AKADEMİK PERSPEKTİFTEN VETERİNER İÇ HASTALIKLARI

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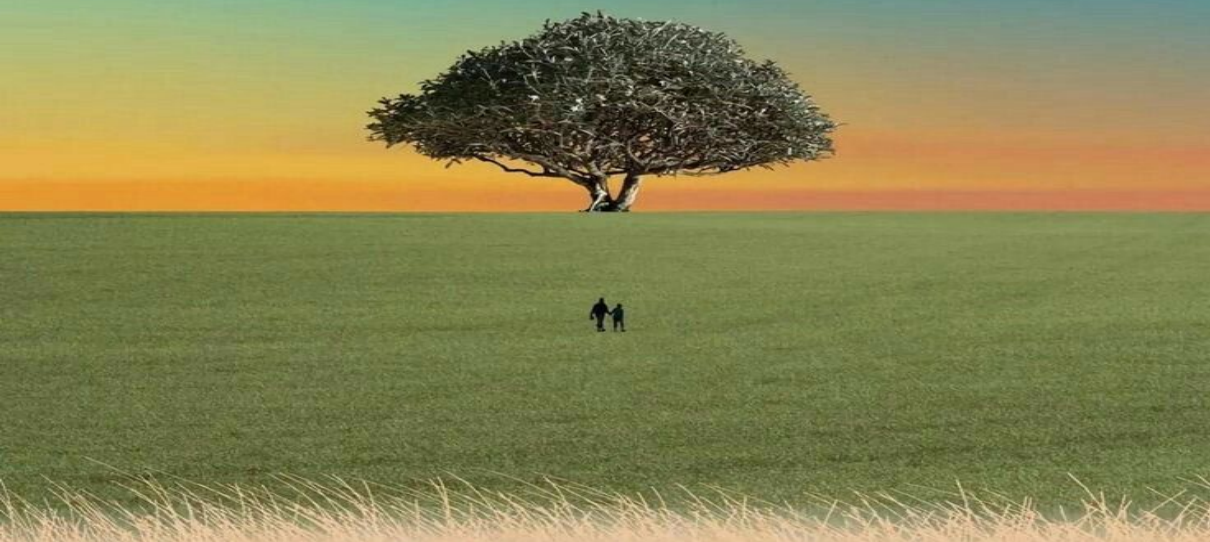

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2025

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E_ISBN 978-625-5596-86-4

Haziran 2025 – Afyonkarahisar

Dizgi/Mizanpaj: YAZ Yayınları

Kapak Tasarım: YAZ Yayınları

YAZ Yayınları. Yayıncı Sertifika No: 73086

M.İhtisas OSB Mah. 4A Cad. No:3/3
İscehisar/AFYONKARAHİSAR

www.yazyayinlari.com

yazyayinlari@gmail.com

info@yazyayinlari.com

İÇİNDEKİLER

SCHMALLENBERG DISEASE IN SHEEP AND GOATS: EPIDEMIOLOGY, DIAGNOSIS AND CONTROL METHODS

Fatma ATLI[1]

Çağrı KANDEMİR[2]

Turgay TAŞKIN[3]

1. INTRODUCTION

The Simbu serogroup of the genus Orthobunyavirus includes the Schmallenberg virus (SBV), a newly discovered infectious disease (Hoffmann et al., 2012). According to Beer et al., (2013), the first known outbreak of SBV in Europe was caused by a member of the Simbu serogroup. It is believed that biting insect vectors (Culicoides species) spread SBV. Schmallenberg virus infection is a recently discovered viral disease that affects European ruminants and is contracted through bites from Culicoides midges. Abortion and stillbirths linked to congenital abnormalities in sheep and goats, as well as fever, inappetence, decreased milk output, loss of condition, and diarrhoea in cattle, are its defining characteristics (Gibbens, 2012). Numerous viruses that are detrimental to both vertebrate and invertebrate hosts are members of the Bunyaviridae family. The lack of SBV vaccines presents a major risk to gullible ruminant livestock

[1] Öğr. Gör. Dr. Ege University Faculty of Agriculture, Department of Animal Science, Bornova-İzmir, ORCID: 0000-0001-6536-5594.

[2] Doç.Dr. Ege University Faculty of Agriculture, Department of Animal Science, Bornova-İzmir, ORCID: 0000-0001-7378-6962.

[3] Prof.Dr. Ege University Faculty of Agriculture, Department of Animal Science, Bornova-İzmir, ORCID: 0000-0001-8528-9760.

populations. We know relatively little about the pathophysiology and pathogenesis of Schmallenberg viral illness because it was only recently discovered. The data on this recently discovered disease that have been reported thus far were covered in the current review (Herder et al., 2012).

Early-stage infections in sheep can result in fetal abnormalities and occasionally stillbirth. Arthrogryposis, skeletal muscle dysplasia, cervical and thoracic vertebral column abnormalities, overshot jaw, and neurological symptoms are among the malformations in fetuses and lambs linked to SBV infection (van den Bergh et al., 2012) (Fig. 1). During the same pregnancy, ewes may give birth to both normal and malformed lambs (Ducomble et al., 2012). Lambs infected by SBV were delivered at term; some were stillborn, while others were badly malformed yet lived. Ewes have died during labour due to dystocia brought on by malformed lambs (Lievaart-Peterson et al., 2012).

Fig 1. A typical Schmallenberg virus-affected calf showing arthrogyposis (limb fusion) of the hind limbs (photo courtesy of Dr Rachael Tarlinton, University of Nottingham).

2. STRUCTURE OF THE VIRUS

The Schmallenberg virus got its name from the area where blood samples from afflicted dairy cattle were taken, and the virus was later discovered. Hoffmann et al. (2012) state that the virus shares traits with the Shamonda virus (97%), Aino virus (71%), Akabane virus (69%), and the genus Orthobunyavirus, which belongs to the Bunyaviridae family. Schmallenberg virus is a single-stranded, segmented, enclosed, negative-sense virüs (Yanase et al., 2012). Reassortment, which is the blending of a species' genetic material into distinct pairings in other individuals and can be brought on by several reasons, is made possible by the segmented genome of the Bunyaviridae.

New viral strains may arise due to this (Goller et al., 2012). In RNA viruses, reassortment is a type of genetic recombination. It involves packing segments of varying lineage into a single virion and is limited to viruses with segmented genomes. Like RNA recombination, reassortment necessitates many viral infections in a cell (Simon-Loriere and Holmes, 2011). According to phylogenetic analysis, Schmallenberg virus may be a reassortant that includes parts from both Shamonda and Sathuperi viruses (Yanase et al., 2012). Probably one of the progenitors of the reassortant Shamonda virus, the Schmallenberg virus belongs to the Sathuperi viral species (Goller et al., 2012).

3. EPIDEMIOLOGY

In the Arabian Peninsula, Europe and North and South America, several deadly arboviruses have surfaced and produced epidemics in humans and/or animals (Elliott et al., 2013). These include the Rift Valley fever, Zika virus, West Nile, Chikungunya, and Bluetongue virus (BTV) (Conraths et al., 2009). Elbers et al., (2012) ascribe their existence in part to the phenomenon of climate change.

The Schmallenberg virus first appeared in the fall of 2011 in Northern Europe, where BTV serotype 8 (BTV-8) originally appeared in 2006. Newborn calves, lambs, and children infected with the Schmallenberg virus may develop congenital abnormalities, hydranencephaly syndrome and arthrogryposis (Luttikholt et al., 2014). Since infected midges are easily conveyed on air currents, the quick spread of SBV to the continent's other regions was mostly caused by wind.

According to estimates, SBV spreads between 0.9 and 1.5 km every day. New infections recurred throughout the summer of 2012 in the same locations, even though the seroprevalence reached up to 98% recorded in epidemic zones in 2012 and 2011. Using both serological and genomic detection methods, the comeback of SBV infection in Belgium was identified in 2012 (Sedda and Rogers, 2013). It became clear in June 2012 that the virus could not be eradicated by the severe winter months in ruminants in Germany because new cases were also recorded.

The Netherlands saw another outbreak of SBV in sheep and cattle in late 2014, and heifer prevalence and SBV-specific antibody titers rose in 2016 (Balmer et al., 2014). Antigenic variants that evade the immunity gained against their ancestors or a global loss in herd immunity may be the cause of future cyclic epizootic reemergences (Luttikholt et al., 2014).

4. WAYS OF TRANSMISSION

Several Culicoides species, such as Culicoides dewulfi, Culicoides obsoletus, and Culicoides pulicaris, can transmit the Schmallenberg virus, which is carried by arthropods (Elbers et al., 2014). Culex, Anopheles, and Culiseta mosquitoes that spend the winter in Although it is impossible to rule out a role for mosquitoes, farms in the Netherlands that were infected with the Schmallenberg virus in 2012 did not exhibit any symptoms of the

infection. Scholte and colleagues (2014). Potential vectors have access to adequate viral amounts only for the short time that viremia is present. The decline in the viral burden of the Schmallenberg virus in biting Culicoides species (Elbers et al., 2014) indicates that arthropods are the main vector of transmission for the infection and that its prevalence is decreasing. The existence of Culicoides significantly affects how viruses spread in endemic areas.

