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A Review of Clinico-epidemiology Bovine Anaplasmosis

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Abstract. This paper aims to review the clinico-epidemiology of bovine anaplasmosis. Bovine anaplasmosis is a vector-borne disease affecting ruminants that can result in significant economic losses within the livestock industry, due to high morbidity and mortality rates in susceptible cattle. The modes of transmission of bovine anaplasmosis comprise mechanical (blood-contaminated fomites such as needles, ear tagging, horn cutting and castration equipment), biological (tick bites) and transplacental (from mother to foetus). Bovine anaplasmosis is prevalent in tropical and subtropical regions across the globe. All ages are at risk of *A. marginale* infection, with disease severity escalating with age. Common clinical signs of bovine anaplasmosis comprise fever, anorexia, rapid deterioration of body condition, a pronounced decline in milk production, pale mucosa and jaundice, an increased heart and respiratory rate, muscle weakness and depression. Diagnosis of bovine anaplasmosis using the blood smear method is limited to animals infected with *A. marginale* during the acute phase, and cannot detect infection in subclinical or carrier animals, necessitating serological examination of antibodies and confirmation of antigens by molecular detection methods. While oxytetracycline treatment is effective for acute cases, carrier animals do not respond to it. Control measures for bovine anaplasmosis differ depending on location and include various methods such as maintaining *Anaplasma*-free herds, controlling vectors, administering antibiotics and vaccination.

Keywords: *Anaplasma marginale*, bovine anaplasmosis, clinical sign, vectors.

I. INTRODUCTION

Anaplasmosis has a significant impact on animal health and productivity. Bovine Anaplasmosis remains a significant reason for economic loss in livestock industries in tropical and subtropical regions, including Asia, Africa, Australia, Southern Europe, and Central and South America [1]. On the other hand, admitting Anaplasma as a genus has recently become a public health concern. It has contributed to the growing interest in this bacterium, resulting in greater knowledge of molecular biology, genetics, and pathobiology [2].

Bovine Anaplasmosis is a blood-borne parasitic disease that affects cattle around the world. The disease is transmitted by ticks by the mechanical transfer of fresh blood from infected to susceptible cattle from biting flies or by blood-contaminated fomites, including needles, ear tagging, dehorning, and castration equipment. In some regions, the transplacental transmission of *Anaplasma marginale* may contribute to the epidemiology of bovine Anaplasmosis [3]-[5]. The disease can lead to severe anaemia, weight loss, and death in infected animals [6], [7].

Farmers should regularly inspect and deworm their cattle and use tick-control methods such as insecticides to prevent the spread of bovine Anaplasmosis. Vaccines are also available to help protect cattle against the disease. Vaccines and future research on these organisms must be considered in developing diagnostic assays [8]-[10]. Limited reviews are available in this perspective. The current review focuses on updated knowledge of the epidemiology ecology of bovine Anaplasmosis for effective prevention and control of Anaplasmosis in cattle.

II. EPIDEMIOLOGY

Description of the agent

The genus Anaplasma contains at least six species: *Anaplasma bovis*, *Anaplasma centrale*, *Anaplasma marginale*, *Anaplasma phagocytophilum*, *Anaplasma platys*, and *Anaplasma ovis* [11]. *Anaplasma* spp. are etiologic agents of veterinary disease affecting domestic ruminants, equines, dogs, and cats worldwide. In future, recently identified agents such as *Anaplasma capra* and *Anaplasma odocoilei* [1], [11], [12]. *Anaplasma phagocytophilum* is potentially a zoonotic disease infected human. Reports of human infections caused by other species, such as *A. platys*, *A. ovis*, and *A. capra*, suggest a broader medical relevance of this taxon [13]-[15].

Anaplasma exhibits a biological cycle involving infection of both invertebrate and vertebrate hosts. Ticks are regarded as primary vectors, with different cell types targeted by these agents in a replication cycle, including invasion of salivary glands and transmission in saliva released during blood feeding. Alternative transmission routes include mechanical transfer by other hematophagous arthropods or fomites, such as contaminated veterinary instruments, and transfusion-transmitted infections [3], [6]. *Anaplasma* spp.

display unique cell tropisms in vertebrate hosts; depending on the species, different hematopoietic lineage cells are specifically infected (erythrocytes, monocytes/macrophages, granulocytes, or platelets) [17]-[19]. The most important biological, ecological, and epidemiological features of *Anaplasma* spp. are shown in Table 1.

