the chromosome for the life of the cell once viral DNA stays integrated inside cell and host immune response that rapidly recognizes and eliminates invading viruses via innate antiviral immunity and Interferon β (IFN- β) expression (Sigurdsson *et al*, 1952; Andr sdottir *et al*, 2002; Morin *et al*, 2002; Torsteinsdottir *et al*, 2003; Fu *et al*, 2020).

Economic Importance

Many countries around the world have a high frequency of the disease. Some countries have not yet reported the sickness, but it is in the latent stage in others. Many countries have chosen to implement a national or breed-specific control programme. Infected herds have a higher cull rate, with up to 10% of goats

culled each year for arthritis, and sick animals are not allowed to compete. Although there are conflicting findings on the impact of infection on goat herd productivity, seropositive goats are said to have significantly decreased milk output, a shorter lactation period, a lower 300-day milk yield, and poorer reproductive function (Smith and Cutlip, 1988; Paul *et al*, 2021).

Pathogenesis

Infection with the CAE virus causes arthritis in adults and encephalitis in kids aged 2 to 6 months. Virus-infected macrophages in colostrum and milk pass through the gastrointestinal mucosa unaffected. Infected mononuclear cells then transmit the infection throughout the body. The typical lymphoproliferative lesions in target organs such as the lungs, synovium, choroid plexus, and udder are caused by periodic viral replication and macrophage maturation. The capacity of the CAE virus to get sequestered as provirus in host cells aids its persistence in the host. A robust humoral and cell-mediated immune response is induced by infection, yet neither is protective (Lofsted *et al*, 2016). The CAE virus infects a fraction of monocyte-macrophage cells and causes virus expression and shedding as infected monocytes grow into macrophages. Mammary gland, choroid plexus, synovium, and draining lymph nodes are among the sites where macrophages disseminate (Adams *et al*,

Caprine Arthritis-Encephalitis: A Holistic Review of Disease.

1983; Radostitis *et al*, 2003). CAE clinical symptoms and lesions are linked to viral replication in infected macrophages. A powerful, but non-protective, humoral and cell-mediated immune response is induced by active viral infection (McGuire *et al*, 1986; Smith and Sherman, 1994; Rowe *et al*, 1997; Radostitis *et al*, 2003; Pugh, 2002). Lentivirus can establish a preference for epithelial cells and multiply within them (Zink, 1987; Carpenter *et al*, 1989; Mselli-Lakhal *et al*, 2001; Radostitis *et al*, 2003).

Lentivirus infections include a high prevalence of subclinical infection, a lengthy but varied prepatent period, virus persistence in the host, multiple organ system involvement, and a chronic illness history with recurring acute episodes. The capacity of the Lentivirus to sequester as provirus in host cells without the need for frequent multiplication aids virus persistence in the host. Disease activation appears to be linked to virus activation and translational activity in infected cells. By delaying monocyte maturation, slowing virus maturation, and inciting the immune proliferative response characteristic of CAE lesions through increased expression of Class Ia histocompatibility antigens on macrophages, lymphocyte-derived gamma interferon may play a key role in the pathogenesis of CAE (Bulgin, 1990).

CAE is an immunopathologic illness in which the immune system reacts to viral antigens, particularly surface glycoproteins, resulting in lesions. The severity of joint lesions is related to the presence of virus and antiviral antibodies in the joint, and lymphocytes and macrophages predominate in CAE lesions. By stimulating monocyte migration and macrophage proliferation in parasitized lung, lung worms may predispose infected goats to the pneumonic form of CAE. Kids who have been infected since birth can have an active antibody response as early as four weeks after birth, and usually by ten weeks. Antibodies are persistent for life after the antibody response begins, albeit serum concentrations may wax and wane at different times. Because antiviral gp90 and gp125 antibody is plentiful in the synovial fluid of infected goats, the elevated immunoglobulin G1 concentrations reported at this site 6 month after Caprine arthritis-encephalitis virus infection are most likely due to this (Johnson, 1983). Synovial membrane cells have macrophage-like features and operate as a second cell for CAEV multiplication in vivo. A high concentration of immune reactants, including cells and immunoglobulins, is found in synovial fluid from arthritic joints; a large amount of synovial fluid