In Asia and Africa, bunyaviruses linked to human and animal diseases are frequently spread by insect vectors like biting flies (Culicoides spp.) and mosquitoes. It was immediately clear that Culicoides species aid in the dissemination of SBV after it was discovered (van Der Poel et al., 2014). SBV genome sequences were found in biting flies, specifically in the Ceratopogonidae family's Culicoides obsoletus species collective. Additionally, it was shown that several Culicoides species, including Culicoides dewulfi and Culicoides punctatus, tested positive for SBV genomic markers. SBV genomic markers were detected in culicoides captured in Belgium, Italy, the Netherlands, and Denmark beginning in 2011's summer and fall. Additionally, it was shown that, in laboratory settings, the BTV vector Culicoides sonorensis facilitates the replication and spread of SBV (Delooz et al., 2017). According to Wernike et al. (2013), naive animals infected with the SBV virus have been found to have blood containing viral RNA for several days. This suggests that biting insects may contract the virus and subsequently spread it to additional vulnerable animals through blood feeding. Given that SBV has been connected to birth defects in lambs, goat kids, and calves, vertical transmission from mothers to their progeny is especially significant. SBV also spreads vertically across the placenta (Wernike et al., 2013).

Semen from cows has been found to contain SBV. Eleven bulls with known SBV antibody status had their semen tested for

the SBV genome by the FLI. A quantitative real-time RT-PCR device created at the FLI and an optimised RNA extraction technique were used to examine every sample. Investigations are ongoing to determine whether SBV can be spread via semen that shows a positive result for the virus. It is quite unlikely, nevertheless, that SBV can be transmitted straight from one animal to another (USDA-APHIS, 2012). Additionally, it doesn't seem like the virus spreads orally. Blood and serum were revealed to contain viral RNA, and these samples for several days in naive calves that were infected with SBV both subcutaneously and orally. In contrast, animals that were injected orally and uninfected controls showed no signs of viral RNA for the course of the investigation (Wernike et al., 2013).

Since zoonotic viruses—aside from the Oropouche virus—are uncommon in this group, a human risk is not anticipated due to SBV's close ties to the Sathuperi, Aino, Shamonda, and Akabane viruses. The Robert Koch Institute found no evidence of infection in those who were close to sick animals (FLI, 2013a). However, further research has to be done.

5. CLINICAL SIGNS

Adult ruminants' clinical signs of SBV infection are typically nonspecific. Fever (> 40 °C) is the outcome of an acute infection in adult cows. The brief viraemic phase (one to six days) is followed by anorexia, poor general health, a 50% drop in milk production, and diarrhoea (Chaintoutis et al., 2014). Full recovery occurs in two to three weeks. These symptoms have been most frequently noticed during the April–November vector-active season. Although illness outbreaks in impacted herds typically last two to three weeks, the possibility of another epidemiological manifestation cannot be ruled out (Yilmaz et al. 2014).

However, SBV infection is primarily asymptomatic in adult goats and sheep. Although reports of clinical illness in adult animals are scarce (6% of cattle, 3% of sheep, and 1% of goats), SBV acute clinical cases are rare. (Goffredo et ai., 2013). At least one case of goats exhibiting clinical symptoms of diarrhoea and decreased milk production has been documented. Although the precise similar symptoms have been noted, the reason for diarrhoea, fever, and decreased milk production in sheep is yet unknown. (Rasmussen et al., 2012).

SBV infection in cattle and sheep in experimental settings has a brief 5- to 7-day viremic stage that begins days two or three following infection (pi), peaking on day 4 pi. Abortion, stillbirth, and deformed puppies linked to SBV infection in sheep and cattle have comparable clinical consequences to those seen with other Simbu serogroup viruses, including Aino and Akabane (Schulz et al., 2014) (Fig. 2, 3, 4).

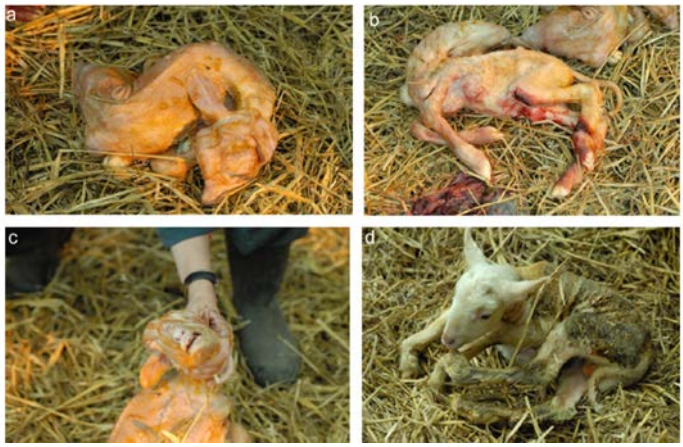

Fig. 2. Congenital deformities in stillborn (a–c) or living (d) lambs include arthrogryposis, scoliosis, torticollis, and kyphosis, and a flattened head with lower jaw brachygnathia. Clinical manifestations of Schmallenberg disease in sheep are also present.

Source: K. Lievaart-Peterson et al. 2012 / Veterinary Microbiology 181 (2015) 147–153

Fig 3. Newborn lamb affected by Dandy-Walker syndrome.
Fig 4. Septicemia in a one-day-old lamb.

The clinical signs (if born alive) would be similar to SBV (https://www.nadis.org.uk/disease-a-z/sheep/schmallenberg-virus-sbv/).

During SBV infection, there has been proof of a link between congenitally deformed lambs and herd immunity. A rise in seroprevalence against SBV occurs after a decrease in herd immunity. Torticollis, scoliosis, arthrogryposis, lordosis, and brachygnathia inferior are among the common musculoskeletal abnormalities seen in fetuses undergoing transplacental infection. Cleft palate and sacral spina bifida are also seen in stillborn lambs (Kęsik-Maliszewska et al., 2019). When twins are born, musculoskeletal problems are not always homogeneous, thus, one twin may have deformities while the other is born healthy with no clinical indications of malformations. According to a recent study, when experimentally in utero SBV-infected pregnant heifers were infected between 60 and 150 days of gestation (first and second trimester), only one abortion and one deformed fetus were reported out of 36 animals. This indicates that extremely low rates of fetal miscarriage and deformity resulted from experimental in utero infection of cow fetuses (Veronesi et al., 2013). Congenital malformations in fetuses and newborns are the primary clinical symptoms, which are similar to those caused by an Akabane virus infection.

The term "AHS" refers to congenital anomalies such as stillbirth, premature delivery, mummified fetuses, arthrogryposis,

hydranencephaly, ataxia, joint deformities, torticollis, paralysis, muscular atrophy, kyphosis, scoliosis, behavioural disorders, and blindness. (USDA-APHIS 2012). In kids, lambs, and calves, transplacental infection with SBV causes severe congenital malformations like arthrogryposis, malformations of the skull (brachygnathia inferior, macrocephaly), the vertebral column (kyphosis, scoliosis, lordosis, and torticollis), and the brain (cerebellar hypoplasia, hydranencephaly, porencephaly, and hypoplasia of the brain stem).

When juvenile ruminants' central nervous systems (CNS) contain SBV, hydranencephaly, hydrocephalus, porencephaly, lissencephaly, micromyelia, cerebellar and cerebral hypoplasia are frequently seen during necropsy (Goffredo et al., 2013). Microscopic abnormalities include lymphohistiocytic meningoencephalomyelitis, glial nodules mostly in the hippocampus and mesencephalon of goats and lambs, and necrosis and neuronal degeneration primarily in the calves' brain stem. Lesions are probably the source of the musculoskeletal problems in the spinal cord abnormalities that show up in fetuses as arthrogryposis (Rasmussen et al., 2012). Because of these musculoskeletal anomalies, the syndrome of hydranencephaly and arthrogryposis (AG-HE syndrome) was identified in SBV-infected neonates or aborted fetuses (Steinrigl et al., 2014).

6. VIRAL ISOLATION AND IDENTIFICATION

Schmallenberg virus grows in cells obtained from humans and other animal species (Varela et al., 2013). In the choroid plexus cells of sheep, SBV developed effectively, bovine fetal aortic endothelial cells, dog MDCK, human 293T, and hamster BHK-21 and BSR cells, reached titers of 10 PFU/ml 48 hours after the infection and produced cytopathic effects in most cell lines except BFAE cells (Bilk et al., 2012). The best cell lines for

SBV culture in sheep were CPT-Tert cells. There were various plaques, each around 3 mm in diameter. inside these cells, seventy-two hours following infection. In addition to an antibody test, a quantitative reverse transcription PCR in real-time test has been developed for the rapid detection of Schmallenberg virus and can be used by institutions in England, Belgium, France, the Netherlands, Italy, and Switzerland (Fischer et al., 2012). Other complementary and confirmatory tests used on a disease-by-disease assays for viral neutralisation and indirect immunofluorescence are among the foundations FLI, 2013a). Scientists in Germany and the Netherlands have developed an antibody-based virus neutralisation test (VNT) suitable for mass testing to measure past exposure in animals by producing antibodies to SBV in cows and sheep from herds suspected or known to be affected. The specificity of this VNT is claimed to be >99%, and its sensitivity is nearly 100% (Loeffen et al., 2012). A new indirect ELISA test to detect antibodies to SBV has also been created by IDEXX Livestock and Poultry Diagnostics scientists. It is stated that the test has a high specificity of 99.5% and sensitivity of 98.1%, making it suitable for screening SBV infection in animals (IDEXX, 2013). The recombinant nucleocapsid protein-based ELISA assay of SBV has been assessed and confirmed by three European Reference Laboratories to detect SBV-specific IgG antibodies in ruminant serum (Breard et al., 2013). The ELISA test is quite sensitive, despite the possibility of cross-reactions with other Orthobunyaviruses from the Simbu serogroup, a specific, robust and proven technique for detecting anti-SBV antibodies, which can be used for disease monitoring research and SBV serodiagnosis in European ruminant animals.