Table 1. The main host, disease, and characteristic of *Anaplasma* spp.

Agent	Disease	Host calls	Vector	Main host
Anaplasma marginale	Bovine Anaplasmosis	Erythrocytes	*Ixodes* spp., *Dermacentor* spp., *Rhipicephalus* spp.	Cattle, buffaloes
Anaplasma centrale	Bovine Anaplasmosis	Erythrocytes	*Ixodes* spp., *Rhipicephalus* spp.	Cattle, wild ruminants
Anaplasma ovis	Ovine Anaplasmosis	Erythrocytes	*Dermacentor spp., Rhipicephalus spp., Melophagus spp.*	Sheep, goats, wild ruminants
Anaplasma bovis	Bovine Anaplasmosis	Monocytes	*Amblyomma spp., Rhipicephalus spp., Hyalomma spp., Haemaphysalis spp.*	Cattle, buffaloes
Anaplasma platys	Canine Anaplasmosis	Platelets	*Rhipicephalus* spp.	Dogs
Anaplasma phagocytophilum	Human and animal granulocytic anaplasmosis, equine Anaplasmosis, tick-borne fever of ruminants,	Granulocytes, endothelial cells	*Ixodes* spp.	Small ruminants, wild ruminants, horses, humans, rodents,

	Anaplasmosis of dogs and cats	carnivores, insectivores

Source: Abdisa (2019), Silaghi et al. (2017)

Several strains of *A. marginale* have been identified in various geographical regions. They exhibit morphological differences, unique protein sequences, varied antigenic characteristics and varying transmission abilities through tick bites [20]-[24].

The interaction between *A. marginale* and host cells is largely dependent on their major surface proteins, which determine their capability to cause disease. Six MSPs were identified on *A. marginale*, derived from bovine erythrocytes [20], [21]. These were found to be conserved on tick and cell culture-derived organisms [23]-[25]. Of these MSPs, MSP1a, MSP4 and MSP5 are from single genes and do not vary antigenically within strains. However, MSP1b, MSP2 and MSP3 are from multigene families and may vary antigenically, particularly in persistently infected cattle [23], [24], [26].

Due to the variability within the reiterated section of the msp1a gene, it has been employed as a reliable genetic marker for detecting *A. marginale* strains in distinct geographical regions [23], 26], [27]. The gene, *msp1a*, which encodes MSP1a, is preserved during rickettsia multiplication in both cattle and ticks [20], [22]. Moreover, it has been demonstrated to play a role in adhering to bovine erythrocytes and tick cells [20], [24], [26]. Major surface protein 5 is a highly conserved surface protein that serves as a diagnostic antigen and is effective in a commercially-available competitive enzyme-linked immunosorbent assay (cELISA). Recent studies have suggested that the different *A.marginale* genotypes within herds in an endemic area may be explained by independent transmission events via infected cattle movements, rather than tick movements [20], [25], [26].

Distribution of disease and animal infected

Bovine Anaplasmosis is a major cause of morbidity and mortality in cattle, particularly crossbred cattle in tropical and subtropical regions. The geographical distribution of the disease depends on the density and distribution

of tick vectors and reservoir hosts. The distribution of Anaplasmosis may continue to change due to global warming, which may affect tick host movement [10].

Anaplasma marginale, the main cause of Anaplasmosis in cattle, can infect other ruminants but is pathogenic only in cattle. It has a wide host range, including several wild species. The epidemiological contribution of domestic and wild animals to the prevalence of the disease is insufficient due to the lack of further research [11]. The severity of Anaplasmosis is related to several factors, such as strain virulence, age-related host susceptibility and breed resistance. Calves under one year old may show mild or no symptoms, but cows over two years old will likely experience severe, acute and potentially fatal disease. The disease incidence in *Bos taurus* cattle will appear more severe and acute than in *Bos indicus* cattle [12], [13].