antibody is specific for CAEV; virus can often be isolated from synovial fluid; and virus isolation from synovial fluid correlates with the severity of arthritis as measured by the joint score. Furthermore, goats challenged with CAEV during chronic CAEV infection or following inactivated virus vaccination develop more severe arthritis than uninfected non-vaccinated goats (Dawson, 1997). CAEV arthritis is an immunopathologic condition in which particular antibodies and sensitized cells react in the synovial cavity to CAEV antigen. Antigenically variable neutralization-sensitive epitopes expressed by virus isolates, as well as the immune response to these variants, contribute to periods of inflammation and arthritis development (Dawson, 1997). Caprine arthritis-encephalitis virus (CAEV)-infected goats develop chronic arthritis and cachexia, both of which are progressive. The immunopathogenic mechanisms behind these progressively worsening clinical symptoms have yet to be fully understood.

There is formation of syncytia by fusion of infected cells within surrounding susceptible cells, probably due to the contact of the viral envelop glycoproteins with cell receptor which plays important role in the CAEV specific CPE (Cytopathogenic effect) (Gendelman *et al*, 1997). The process of apoptosis is commonest cytopathogenic effects of various viruses, including several Lentiviruses (Shen and Shank, 1995) which includes chromatin condensation and nuclear fragmentation. During the initial days of virus infection, erstwhile to syncytia formation reports suggest that individual cells manifest an apoptotic nucleus which suggest that though the progression of cell apoptosis correlated with the development of CPE, for CAEV-induced apoptosis, syncytia formation is not a criterion (Gendelman *et al*, 1997). Fragmentation of chromatin occurs due to activation of an endogenous, Ca/Mg-dependent endonuclease activity (Bertner *et al*, 1995). The Sub-G1' cell population of CAEV-infected cell increase progressively with the spread of virus, up to a peak level reaching after 8 days of infection.

Finally, based on current research, it is concluded that the virus evades a suitable immune response through multiple methods detailed below (Perk, 1995; Narayan *et al*, 1988):

1. The viruses neutralize one of the host's nonspecific defense mechanisms by infecting monocyte-macrophage cells.
2. By infecting stem cells in the bone marrow and limiting virus gene expression in these cells, cytotoxic cells are unable to recognize these

cells, and the virus remains a reservoir in the body.

3. In a state of latency, proviral DNA incorporated in host cells can remain unexpressed for long periods of time.
4. During infection, CAEV does not produce neutralizing antibodies. CAEV is difficult to control due to the features, which cause latency, persistence, and eventual spread throughout the host, and are responsible for the chronic, painful, debilitating, and wasting indications displayed by infected animals.

Clinical Signs

Nearly 20% of CAE virus-infected goats manifest clinical signs during their lifetime and after Caprine arthritis and encephalitis (CAE) virus infection clinical manifestations of this disease are as follows (Machen *et al*, 2002; Lofstedt, 2016):

1. Polysynovitis-arthritis in adult goats and less commonly as progressive paresis (leukoencephalomyelitis) in kids, other less commonly found signs include and distant examination reveals joint capsule distention mainly carpal joints and varying degrees of lameness.
2. Subclinical or clinical interstitial pneumonia leading to dyspnea, indurative mastitis ("hard udder"), and chronic wasting.
3. There is reduction in the productivity after infection in dairy goats which cannot be cured till lifetime i.e., reduction in productivity for lifetime
4. Affected goats appear as gaunt and usually have poor hair coats.
5. Encephalomyelitis commonly seen in kids of age group 2–4 months but older kids and adult goats can also get affected which is exhibited by ataxia, weakness and hind limb placing deficits.
6. Other common findings include hypertonia and hyperreflexia.