7. CONTROL AND TREATMENT

There isn't currently any vaccination or therapy for SBV. Since it is a novel condition, more research is required to identify potential preventative measures. There are no limits on movement because SBV is not a disease that requires reporting (Carpenter et al., 2008). Based on the information at hand, the virus is present in acutely infected animals during this viremia phase. There has been no attempt at culling diseased animals, and it would be pointless anyhow. Applying pesticides and pathogens to areas where larvae develop, implementing environmental interventions to eradicate larval breeding grounds, treating resting areas like animal shelters or animal hosts with insecticides, keeping animals in screened buildings, and employing repellents or host kairomones to draw in and kill adult mosquitoes are some potential strategies to control Culicoides vectors (FLI, 2013b). Currently, the best approaches are to reduce local breeding sites, utilise mosquito-proof housing for ill or valuable animals, and treat cattle and animal shelters with pyrethrin insecticides (Conraths et al., 2013). Pour-on pesticides, however, have not proved effective in lowering the density of biting mosquitoes in circumstances (Bauer et al., 2009). Controlling mosquitoes is unlikely to be successful because they are so common and appear especially effective at spreading SBV. Furthermore, the possibility of developing an SBV vaccine to be released seems quite good, as the timing of breeding or insemination of female animals is available for selection to avoid the vector's active season at 4–8 weeks of gestation. Various research groups have developed prototypes of inactivated vaccines, but none have yet received marketing authorisation. Lambing issues may result from malformations that harm lambs exposed to the virus during pregnancy. Using too much force at lambing or calving could put the health of the calf and cow, as well as the lamb and ewe, at risk. Breeders should inform their veterinarian that a Caesarean

section might be necessary to ensure a safe delivery. Due to the characteristics of the deformities, these Caesareans might be more challenging than typical. For the sake of their well-being, lambs born alive with serious abnormalities ought to be put down.

Several vaccines were introduced after the initial outbreak, but are not presently offered for sale. Unpublished data from the current outbreak suggest that previously vaccinated animals or those infected in the initial outbreak are not necessarily protected from re-infection. Insecticide application may help reduce the number of mosquitoes biting individual animals, but has been unable to exert authority over mosquito numbers on a large scale. Shifting the mating season for sheep flocks to later months is probably the most practical solution to minimise the risk of Schmallenberg, and mosquito numbers may remain high until October in years with late frosts.

The Schmallenberg virus is unlikely to infect people, according to a European risk assessment. The most closely related viruses only infect animals, and no human cases have been found in any nation thus far (Simcock, 2019). Due to the possibility of contracting further infections, pregnant women should refrain from interacting with sheep and goats throughout the lambing or calving process.

8. EFFECT OF SCHMALLENBERG VIRUS ON PRODUCTIVITY

Schmallenberg virus disease parameters (Table 1) were included in the production models under two scenarios according to literature and an expert workshop (Waret-Szkuta et al., 2017). A herd that is very vulnerable to the disease, for example, when the susceptible gestation period falls with a season with significant vector activity, is represented by the high-impact scenario; in contrast, a less vulnerable herd is represented by the

low-impact scenario. For the most variable and uncertain, the minimum, most likely, and greatest values factors were agreed upon (Zagmutt et al., 2013). The net value of infection at the farm level, which represents the expenses of SBV, was compared using partial budget analysis. Table 1 shows each system's net SBV value (in sheep/year). The highest costs for the pasture-grass, quality cheese dairy system were due to lost revenues from unproduced milk (Häsler et al., 2015). In beef cattle production systems, costs are mainly deducted from unsold young lambs (50-55% of total), replacement of dead or culled ewes (22-23%) and income lost from SBV-caused dead ewes (12–13% of total expenses). The primary costs for dairy sheep relate to income from milk lost due to ewes being culled or killed due to SBV (50% of total expense) and income from lambs not being sold because lambs are needed to replace the lost animal (37% of total costs).

Table 1. Characteristics of high and low impact scenarios in the Schmallenberg virus outbreak

Features	**High Impact**	**Low Impact**	**Source**
Percentage of ewes that had stillborn or disabled lambs due to SBV	%80	%80	Mee J. (2012); Meijering A. (1984); Saegerman et al., 2013
Percentage of ewes that had difficult births due to SBV requiring a Caesarean section	%2-10	%2-10	Hoffmann et al., 2012; Conraths et al., 2012
Percentage of ewes that had miscarriages due to SBV	%1-3.5	%1-2	Saegerman et al., 2013
Percentage of lambs that were stillborn, disabled or perished from SBV at the age of one week	%2-12	%1-3	GDS, 2012; Van den Brom et al., 2012
Percentage of ewes that had miscarriages treated with antibiotics	%1	%1	Expert opinion
Percentage of ewes that had clinical signs due to SBV (excluding dystocia and abortions)	%3-31	%0	Martinelle et al., 2012
Percentage of ewes that had difficult births and died due to SBV	%50	%50	Scott, 2003
Percentage of ewes that were culled due to dystocia	%20	%20	Expert opinion

9. THE FUTURE OF THE DISEASE

The Schmallenberg virus is still circulating today and has already penetrated European borders. If there are susceptible host populations and vectors, the Schmallenberg virus will continue to spread and/or become endemic. The virus needs hosts to survive, in addition to the presence of vectors and a domestic and wild reservoir in endemic areas. Antibodies that neutralise the virus can protect hosts and their fetuses from Schmallenberg disease. How long natural or vaccine-derived antibodies will shield the host and stop placental transfer is still unknown. Crucially, every generation introduces fresh vulnerable hosts. The herd turnover rate might vary depending on systems, production techniques, and farm management. Turnover rates of 20% to 25% are not unusual on commercial farms, which leads to a declining epizootic each year due to a high percentage of vulnerable animals in a population. When the Schmallenberg virus recurs every five to ten years in Europe, it will most likely be considered a serious epidemic with clinical cases. Schmallenberg disease may resurface after a time of no clinical symptoms, particularly along the endemic area's borders, when the weather changes that favour Orthobunyaviruses and vectors, or when a sizable portion of hosts are (re)susceptible. Orthobunyaviruses and Culicoides vectors both have a poor rate of growth at temperatures lower than 15 °C. Another possibility is that the virus will reemerge in the future due to reintroduction from endemic regions. Schmallenberg virus or a closely similar virus may be windborne if it turns out to be the ancestor of Shamonda virus, as hypothesised by Goller et al. (2012).

10. RESULT

An infection with the Schmallenberg virus is a new infectious illness that can lead to major economic losses,

especially in sheep and goat farming. In cattle, the disease is usually acute with visible clinical signs such as decreased milk yield, fever, and diarrhoea that resolves within 2–3 weeks after the animal recovers. SBV infection, on the other hand, is nearly asymptomatic in sheep and goats and is transferred during pregnancy from the mother to the fetus. This can result in miscarriages, stillbirths, and several genetic abnormalities, most of which affect the skeletal and neurological systems. While the disease was initially limited to Northern and Western Europe, SBV antibodies were detected in cattle, sheep, goats, and buffalo in a study that was done in the past in Turkey from 2006 and 2013 (Azkur et al., 2013). This indicates not only that the virus existed before its discovery in Germany in 2011, but also that it has spread to countries in Eastern Europe. Since Culicodes mosquitoes can transmit the illness that transcends national boundaries (De Regge et al., 2012; Veronesi et al., 2013), even though the presence of SBV in vector insects has not yet been confirmed in our nation, this could be concerning for landlocked Asian and Eastern European nations that already harbour these vector species that are in charge of spreading bluetongue viruses and the Akabane in these areas. If SBV spreads to South Asian countries in particular, the virus could significantly affect dense ruminant populations, given the limited resources and control possibilities and the favourable climatic conditions for Culicoides vectors. Random screening of ruminants and agricultural animals in other nations would be a sensible strategy, especially because molecular and serological diagnostic tools for SBV infection are easily accessible.