Calves are much more resistant to disease than older cows. This resistance is not due to maternal antibodies; calves can regenerate red blood cells faster than adult cows. In endemic areas, where animals are first infected with *A. marginale* early in life, losses from Anaplasmosis are lower than in non-endemic areas [14], [28]. Animals that recover from the disease can become lifelong carriers and serve as reservoirs for transmission to other susceptible hosts. However, these chronically infected cattle can relapse into Anaplasmosis during periods of immunosuppression (mainly due to the administration of corticosteroids), when infected with other pathogens or after splenectomy. Breeders, kennel workers and veterinarians can act as reservoirs or carriers for further transmission. Serious losses occur when adult cattle are moved to an endemic area but do not have sufficient immunity.

III. CLINICO-BIOLOGY OF THE DISEASE

Transmission

Anaplasma marginale is usually transmitted by two different routes: the biological route via the tick vector and the mechanical route [10], [11], [17]. Mechanical transmission can occur through insect bites, repeated use of syringes, horn-cutting tools, ear-marking tools, castration knives or other surgical instruments, and tattooing tools [1], [8]. In mechanical transmission, the organism is transmitted through the

blood-contaminated mouthparts of biting flies or with blood-contaminated equipment. *Tabanus* and *Stomoxys* flies can transmit the organism and remain mechanically infective for up to two hours after biting an infected animal. Blood-contaminated equipment, such as vaccination needles, can also transmit *A. marginale* from infected to uninfected animals [19], [20].

Biological transmission occurs via the tick vector. After the tick ingests the organism through the blood, the organism infects the tick's digestive cells and completes part of its life cycle. Over time, other tissues in the tick, including the salivary glands, become infected. A tick biting a cow transmits the organism in its saliva. Ticks can develop a persistent infection and transmit the organism to multiple animals within an individual or neighbouring animal population [20], [22]. Transplacental transmission occurs when the organism is transmitted from the mother to the foetus. This transmission can occur during the second or third trimester of pregnancy [22], [23].

Anaplasmosis is generally rarely reported in *Bos taurus* cattle breeds due to their resistance to heavy tick infestation, but they are more likely to develop acute Anaplasmosis than zebu crossbreeds [1]. Anaplasmosis infection is higher in females than males due to hormonal factors, milk production and gestation, leading to a reduced immune system [29]. Anaplasmosis is associated with vectors, and its prevalence is higher in hot and humid weather associated with the presence of biological vectors, namely ticks.

Clinical sign

Bovine Anaplasmosis has different clinical phases, including peracute, acute, chronic and mild. Acute Anaplasmosis is the most common and usually occurs in summer and autumn during the high biological vector season. Anorexic fever, rapid decline in body condition, severe decrease in milk production, pale mucous membranes and jaundice, increased heart and respiratory rates, muscle weakness and depression are common clinical signs. Cerebral anoxia occurs particularly in beef cattle. Abortion may occur in females and temporary infertility in males. As the haemolysis is extravascular, haemoglobinuria does not occur [13].

Peracute Anaplasmosis is most common in dairy cattle and can cause death within hours of the onset of severe clinical signs

such as jaundice [28]. Chronic disease occurs in animals that are severely infected but do not die. It can take weeks to months for animals to recover, during which production losses can be significant (weight loss and infertility). Clinical signs of Anaplasmosis include fever, jaundice, anorexia and lethargy, which can reduce milk production [28], [29].

Other signs include decreased appetite, constipation, hard faeces, panting, sudden drop in milk production, fever (41°C), enlarged abdomen, ataxia and depression. The urine may be brown, but babesiosis has no haemoglobinuria. Surviving cows recover over several weeks when haematological parameters gradually return to normal [14].

Diagnosis

The diagnosis of Anaplasmosis in cattle depends on the animal's clinical history and laboratory examination. Suppose the animal has a history of tick infestation and, after an incubation period of 2-7 days, the animal suddenly develops clinical signs of muscle pain, anorexia, fever, with mucous membrane haemorrhages and skin petechiae associated with thrombocytopenia and leucopenia. In that case, Anaplasmosis may be suspected [11].