7. Progression of signs occurs which include para-paresis or tetraparesis and paralysis. Depression, head tilt, circling, opisthotonos, torticollis, and paddling have also been reported in kids.
8. In kids, the interstitial pneumonia component of CAE virus infection rarely produces any clinical picture.
9. Milk quality is usually unpretentious. While the mammary gland may soften and yield close to normal amounts of milk and production is low in many goats with indurative mastitis.

Necropsy Findings

The synovial lining (pannus), extensive osteophyte formation, free floating concretions (rice bodies or joint mice), degenerative joint disease with destruction of subchondral bone, ulceration and erosion of articular cartilages, and mineralization of the surrounding tissues of the joint can all be seen during post-mortem examination of the joints.

Pathologic lesions of CAE virus infection are mostly described as lymphoproliferative with degenerative mononuclear cell infiltration. Thickening of the joint capsule and marked proliferation of synovial villi are common lesions exhibited in joints. Soft-tissue calcification comprising joint capsules, tendon sheaths, and bursa is not uncommon in chronic cases. In advanced cases, there is rupture of ligaments and tendons, peri-articular osteophyte formation and severe cartilage destruction. Hyperplasia, subsynovial mononuclear cell infiltration, villous hypertrophy, synovial edema, and synovial necrosis are microscopic findings of articular lesions. Gross lesions associated with the neurologic form of CAE are seen most commonly in the cervical and lumbosacral spinal cord segments and consist of asymmetric, brownish pink, swollen areas.

On gross examination, lungs of affected goats are firm and gray-pink with multiple, small, white foci, and do not collapse. There is invariable enlargement of bronchial lymph nodes. Histopathological examination reveals multifocal, mononuclear cell inflammatory infiltrates and varying degrees of demyelination. Histologic findings comprise chronic interstitial pneumonia with mononuclear cell infiltration in alveolar septae and in perivascular and

Caprine Arthritis-Encephalitis: A Holistic Review of Disease.

peri-bronchial regions and there is mononuclear infiltration of periductular stroma which obliterates normal mammary tissue in does with udder induration. (Lofstedt, 2016).

Clinical Pathology and Diagnosis

To diagnose CAE, we need a mix of history, clinical indicators, biochemical, a positive serology test, and postmortem lesions from all other potential disorders (Smith and Sherman, 1994; Matthews, 1999).

1. The virus changes the pH, chloride concentration, and electro-conductivity of the milk. (Gregory *et al*, 2009).
2. Synovial fluid and joint examination after arthrocentesis reveals severe synovial fluid with a dark yellow to reddish brown color. A higher number of lymphocytes and macrophages are also present in the fluid (mononuclear cells). The nuclear cell count in the synovial fluid is larger than 1000 cells/l, and lymphocytes are the most common cell type (Knight, 1982; Linklater and Smith, 1993).
3. Mammary gland examination; the interstitial mastitis caused by CAE virus infection is reliably detected by histological investigation since normal goat milk might contain a considerable number of epithelial cells and macrophages. Within the interstitium, histopathology reveals inflammatory cell foci. Around the alveolar ducts, there is extensive nodular lymphoid growth. Chronic inflammatory cells and enhanced connective tissue deposition replace the parenchyma in chronic mastitis (Pugh, 2002).
4. Biochemical changes due to CAE infection includes higher serum alkaline phosphatase and γ -glutamyl transferase levels, which is a sign of hepatic and bone disease.
5. Infected goats have greater serum tumour necrosis factor (TNF- α) levels. Persistent increased levels of TNF- α leads to cachexia in infected goats.

6. Protein levels and mononuclear pleocytosis is seen in CSF fluid from goats suffering with leukoencephalomyelitis (Mdurvwa *et al*, 1994).
7. Radiograph reveals soft tissue edema, peri-articular osteophyte development, and calcification of the peri-articular structure (Knight and Jokinen, 1982; Linklater and Smith 1993).
8. Ultrasonography shows loss of echogenicity, surface erosions, and subchondral bone exposure seen in goats infected with CAEV (da Silva Moura *et al*, 2016).
9. Serological tests are usually used to make a diagnosis. Agar gel immunodiffusion test (AGID) is the recommended test, but ELISA is also available.
10. Molecular Detection of CAE Virus using PCR amplification for detection of CAEV DNA in cultured cells using primers for the *pol* gene (Zanoni *et al*, 1990) and in PBMC and milk from infected goats using primers for the *gag* gene (Rimstad *et al*, 1993).