11. SUGGESTIONS

A new viral disease called Schmallenberg virus infection can result in significant financial losses for farm animals,

particularly in small-scale ruminant production. The disease typically manifests in cattle as acute symptoms, including fever, diarrhoea, and decreased milk production, which go away two to three weeks after the animal recovers. SBV infection, on the other hand, is nearly asymptomatic in sheep and goats and is transferred during pregnancy from the mother to the fetus. This can result in stillbirths, miscarriages, and a variety of congenital abnormalities, most of which affect the skeletal and neurological systems. The Simbu serogroup virus, Schmallenberg virus, is a member of the Orthobunyavirus genus's Sathuperi virus species within the Bunyaviridae family. Such viruses' segmented genomes allow for reassortment, and it has been proposed that the Schmallenberg virus is a reassortment made up of parts of the Shamonda and Sathuperi viruses. However, recent studies suggest that the Schmallenberg virus is most likely an ancestor of the reassorted Shamonda virus and may have existed before the notable Schmallenberg disease outbreak in North-Western Europe. Based on serological results collected in Turkey, it is highly improbable that the Schmallenberg virus is spreading throughout Europe or its neighbouring nations. Pathogen detection is crucial since even seroepidemiological studies can produce inaccurate findings about regional distribution. It is still highly probable that Schmallenberg disease emerged newly in 2011 in North-Western Europe. The Schmallenberg virus continues to exist in its original area and is radially spreading towards and along the borders of Europe. Schmallenberg disease will probably decline further in endemic areas due to the currently high seroprevalence. However, if seroprevalence decreases, it is likely to re-emerge. As long as Schmallenberg virus circulates in Europe, a major epidemic with clinical cases can be considered when it re-emerges every four to five years.

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CONDITIONS WITH ENDOTOXEMIA AND SUDDEN DEATH IN RUMINANTS

Fatma ATLI[1]

1. INTRODUCTION

The presence of Gram-negative bacteria's outer cell wall layer in the bloodstream, which contains lipopolysaccharide, also referred to as endotoxin, causes endotoxaemia, an inflammatory disease (Burhop et al., 1985). Sheep are particularly vulnerable to this illness, which results in a high mortality rate among afflicted animals. Numerous studies have focused on the treatment plans for endotoxemia and its aftereffects in sheep (Byrne et al., 2018). Additionally, ovine models have been used to assess various aspects of endotoxaemia for the past 50 years, and sheep are among the most often utilized animal species in experimental investigations on the disease. Numerous studies on experimentally generated endotoxaemia in sheep are already available, and knowledge of new therapeutic approaches in this species helps to better understand and treat the illness (Constable et al., 2018).

2. ANTIGENIC TOXINS

Bacteria and, to a lesser extent, helminths create these. Both pathogen groups function as antigens, promoting the production of antibodies. Exotoxins and endotoxins are two categories of antigenic toxins (Dellinger et al., 2008).

[1] Öğr. Gör. Dr. Ege University Faculty of Agriculture, Department of Animal Science, Bornova-İzmir, ORCID: 0000-0001-6536-5594

3. EXOTOXINS

These are bacterially generated proteins that permeate the surrounding medium. Both their pharmacologic actions and the antibodies they elicit are particular. Commercial antitoxins are available for the significant bacterial exotoxins produced by Clostridium species (Dunkel and Corley, 2015). They can be created in high quantities by excessive intestinal growth (like in enterotoxemia) or by tissue growth or consumed preformed (like in botulism).

4. ENTEROTOXINS

These are exotoxins that primarily affect intestinal mucosa, disrupting fluid and electrolyte balance. The most prominent example is the enterotoxin secreted by enterotoxigenic E. coli, which produces a hypersecretory diarrhea in neonatal farm animals (Lewis et al., 2012).

5. ENDOTOXINS

One of the main causes of morbidity and death in farm animals is the endotoxins of several gram-negative bacterial species. The lipopolysaccharides called endotoxins are present in the bacterial outer wall (Moore and Vandenplas, 2014). When bacteria proliferate quickly and produce unused portions of their cell walls, or more frequently, when the bacterial cell wall ruptures, endotoxins are discharged into the immediate environment (Osterbur et al.,2014). When there is a severe localized infection, like coliform mastitis in dairy cattle, or a disseminated infection, such coliform septicemia in newborn calves, endotoxin can enter the bloodstream (Patel and Balk, 2012).

The digestive tract contains endotoxins and gram-negative bacteria as part of its natural microbiota. Unless the intestinal mucosa is damaged, as in enteritis or, more specifically, acute intestinal blockage, endotoxins are typically not absorbed through it (Russell, 2006). The liver normally detoxifies modest amounts of endotoxins that enter the bloodstream, but endo-toxemia can occur if hepatic function is compromised or if the toxin levels are high.

Endotoxemia is the most prevalent type of toxemia in large animals, particularly sheep. It has frequently been said that the evolution of endotoxemia plays a significant role in the etiology of several clinical disorders. The literal definition of endotoxemia is the presence of endotoxin in the blood. In clinical contexts, the phrase refers solely to the presence of clinical symptoms that are usually brought on by circulating endotoxins. Infections with gram-negative bacteria are somewhat prevalent in domestic ruminants. According to Foley and Schlafer (1994), they can result in an endotoxemia with a range of systemic symptoms, such as fever, tachycardia, and respiratory distress. Gram-negative bacteria's cell membranes contain a lipopolysaccharide (LPS), which is a significant pathogen and a strong stimulator of the immunological and inflammatory systems, including endothelial cells, macrophages, and monocytes. It plays a part in the systemic alterations that endotoxic shock causes (Barton, 2000). Systemic inflammation, various organ damage, circulatory collapse, disturbance of normal homeostasis, and death are characteristics of the systemic alterations.

When endotoxins (lipopolysaccharide [LPS]) are present, the host's defensive mechanisms are widely activated, resulting in endotoxemia, a clinical systemic state linked to Gram-negative sepsis (Radostits et al., 2006). According to Daudel et al. (2006), endotoxins from a number of Gram-negative bacterial species are

a leading cause of sickness and death in agricultural animals, particularly sheep, in veterinary treatment (Cullor, 1992). Although the precise number of financial losses resulting from endotoxemia is unknown, toxemia-related illnesses such inflammatory disorders (pneumonia, pleuritis, enteritis, pericarditis, etc.) are prevalent and result in significant cost losses. E. coli, which produces coliform septicemia in newborn farm animals and has been widely utilized as a model for experimental endotoxemia, is the standard known source of endotoxins.

Gram-negative bacteria's outer cell wall layer contains lipopolysaccharide (LPS), also referred to as endotoxin, which is a strong inflammatory agent that causes a variety of specific and non-specific inflammatory responses in mammals (Radostits et al., 2006). Endotoxaemia has been used as a model to assess the inflammatory responses in both humans and animals since it is an inflammatory condition that indicates the presence of LPS in the blood.

Ovine models have been utilized to investigate the therapeutic features of endotoxaemia for the past few decades, with the re-outcomes that are used and extrapolated to other large animals. Numerous models of ovine endotoxemia have been established and developed thus far, and different facets of this condition have been assessed. There are two main types of these models: the first involves the exogenous administration of live organisms or their LPSs (Chalmeh et al., 2013), and the second involves the release of the endogenous microbial flora into the bloodstream through procedures like caecal ligation and puncture, which is also a model of peritonitis (Fink, 2014). However, injecting varying dosages of live Gram-negative bacteria or a component of their cell wall is the most common method for inducing endotoxaemia.

Numerous animal models and human subjects have been used in endotoxemia research. In previous studies, small laboratory animals like mice and rabbits have been used to study the immunological consequences of endotoxaemia, larger animals like sheep have been the subject of hemodynamic and cardiovascular studies (Chalmeh et al., 2013) Recent research, however, indicates that ovine endotoxaemia is a reliable model for evaluating the impact of endotoxaemia on many aspects of treatment.

Numerous therapeutic approaches have been developed in recent years to treat and prevent endotoxemia. Antibiotic use to manage the infection and critical care assistance to address the underlying issues in the respiratory, circulatory, and other organ systems are recommended for endotoxemia. Only a small number of these treatments, nevertheless, have been shown to be successful (Radostits et al., 2006). One of the ways utilized for the treatment of endotoxemia is inactivation of LPS, which can be attained via neutralization of endotoxin. This objective can be accomplished by administering polymyxin, a bactericidal antibiotic that is a member of the class of peptide antibiotics that have been shown to selectively target Lipid A, the active component of LPS (Wynn et al., 2010).

6. METABOLIC TOXINS

These can build up as a result of either abnormal metabolism or incomplete removal of harmful substances that are typically created by bodily metabolism (Lewis et al., 2012).

7. PATHOGENESIS OF ENDOTOXEMIA

Endotoxemia affects nearly every bodily system and causes a remarkable range of pathophysiologic outcomes. The

endotoxins that E. coli produces are the most well-known among all the bacteria that create them (Dellinger et al., 2008). Small amounts of endotoxins are absorbed into the portal circulation, despite the intestinal mucosa's highly effective barrier preventing endotoxins from moving transmural. Endotoxins are typically found in the intestine. The amount of endotoxins in plasma rises with hepatic failure. When the mucosal barrier is compromised by intestinal ischemia, trauma, ionizing radiation, bacterial overgrowth, decreased luminal pH, or inflammatory intestinal illness, much higher amounts of endotoxins are released from the intestine (Lewis et al., 2012). These disorders not only momentarily impair the liver's ability to eliminate endotoxins from the portal circulation, but they also permit endotoxins to travel transmural into the peritoneal cavity, from where they enter the peripheral circulation.