The most common laboratory method to identify the organism is a microscopic examination of blood smears with Giemsa staining. However, this method cannot detect low-grade rickettsial diseases like those in the subclinical phase and pre-symptomatic or carrier animals. Microscopic examination with Giemsa staining can distinguish Anaplasmosis from Babesiosis and other diseases that cause anaemia and jaundice, such as leptospirosis and theileriosis [3], [30]. Inclusion bodies of *Anaplasma marginale* organisms are usually located at the edge of the infected erythrocytes, whereas those of *A. centrale* are more centrally located [3]. If the *Anaplasma* infection persists after the acute phase, it may not be detectable by microscopy. In addition, it is difficult to distinguish the agent from similar structures such as Howell-Jolly bodies, Heinz bodies and staining artefacts in career cattle, making this method unreliable [3], [31].

In these cases, infection is usually diagnosed by serological detection of antibodies, confirmed by molecular detection methods. Several serological tests have been extensively used for

epidemiological studies: complement fixation (CF) test, capillary agglutination test, card agglutination test (CAT), indirect fluorescent antibody (IFA) test and various enzyme-linked immunosorbent assays (ELISA) such as cELISA, indirect ELISA and dot ELISA. The two serological tests currently preferred for identifying infected animals are the cELISA and the CAT [3], [31]. Nucleic acid-based tests polymerase chain reaction (PCR) have also been developed to detect low infection levels in carrier cattle and tick vectors. At necropsy, thin blood smears from the liver, kidneys, spleen, lungs and peripheral blood can be taken for microscopic examination [30], [31].

The gold standard for detecting *A. marginale* blood is the sub-inoculate blood from the suspect animal into a splenectomised calf, which is highly susceptible to infection [32]. If the donor is infected, *A. marginale* is observed in smears from the splenectomised calf, usually within 4 weeks, but this period can extend to 8 weeks. However, this method is costly and raises welfare issues as the splenectomised calves become very ill after sub-inoculation of infected blood and often have to be euthanised [31]. For these reasons, it would not be feasible to use subinoculation of splenectomised calves as the gold standard for the validation of tests. Thus, older tests have typically been validated by microscopic detection of *A. marginale* or by comparison with other serological results, and newer ELISA tests have typically been validated by PCR methods that have not been formally validated.

Treatment and control

Animals that have recovered from Anaplasmosis become carriers. The advantage of carrier animals is that they have lifelong immunity and rarely show clinical signs. However, they can serve as a reservoir of the organism in the environment or the livestock population [26]. Long-term repeated administration of antibiotics with oxytetracycline and chlortetracycline is less effective in treating Anaplasmosis and may lead to microbial resistance [20], [23]. Currently, available control measures for tick-borne diseases include using acaricides to reduce the tick population, chemoprophylaxis and vaccination. These measures can prevent losses caused by ticks and the diseases they transmit [23], [33]. Control measures for bovine Anaplasmosis vary with

geographical location and include maintenance of anaplasma-free cattle, vector control, administration of antibiotics and vaccination [26], [34]. Early diagnosis and treatment are essential for effectively controlling Anaplasmosis, while continuous surveillance should be carried out to control the disease.

IV. CONCLUSION

Bovine anaplasmosis is one of the most important diseases of ruminants worldwide, causing significant economic losses in the livestock industry due to the high morbidity and mortality in susceptible cattle herds. Bovine anaplasmosis, caused by *A. bovis*, *A. centrale*, *A. marginale* and *A. phagocytophilum*, is an infectious but non-contagious disease. The mode of transmission of Bovine anaplasmosis includes mechanical (blood-contaminated fomites (needles, ear tagging, dehorning and castration equipment), biological (tick bites) and transplacental (cow to fetus). Bovine anaplasmosis occurs in tropical and subtropical regions worldwide. While anaplasmosis is transmitted biologically by tick, mechanical transmission by blood-contaminated mouthparts of biting flies or fomites also frequently occurs. Mechanical transmission may be the only means of spreading anaplasmosis in areas where tick vectors are absent or cannot transmit the local *Anaplasma* parasites. Cattle can develop persistent anaplasmosis infections and thus serve as reservoirs of infection for both mechanical and/or biological transmission of the pathogen and difficult to treat disease with antibiotics. It is better to prevent and control future outbreaks and the spread of anaplasmosis to naïve herd than treatment. Problems of acaridae resistance, chemical residues in food and the environment and the unsuitability of tick resistant cattle for all production systems make the current situation unsatisfactory and require the development of absolute control through effective vaccine.

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