Differential diagnosis

Traumatic arthritis and infectious arthritis produced by *Mycoplasma* species are among the differential diagnoses for CAEV-induced arthritis. Enzootic ataxia, cerebrospinal nematodiasis, spinal cord trauma or abscess, and congenital defects of the spinal cord and vertebral column should all be evaluated in young kids with increasing paresis. Polioencephalomalacia, listeriosis, and rabies are all possibilities in goats with indications of brain involvement. In adult goats, the pulmonary form can mimic the pulmonary form of caseous lymphadenitis (OIE, 2017).

Treatment

Any of the clinical symptoms linked with CAE virus infection has no specific treatment. Individual goats, on the other hand, may benefit from supportive therapy. Regular foot trimming, the use of soft additional bedding, and the administration of NSAIDs such as phenylbutazone or aspirin may help goats with polysynovitis-arthritis (Bulgin, 1990). The dose of 100

mg/kg aspirin every 12 hours or 10 mg/kg phenyl butazone once a day can be given.

Secondary bacterial infections that may exacerbate the interstitial pneumonia or indurative mastitis components of CAE virus infection are treated with antibiotics (Lofstedt, 2016).

Another treatment regimen could be used in arthritic animals using Naringenim. Naringenin is one of the most important and abundant known flavonoids found in grapefruit and other citrus fruits. Experimental studies have been conducted on the rats after induced arthritis and ameliorated using Naringenim with good results. This could be one possible addition to routine treatment regimen with good results in CAE affected goats showing clear manifestation of arthritis (Hajizadeh *et al*, 2021).

Prevention and Control

There is no known cure for CAE, and no effective pre-infection vaccine is commercially available. To lower the incidence and prevent spread of the disease, herd surveillance and careful management are essential. COST action financed by the European Union to better manage their SRLV research programmes and (ii) coordinate efforts to combat these two illnesses. After five years of work, a consensus conference – the first in the field of veterinary medicine – reviewed the current situation and discussed three important questions in the field of SRLVs: routes of transmission, consequences of infection, and the potential role of eradication programmes at either a European or local level, depending on the situation (Peterhans *et al*, 2004). One or more of the following have been suggested for CAE control in commercial herds (Lofstedt, 2016):

1. Permanent isolation of kids right from birth in endemic areas.
2. Heat-treated colostrum (45°C [113°F] for 60 minutes) and pasteurised milk feeding.
3. Semiannual serologic testing of the herd, with identification and segregation of seronegative and seropositive goats, the groups should be isolated by at least 6 feet (1.8 metres).
4. Final culling of seropositive goats. If the herds are segregated into seropositive and

seronegative groups as part of the control programme, and common equipment should be disinfected with phenolic or quaternary ammonium compounds (Lofstedt, 2016).

5. Complete control can be achieved by preventing/minimizing perinatal infection transmission to the child, notably in colostrums and milk, as well as identifying diseased animals and physically separating them from non-infected animals or removing them from the herd (Radostitis *et al*, 2003; Bulgin, 1990; Dawson 1997).

Conclusion

Small ruminant lentiviruses induce clinical disease in a minority of infected infect goats and sheep. Clinical cases may fade in a population after following proper control policies and eradication campaign. The spread of less virulent strains often parallels the elimination of their virulent counterparts which impedes the complete elimination of these lentiviruses. Once the arrays of pathogenesis are known, then a suitable vaccine or drug can be formulated against the CAEV and animals can be safeguarded against this disease.

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Caprine Arthritis-Encephalitis: A Holistic Review of Disease.

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Caprine Arthritis-Encephalitis: A Holistic Review of Disease.

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