When gram-negative bacteria get into tissues and/or blood, endotoxemia can also happen. The majority of these organisms obtain blood from primary foci of systemic or superficial tissue infections and release endotoxins during rapid growth (Osterbur et al.,2014). Coliform septicemia in neonatal farm animals is one instance. The mononuclear phagocyte system eliminates the endotoxins from circulation once they enter the bloodstream, and the phagocytes' reaction to the lipopolysaccharides determines how severe the clinical sickness is (Dunkel and Corley, 2015).

Instead of having a direct toxic effect on host cells, endotoxins cause a variety of host cells, such as smooth muscle and endothelial cells, polymorphonuclear granulocytes, platelets, thrombocytes, and monocyte/macrophage cells, to produce soluble and cell-bound mediators (Osterbur et al.,2014). Cytokines, platelet-activating factor, prosta- glandins, leukotrienes, proteinases, toxic oxygen metabolites, and vasoactive amines are among the phlogistic biochemical

mediators released by these cells. The lipopolysaccharide causes macrophages to become highly activated for improved phagocytic, cidal, and secretory activities. Numerous pathophysiologic effects of endotoxemia are caused by the cytokines produced by macrophages (Dellinger et al., 2008). In large animals, pulmonary intravascular macrophages are the primary source of cytokines. Animals have developed the ability to identify and react to gram-negative bacteria's lipopolysaccharide. Many of the impacts of lipopolysaccharides are indirectly mediated through incorrect activation of host defense mechanisms, leading to numerous organ failure and dysfunction, even though they may cause direct harm to the host tissue (Dunkel and Corley, 2015). Importantly, several drugs can reduce the reaction to endotoxins. Detergents, including a nonionic surfactant, have been shown in experiments to reduce the endotoxin-induced reaction in horses. The response to endotoxin administration varies greatly from person to person. Although a large portion of the variability is yet unknown, it seems to have a genetic component.

Thrombane A2 and prostacyclin, two metabolites of arachidonic acid, have higher plasma concentrations in a number of species during endotoxemia. These eicosanoids are most likely the origin of the hemodynamic abnormalities brought on by endotoxins. Phospholipase A2, a cell-membrane enzyme, is activated by endotoxins, which start biological processes (Dellinger et al., 2008). When this enzyme is activated, membrane-bound phospholipids are hydrolyzed, releasing arachidonic acid from the phospholipid component of damaged mammalian cell membranes. Arachidonic acid is transformed by the enzyme cyclooxygenase into intermediate endoperoxides, which serve as substrates for specific synthetases to create prostacyclin, thromboxane, and prostaglandins (Lewis et al., 2012). The main source of thromboxane, a strong vasoconstrictor

that promotes platelet aggregation, is platelets. Vascular endothelial cells produce the majority of prostacyclins, which dilate blood vessels and prevent platelets from clumping together. Shock, disseminated coagulopathy, and multisystemic organ dysfunction may all be caused by the widespread endotoxin-induced production of cyclooxygenase products.

Early in the course of endotoxemia, macrophages and monocytes release tumor necrosis factor-a in a dose-dependent manner, and the activity of TNF-α in the blood is correlated with the severity and prognosis of the disease (Osterbur et al.,2014).

8. SUDDEN DEATH

Depending on the agricultural system type and individual approach, different definitions of sudden death (SD) in ruminants exist. Animals in intense industrial systems, such feedlots and dairy herds, are constantly monitored, allowing for the quick identification of even acute illnesses (Irandoust et al., 2013). Routine herd controls, however, are irregular and rare in extensive sedentary and transhumance systems, which leads to animals being discovered dead after a protracted period of illness. This illness may involve sub-acute or even chronic disorders that ultimately end in the perception of SD. Different writers have different definitions of SD syndrome; some include cases of animals who had more or less visible clinical indications prior to death (Benchohra et al., 2024), while others simply take into account the sudden death of an animal that appeared to be in good health (Andersen, 2003). Studies of bovine-ovine pathology reveal that the most prevalent causes of SD are acute viral infections, digestive abnormalities, and nutritional inadequacies, however a few of cases of SD have been related to lethal poisonings, accidents, and particular parasite agents.

8.1. Reasons For Unexpected Deaths in Ruminants

8.1.1. Infectious Etiologies

Originally, illnesses brought on by specific strains of Clostridium perfringens were referred to as "enterotoxemia" (Simpson et al., 2018). Acute or peracute enterotoxemia is a known cause of SD in animals that were previously thought to be in excellent condition (Lebrun et al., 2010). According to recent studies, the deadly toxins produced by C. perfringens toxinotypes A, B, C, D, and E can cause SD in ruminants (Redondo et al., 2013; Simpson et al., 2018). Clostridia pathogen strains induce syndromes that can be classified as enteric, neurotoxic, and histotoxic (Santos et al., 2019). However, a single condition or a confluence of multiple symptoms can cause animals to die from enterotoxemia (Simpson et al., 2018).

The systemic spread of toxins in blood and tissues causes toxicityemia, which can result in hepatic necrosis, cardiac consequences, intravascular hemolysis, and capillary damage (Uzal and Songer, 2008). Moreover, SD syndrome in sheep and cattle is caused by a number of other strains of the histotoxic Clostridium genus (Abbott, 2018). While toxemia happens when the toxins reach the bloodstream and cause shock and death, infections with histotoxic clostridia happen when wounds are infected with spores or vegetative forms (Junior et al., 2020). Clostridial enterotoxemia is suggested by SD with severe hemorrhagic jejunitis and hemorrhagic intestinal contents seen during postmortem examination. Furthermore, clostridial enterotoxemia is characterized by the rapid putrefaction of the abdominal viscera, which results in gas and a foul odor (Lebrun et al., 2010). However, the precise diagnosis of clostridial SD depends on clinical, necropsy, epidemiological, and histological data (Santos et al., 2019).

In sheep and goats, Histophilus species have also been linked to respiratory illnesses; in most cases, Histophilus somni pneumonia manifests as death. According to Underwood et al., (2015), thromboembolic meningoencephalitis and septicemia can both be fatal. Furthermore, in severe situations, SD has been linked to the acute form of bovine respiratory syncytial virus (BRSV) infection (Scott et al., 2011). Within 18 hours of the infection course, bovine herpesvirus 5 (BoHV-5) is commonly linked to neurological disorders and SD in young calves (Lunardi et al., 2009). High mortality rates have been reported in goat herds due to Mycoplasma mycoides subspecies capri or Mycoplasma mycoides subspecies mycoides (Debien et al., 2013).

The most common cause of SD is acute pneumonia, namely shipping fever complex. All ruminants can contract pasteurellosis, a bacterial disease marked by bronchopneumonia, septicemia, and SD, from two common pathogens: Pasteurella multocida and Mannheimia haemolytica (Underwood et al., 2015). Previously known as Pasteurella haemolytica A1, Mannheimia haemolytica is specifically linked to SD in sheep (Gilmour, 1980) and can also cause septicemia in infants and young lambs (Brogden et al., 1998). Furthermore, Bibersteinia trehalosi-induced acute pneumonia in cattle has been linked to significant death rates (Cortese et al. 2012).

Splenic fever and anthrax are caused by Bacillus anthracis. When Bacillus anthracis spores infect plant or soil, sudden unexplained mortality most frequently occurs in grazing herbivores (Rao et al., 2019). A few cases of ataxic terminal septicemia are observed in affected animals, along with nasal, oral, and anal or vulva bleeding (dark blood) (Abbott, 2018). Cowdria ruminantium is the causative agent of heartwater (cowdriosis), one of the most significant tick-borne illnesses affecting domestic ruminants in southern Africa (Van de Pypekamp and Prozesky 1987). The primary indication of

fulminating fever in an otherwise healthy animal is paroxysmal convulsions, respiratory problems, and quick collapse; however, it is sometimes lethal, and both sheep and goats may die unexpectedly.

Anaphylactic shock and SD appear to be caused by coliforms (Andersen, 2003). Cattle, goats, and lambs can all have coliform septicemia, which can cause SD in lambs younger than ten days. Cow deaths can occasionally result from peracute toxic coliform mastitis, which happens during the peripartum or early lactation period. Disseminated intravascular coagulation (DIC) is probably the cause of many endotoxic mastitis-related deaths. Toxemia linked to specific infections, particularly E. coli, is a significant cause of SD in neonates. The most frequent cause of bacterial infections that impact the central nervous system is Listeria monocytogenes. Neonatal listeriosis can cause SD in 2- to 4-day-old calves, and goats seem to be more susceptible to this infection than cattle or sheep (Rao et al., 2019).

Bovine herpesvirus 6 (BoHV-6) is the causative agent of malignant catarrhal fever, a serious illness that mostly affects cattle that can result in SD (Underwood et al., 2015). An RNA Picornavirus of the genus Aphthovirus causes foot-and-mouth disease (FMD), a highly contagious illness that is challenging to identify in sheep because of its subacute form. The virus can cause SD in relatively young animals by infecting the myocardium (Ryan et al., 2008).

A high rate of case fatalities when endotoxic big animals exhibit clinical indications of septic shock (severe sepsis with hypotension despite vigorous intravenous fluid therapy), current treatment strategies are only moderately effective (Andersen, 2003).

Gram-negative bacteria, including Salmonella spp., E. coli, Pasteurella spp., and H. somni, are responsible for a number

of bovine illnesses, including endotoxemia (Gilmour, 1980). Mastitis, peritonitis, pneumonia and pleuritis, pericarditis, septic metritis, neonatal septicemia, myositis, meningoencephalitis, and some enteritides are among the conditions that cause toxemia in varying degrees of severity. In some animals with gastrointestinal disorders, endotoxemia is also one of the most frequent causes of mortality due to a physical blockage that results in ischemic necrosis and strangling (Junior et al., 2020).

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THE FcR RECEPTOR'S ROLE IN CALVES' PASSIVE IMMUNITY

Fatma ATLI[1]

Sezgin ŞENTÜRK[2]

1. INTRODUCTION

The immune system is vital to life and shields animals from microbial invasion. Although fetal calves can react to foreign invaders early in pregnancy, the placenta and the mother's immune system offer the fetal calf extra protection. According to Lemley et al., (2021), the ruminant placenta is characterized as cotyledonary morphologically and as syndesmochorial histologically. The cow's syndesmochorial placenta separates the fetal and maternal blood supply by forming a syncytium between the fetal trophectoderm and the maternal endometrium (Arthur, 1996). Immunoglobulin transmission in utero is prevented by this division of the mother's and fetus' blood supply (Gaspers, 2018). Calves that are born agammaglobulinemic—that is, with little to no immunoglobulins in circulation—are referred to as immuno-naïve because the transfer of immunoglobulins during pregnancy is prevented (Weaver et al., 2000). Despite being immuno-naïve while still in utero, the fetus's diverse innate and adaptive immune defenses develop as well (Barrington and Parish, 2001). The calf can react to a range of antigens by the time parturition occurs and

[1] Öğr. Gör. Dr. Ege University Faculty of Agriculture, Department of Animal Science, Bornova-İzmir, ORCID: 0000-0001-6536-5594.

[2] Prof. Dr. Bursa Uludag University Faculty of Veterinary, Depertment of Internal Medicine, Nilüfer-Bursa, ORCID: 0000-0002-2465-9913.

it is born, but not as fully as when it is fully developed (Gaspers, 2018).

The first month of birth is the most crucial time for raising dairy heifers because of the increased risk of diseases and mortality (Svensson et al., 2006). Calves primarily experience gastrointestinal illnesses during this time due to infectious pathogens such as Cryptosporidium parvum, rotavirus, coronavirus, and Escherichia coli (McGuirk, 2008). According to Curtis et al. (1988), and van der Fels-Klerx et al. (2002), calves that survive diarrhea typically exhibit slower growth rates and are more prone to other illnesses, particularly bovine respiratory disease complex, which may have long-term detrimental effects on their performance during the first lactation. There are no established defenses against illnesses in newborn calves. Due to the large size of cow antibodies and the placental structure (syndesmochorial placenta), which prevents antibodies from being transferred from mother to fetus, calves are born with low levels of immunoglobulin and are not protected against disease agents until they are given enough colostrum. Passive immunity is the type of immunity that develops when a calf consumes colostrum (Fischer-Tlustos et al., 2021).

Passive immunity ends when maternal antibodies are destroyed, which takes 3-4 weeks (Lora et al., 2018).

One of the key elements influencing colostrum management is calf health and survival because calves are born almost without antibodies (Godden, 2008). Calf serum immunoglobulin concentrations, which indicate the success of colostral transfer, have been demonstrated to be an important indicator of preweaning morbidity and mortality. According to Perino et al., (1997), calves with low blood IgG concentrations (less than 8 mg/ml) 24 hours after delivery have a 3.2–9.5 times

higher risk of getting sick and a 5.4 times higher risk of dying before weaning.

Bovine rotaviruses (BRV) and bovine coronaviruses (BCV) cause diarrhea-characterized infections in newborns and usually subclinical infections in adult cattle (Vega and Parreño, 2014). Seroepidemiological studies (Burgu, 1995; Duman and Aycan, 2010) have shown that subclinical infection rates with these agents are quite high in adult cattle and therefore adult cattle have varying levels of immunity. Cattle carrying BRV and BCV-specific antibodies play a crucial part in shielding the infant from infection with the antibodies they transfer to their calves through colostrum and milk (Şentürk, 2018). The antibody titer transferred to calves born from naturally infected mothers varies according to elements like the time of infection of the mother, the level of antigenic stimulation, etc. It is also known that serum antibody levels are generally not very high in naturally infected adult cattle and therefore the antibodies transferred to the newborn calf through milk and colostrum are often insufficient to protect the newborn from infection (Neto et al., 2004).

The percentage of live-born calves raised to puberty effectively determines how profitable a dairy business can be. Despite significant progress in animal breeding, perinatal mortality rates are still high, especially on Holstein dairy farms, and vary from 2.4% to 9.7%. To reduce this gap, a number of rearing stage-related factors are being investigated (Gulliksen et al., 2009).

There are various techniques for the buildup of proteins and immune cells to infiltrate the cow mammary gland. Although the mammary epithelium itself does not synthesis immunoglobulins, the cow mammary gland actively controls the content of different immunoglobulins in colostrum, mostly IgG and to a lesser extent IgA (Stelwagen et al., 2009). According to

Stelwagen et al. (2009), the vast majority of immunoglobulins enter cells via a selective receptor-mediated pathway. Mayer et al. (2005) shown that the mammary epithelial cell (MEC) contains a particular IgG receptor called neonatal Fc receptor (FcRN), which is involved in the active transport of IgG into the lactating cow mammary gland. Intramammary plasma cells produce the IgA present in bovine colostrum (Gaspers, 2018). These immunoglobulins can be made in situ by intramammary plasma cells or obtained from blood. Chemokines facilitate the movement of these plasma cells through the circulation to the mammary gland (Wilson and Butcher, 2004). The receptor for polymeric immunoglobulin (pIgR), which is expressed in the mucosal epithelium, facilitates the passage of IgA across the MEC. IgA and a secretory component of pIgR are released into the alveolar lumen when pIgR is cleaved on the uppermost portion of the MEC (Apodaca et al., 1994).

This article summarizes the current understanding of the metabolism of FcR in passive immunity in newborn calves and highlights the components that require additional investigation to gain a deeper comprehension of how this system functions in these species and to benefit economically from it.

2. THE IMPORTANCE OF PASSIVE IMMUNITY IN NEWBORN CALVES

The transmission of passive immunity (TPI) through colostrum is one of these elements, which is crucial for the newborn calves' survival and well-being (Parreño et al., 2010). The immunoglobulin (Ig) concentration of the colostrum, the time of postpartum colostrum harvesting, the time between parturition and first ingestion, the volume given, the mode of administration, and bacterial contamination are some of the variables that can affect the effectiveness of TPI (Rodas et al., 2025). These

variables may also contribute to the failure of passive immunity transfer (FTPI) (Cordle et al., 1991).

When a newborn does not absorb enough immunoglobulins, FTPI happens (Şentürk, 2018). In addition to higher rates of morbidity and mortality, this syndrome has been linked to delayed puberty, lower weaning weights, and slower development rates (Guilloteau et al., 2009). IgG concentration is the main determinant of the quality of colostrum, which is a rich source of immunoglobulins and nutrients (Rodas et al., 2025). IgG concentration can be measured directly to evaluate this quality, or Brix values can be used indirectly by refractometry. High-quality colostrum has more than 50 mg/mL of IgG, or a reading above 21%; low-quality colostrum has fewer than 30 mg/mL of IgG, or a level below 20% (Yamanaka et al., 2003).

Newborns receive vital protection from the passive transfer of the mother's immunity. It is also known, though, that neonates are first exposed to an extensive array of antigens after birth (Silva et al., 2017). Neonates are therefore more likely to die following infection with common pathogens unless sufficient maternal immune support is given. Thus, maternal immunologic support can be a vital component of a newborn's survival (Parreño et al., 2010).

In order to protect the body from dangerous infections, the immune system has developed extremely intricate recognition, reaction, elimination, and memory pathways (Guilloteau et al., 2009). Heightened susceptibility to infectious illnesses, together with a rise in morbidity and mortality from them, might occur from a breakdown in these pathways or from their ineffective operation (Barrington & Parish, 2001). Additionally, the immune system works to guarantee tolerance to commensal bacteria, food, and additional environmental elements, in addition to "self." Inflammatory disorders may potentially arise from a malfunction

in the tolerogenic pathways. But tolerance is an ongoing process that starts at a very young age, even during pregnancy (Battersby & Gibbons, 2013).

Newborns are vitally shielded by maternal immunity's passive transmission. Newborn animals must distinguish between food antigens and pathogens in a hostile microbial environment, even if their immune systems are fully capable of developing primary immune responses against infection in mammals and birds (Bailey et al., 2005). This is important throughout this formative period of life in addition to throughout adulthood since the response patterns that are "learned" during this time remain relevant (van Keulen et al., 2021). The "antigenic immaturity" of the newborn immune system is caused by the antigenic inexperience and the predominance of suppression factors throughout fetal development. This happens under the "protective umbrella" of passive maternal antibodies and immune cells transferred from mother to child by various processes depending on the species because developing a primary immune response takes time and effort (Barrington & Parish, 2001).

Newborns are initially exposed to an extensive array of antigens after birth. Commensal microbiota acquired after birth aids in gut homeostasis establishment, immune system maturation, and modulation. The young animal experiences two crucial times when it is most exposed to novel antigens: right after birth and during weaning. In both situations, a new diet and the colonization of new bacterial strains and species can result in a significant shift in the antigenic makeup of the intestinal contents (Bailey et al., 2005). Several major immune responses may not be triggered quickly or powerfully enough to stop pathogen proliferation in response to certain antigens, which frequently result in mixed infections and consequences.

3. THE ROLE OF COLOSTRUM IMMUNOGLOBULINS IN IMMUNITY IN CALVES

Neonatal survival is significantly (although temporarily) aided by maternal immune support. Effective methods to ensure the passive transfer of mucosal and systemic immunity from the mother to her offsprings have been created through evolution. As previously stated, it should be understood that in order to prevent unwanted, excessive, and destructive inflammatory and allergic reactions, it is necessary to prevent the immunological response from being triggered against common environmental antigens that are harmless, such as food antigens and specific commensals (bacteria) (M‟Rabet et al., 2008). Consequently, the prevention of sickness and the development of healthy animals depend on the effective absorption of colostrum.

Colostrum contains a range of cells and immunomodulatory and antimicrobial components, such as antibodies (Chatthaa et al., 2013). The mammary gland uses an Fc-receptor-dependent process to concentrate maternal immunoglobulins from the mother's blood into colostrum. Colostrum contains lymphocytes from the common mucosal immune system that move to the gland of the breast (Salmon et al., 2009).

Fetuses of polygastric and monogastric ungulates (ruminants, horses, and pigs) belonging to the order Artiodactyla are born nearly agammaglobulinemic and acquire little to no maternal antibodies via the placenta (Nguyen et al., 2007). These newborns' intestines can transmit immunoglobulins and other macromolecules into the bloodstream through a non-specific route when they consume colostrum. After birth, this process lasts for a short duration, typically 24 to 36 hours. Immunoglobulins only work locally if the intestine undergoes a severe alteration

known as gut closure, which stops them from being absorbed from the intestines (Barrington & Parish, 2001).

Colostrum immunoglobulins are absorbed by pinocytosis, which transports them through the enterocytes. All kinds of immunoglobulins, along with other proteins and macromolecules, appear to be non-discriminately permeable to the enterocytes of newborn calves (Mayer et al., 2002)). Immunoglobulins enter the thoracic duct and the systemic circulation after passing through the glycocalyx on the enterocyte's apical membrane and into their exocytosis into the basolateral membrane the lacteals and intestinal capillaries. (Tizard, 2013). The fact that other protein macromolecule quantities and enzyme activities, including γ-glutamyltransferase (GGT), increase following colostrum intake has been used to support the non-selectivity of this process (Thompson and Pauli, 1981). But Goldstein et al. (1979) found clathrin molecules on the enterocytic microvilli in the calf's ileum and jejunum close to the IgG molecules, which could be proof of a receptor-mediated transport mechanism. The existence of coated pits in vesicles is implied by the presence of clathrin molecules. Additionally, Mayer et al. (2002) discovered that the apical side of enterocytes contains the FcRN transporter protein in neonatal ruminants. Similarly, IgG is transported into the lactating cow mammary gland by the particular IgG receptor FcRN in the MEC (Mayer et al., 2005). Whole leukocytes are shown to pass from the intestinal lumen through the enterocyte and into circulation by Reber et al. (2006). They showed that colostrum contains the cytokines Cd43 and Cd11, which are essential for leukocyte transendothelial migration and aid in the migration through the enterocyte and into the newborn circulation.

Immunoglobulins (Igs) in a particular immune response are released after vaccination or infection. Because they neutralize or eradicate the infection and its harmful byproducts,

they are protective. IgG, IgA, and IgM class antibodies are the most prevalent kinds present in the sera of immunological competent donors. Serum contains very little amounts of together, IgD and IgE make up less than 1% of serum immunoglobulin. The most prevalent isotype in blood and extravascular space, IgG is essential for mediating immunity, despite IgA being the primary antibody linked to the gut (Waldmann and Strober, 1969). The fact that IgG has a lengthy half-life in the bloodstream and that maternal immunity depends on IgG transfer from mother to infant or neonate emphasizes the significance of this isotype.

There are species-specific variations in how humoral immunity is acquired in animals through the transmission of IgG from mother to child. In rodents, maternal IgG is transferred from milk to the fetus postnatally through the neonatal small intestine, while in primates and rabbits, all maternal IgG is transferred through the placenta during fetal life (Ober et al., 2004). IgG and all other macromolecules are obtained from colostrum in ungulates twelve to eighteen hours after birth (Butler and Kehrli, 2005). Despite the fact that maternal immune transport varies in mammals, plasma cells must continuously secrete IgG and shield it from rapid removal in order to maintain a consistent serum IgG level. The longest-surviving of all plasma proteins, IgG was protected against quick breakdown by the existence of a comparable or identical receptor, was deduced by Brambell in 1958 after he described a hypothetical saturable receptor system involved in the maternal IgG transport (Brambell et al., 1958). It was eventually demonstrated that the Brambell receptor (FcRB) mediates both IgG's defense against catabolism and the transmission of IgG during antenatal and/or neonatal periods, where it is expressed as FcRn (neonatal Fc receptor) (Roopenian and Akilesh, 2007). The idea that FcRn also binds albumin and extends the half-lives of these two crucial serum proteins by preventing them from being broken down intracellularly by

endothelial cells is supported by recent results (Anderson et al., 2006).

IgG is the most common immunoglobulin isotype in the blood and extravascular space in animals. It is the primary immunoglobulin isotype that is passed from the mother to her offsprings and plays an important part in mediating immunity (Waldmann & Strober, 1969). In actuality, active IgG transfer from mother to baby or neonate is necessary for maternal passive immunity to a number of pathogenic pathogens (Baintner, 2007).

4. THE NEONATAL Fc RECEPTOR, OR FcRn

The receptor that transmits maternal immunoglobulins from mother to offspring through the neonatal intestine is called FcRn, and it was initially discovered in rodents (Rodewald, 1976). The intestinal brush border's FcRn molecules bind ingested IgGs from the mother's milk and move them through enterocytes to the newborn's systemic circulation (Rodewald and Kraehenbuhl, 1984). According to Simister and Mostov (1989), the functional a heterodimer is the expression of the molecule made up of two subunits: the beta 2-microglobulin (β2m) and an integral membrane α-chain that is similar to molecules of MHC class I.

Contact residues in the IgG Fc component's CH2 and CH3 domains, the α1 and α2 domains of FcRn, and a single contact site in β2m, are necessary for IgG to bind to FcRn (Vaughn et al., 1997). This pH-dependent mechanism exhibits poor or no binding when the pH is neutral (pH > 7.0). and high-affinity binding at pH ≤ 6.5, which is an acidic pH (Vaughn and Bjorkman, 1998). In certain internal vesicles (like early endosomes) and in certain situations on the cell surface (like duodenal enterocytes), this pH specificity guarantees precise binding.

The receptors for B cells (BCR), T cells (TCR), and Fc cells (FcR) are among the receptors that immune system cells use to recognize antigens. FcR recognizes the Fc component of antibodies rather than antigens. Despite this, antibody-FcR complexes act as membrane receptors for antigen without any preset specificity (Daëron, 1997). Antibodies do give antigen specificity to a range of cells, the majority of which lack antigen recognition structures, when they bind to FcR. Under the right circumstances, many FcR use antigen receptors and the same transduction pathways to initiate cell responses, and they share activation patterns with BCR and TCR. Additionally, FcR possesses biological characteristics that antigen receptors do not (Vaughn et al., 1997).

All antibody classes have FcR: FcγR binds IgG, FcαR binds IgA, FcϵR binds IgE, FcμR binds IgM, and FcδR binds IgD (Raghavan and Bjorkman, 1996). Using immunoglobulins and receptors altered by site-directed mutagenesis, relationships between the Fc and FcR component of antibodies have been thoroughly studied. Both membrane receptors and soluble molecules are produced by proteolysis of membrane receptors or alternative splicing of FcR transcripts. Soluble FcR can exhibit a variety of biological functions and maintain its affinity for immunoglobulins (Daëron, 1997).

The Fc region of immunoglobulins is bound by cell surface molecules called FcRs. Every member of the family may identify one possibly a few isotypes of the same immunoglobulin. There are two functional classes into which FcRs can be divided. When antibody–antigen complexes bind to a particular class of receptors on the exterior of effector cells, several biological reactions are triggered. Fcγ receptors for IgG (FcγRI, FcγRII, FcγRIII, and the bovine Fcγ2R), Fcε receptors for IgE (FcεRI, FcεRII), and Fcα receptors for IgA (FcαRI) are some examples of these. Immunoglobulins are transported across epithelial surfaces

by the other receptor classes, which include neonatal IgG transporter (FcRn) and poly IgA receptor (pIgR) (Kacskovics, 2004).

The majority of livestock species have antibody-dependent maternal immunity, which is primarily characterized in ruminants and solely mediated by colostral immunoglobulins. According to Kacskovics et al., (2000), the presence of bovine FcRn transcripts in several organs, including the mammary gland, indicates their role in IgG transcytosis. Actually, transcytosis within clathrin-coated vesicles is how FcRn mediates active transport within cells. According to Raghavan et al., (1995), the transport is bidirectional and pH-dependent, exhibiting high-affinity binding occurs at acidic pH (pH: 6.5) and weak or nonexistent binding occurs at neutral pH (pH: 7.0). This pH specificity guarantees appropriate release in bloodstream circulation (pH: 7.4) as well as specific binding in endosomes and on specific cell types' surfaces (duodenal enterocytes, placental tissue).

FcRn transports IgG from the cell surface to the recycling endosome, and exocytosis can happen via two different pathways, according to a recent study that described in full how FcRn recycles in real time from the endosome to the cell surface: i) whether the vesicle holding the FcRn fully fuses with the plasma membrane and transports the FcRn to the cell surface, as shown by traditional models of membrane receptor exocytosis. (Ober et al., 2004). ii) Kiss-and-run exocytosis, in which the secretory vesicle is structurally intact and only partially fuses with the plasma membrane in repeated cycles. Despite this, it is still possible for FcRn to leave the vesicle and combine with other cell-surface elements. (Baintner, 2007).

In ruminants, such as horses and pigs, the maternal immune transport is only mediated via colostral intake in the brief

postnatal period due to the ungulate placenta's complicated shape and lack of FcRn expression. Antibody transmission from the mother to the offspring in these species is also a dual process of immunoglobulins´ active transport: i) a receptor-mediated process that enriches the mother's lactogenic secretion with isotype-specific immunoglobulins, ii) a non-selective process that absorbs these immunoglobulins by the neonate, and iii) a receptor-mediated process that recycles IgG back into the intestine (Cervenak and Kacskovics, 2009).

5. WHAT EFFECT DOES FcR HAVE ON CELLS' REACTİON TO IMMUNE COMPLEXES?

Many studies have been conducted in recent years on how FcR causes cells to react to immune complexes and what influences the specificity of cellular responses. Research on FcR gradually expanded into cells, revealing links to additional transduction pathways (Ober et al., 2004). Experiments on in vitro reconstitution also produced important advancements. Last but not least, genetically altered mice with an inactivated FcR gene have enabled evaluation of the in vivo significance of in vitro experiment findings. These can be separated into two main categories from a functional perspective: FcR that can activate cells and FcR that cannot. Intracytoplasmic activation motifs, which resemble the signal transduction components of the BCR and TCR, are present in FcR that can activate cells (Baintner, 2007).

These motifs are now known as tyrosine-based activation motifs of immunoreceptors (ITAMs) and are made up of a twice-repeated YxxL sequence that surrounds seven variable residues. There are two kinds of FcR with ITAMs (Kacskovics, 2004). The majority of FcR are of the first type, which are multichain receptors made up of one or two intracytoplasmic signal

transduction subunits regions where ITAM are found, together with a ligand-binding FcRα subunit. The second kind of FcR consists of two human-specific, IgG receptors with single chains that are closely linked known as FcγRIIA and FcγRIIC. Between the two YxxL sequences, they have a single ITAM with 12 residues (rather than 7) (Daëron, 1997).

ITAM is absent from FcR that do not cause cell activation. They fall into two major types as well. The first class of FcR belongs to a group of IgG receptors with a single chain known as FcγRIIB. The intracytoplasmic domain of these receptors has a pattern that prevents cell activation by receptors that might cause cell activation (Nimmerjahn et al., 2005). One YxL sequence, known as the tyrosine-based inhibitory motif of immunoreceptors (ITIM), is present in this motif. The second class of FcR neither promotes nor prevents cell activation. They participate in IgG transcytosis via epithelia. They are the polymeric IgA and IgM receptor (pIgR) and the neonatal FcR for IgG (FcRn). FcγRIIIB, a human IgG receptor lacking ITAM, does not have the potential to trigger on its own but aids in cell signaling by joining forces with other FcR (Lee et al., 2007).

6. INTERACTION OF FcR WITH IMMUNOGLOBULINS

Immune defense is significantly influenced by immunoglobulin Fc domain receptors. Mammalian receptors fall into two distinct functional classes. Immunoglobulins are transported to their primary sites of action by one class of receptors through epithelial tissues (Monteiro and Van De Winkel, 2003). This class includes the neonatal Fc receptor (FcRn), which transports immunoglobulin G (IgG), and the polymeric immunoglobulin receptor (pIgR), which transports immunoglobulin A (IgA) and immunoglobulin M (IgM). When

antibody-antigen complexes attach to another type of receptors found on effector cell surfaces, other biological reactions are triggered. The most well-characterized of these are the immunoglobulin E (IgE) receptors (FcεR) and the IgG receptors (FcγR). The biological reactions that are triggered include phagocytosis, cell-mediated cytotoxicity that is dependent on antibodies, the release of inflammatory mediators, and the control of lymphocyte differentiation and proliferation (Ravetch and Bolland, 2001).

Two copies of the variable Fab region, which houses the antigen binding site, and the relatively constant Fc region, which interacts with effector molecules including Fc receptors (FcRs) and complement proteins, make up immunoglobulin (Ig) molecules (Lee et al., 2007). By (a) enabling the customized delivery of antibody molecules to the body's necessary locations, (b) creating the vital connection between effector responses and Igs' binding of antigens like inflammation and the control of antibody production, and (c) regulating the lifespan of Ig molecules in serum, the Fc domain of Ig molecules' receptors create vital components of immune defense (Monteiro and Van De Winkel, 2003).

7. FcRn'S FUNCTION IN RUMINANT COLOSTRUM IgG DEPOSITION

Livestock animals have a selective concentration of colostral IgG that is 10–40 times higher than plasma levels. Ruminants with specifically enriched IgG1 (colostrum contains 40–50 and roughly 3 mg/ml of IgG1 and IgG2, respectively, while their plasma concentration is nearly equal, i.e., about 9–11 mg/ml) and a significant decrease in maternal plasma IgG1 in the month before parturition have been the best candidates for this phenomenon (Chattha et al., 2013). Days after calving, this

transport stops parallel to the neonates' gut closure, resulting in milk IgG concentrations that are less than 1% of colostrum levels. It has previously been demonstrated that IgG1 preferentially binds to the mammary epithelial cells close to parturition (Barrington and Parish, 2001), and that these cells stain prepartum with anti-IgG1 serum. It has been hypothesized that FcRn could be involved in this process because to its selectivity and the fact that only it can transcytose IgG through epithelial cells (Lee et al., 2007).

According to Mayer et al. (2005), the FcRn is crucial for the transfer of IgG during colostrum synthesis in ruminants, as evidenced by the clear shift in distribution before and after parturition. The fact that distinct haplotypes of the bovine FcRn (bFcRn) genes—heavy chain and beta 2-microglobulin—were linked to the serum IgG level in newborn calves further supported this theory (Clawson et al., 2004). Whether FcRn mediates the transfer of IgG from plasma to milk or colostrum is still unknown, though. Recently, transgenic mice that overexpress bFcRn in their nursing mammary glands were developed in an effort to address this discrepancy. These animals' elevated serum and milk IgG levels indicate that the lactating mammary gland's over-expressed bFcRn contributes to IgG protection, extending the animal's longevity (Ravetch and Bolland, 2001). However, there was no discernible accumulation of either injected bovine IgG or endogenous mouse IgG in the transgenic animals' milk, indicating that over-expression of bFcRn causes IgG to remain in serum rather than accumulate in milk. In other words, bovine IgG1 binds weaker to the bFcRn and so gets easier to the colostrum, but IgG2 binds stronger to this receptor and is therefore recycled to circulation more efficiently. This finding validated the rodent model that was previously mentioned (Monteiro and Van De Winkel, 2003). It is noteworthy that ruminant IgG2's half-life is longer, which indicates a greater binding capacity to the FcRn.

However, we cannot rule out the possibility that the bovine FcRn does not function in mice in the same manner as it does in cows or that there is another, as-yet-undiscovered IgG1 receptor. particularly in a function that is known to be highly diverse between species (Cervenak and Kacskovics, 2009).

Among livestock animals, the majority of studies have focused on cattle this FcRn function to date. The half-life of exogenously injected human IgG was approximately 33 days in calves, which is roughly twice as long as its counterpart in cows. This implies that FcRn plays a role in maintaining cattle's IgG homeostasis. It was also demonstrated that bFcRn binds human IgG much stronger than it binds to bovine IgG (Kacskovics et al., 2004). In other transgenic models recently created, the function of the bFcRn in controlling the IgG half-life was also investigated (Clawson et al., 2004).

Consequently, more investigation is advised to clarify the ways in which FcR influences calves' immunological and metabolic responses. In order to determine the permanence of maternal effects over time, it is also advised that the components of the calf be examined later in life.

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AKADEMİK PERSPEKTİFTEN

VETERİNER İÇ HASTALIKLARI

yaz
yayınları

YAZ Yayınları
M.İhtisas OSB Mah. 4A Cad. No:3/3
İscehisar / AFYONKARAHİSAR
Tel : (0 531) 880 92 99
yazyayinlari@gmail.com • www.yazyayinlari.com