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Review on anaplasmosis in different ruminants

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Abstract

Anaplasma bacteria, particularly *A. marginale*, *A. ovis*, and *A. phagocytophilum*, have attracted researchers' attention in recent years. To a lesser extent, it has to do with the pathogenicity of these bacteria for farm animals and people alike. Anaplasmosis, which is a disease caused by numerous anaplasmosis species, is a major concern for animal producers. Ixodes, Dermacentor, Amblyomma, and Rhipicephalus ticks are the most frequent vectors of Anaplasma bacteria, which may be found in almost every region of the globe. Eukaryotic cells' vacuoles are host to obligatory intracellular bacteria of the *Anaplasma* genus. The obligatory intracellular bacteria Anaplasma centrale, *A. bovis, A. ovis,* and *A. marginale*, infect animal (mostly ruminants) red blood cells and monocytes. Dogs are its primary host, although it may also infect humans and domestic animals. In this study, we discussed six Anaplasma species and their vectors from across the globe.

Introduction

Anaplasmosis is a minor clinical illness caused by intraerythrocytic rickettsia of the genus Anaplasma (Rar, Tkachev et al. 2021). Depressive symptoms, debility, decreased milk production, weight loss, miscarriage, severe anaemia, and jaundice have been reported in endemic areas due to infections with parasites *Anaplasma ovis* and *Anaplasma marginale* (*A. marginale*) (Hosseini-Chegeni and Tavakoli 2020). Bacteria belonging to the genus Anaplasma are members of the kingdom Prokaryote and, more particularly, of the family Anaplasmataceae. There are rickettsial tick infections called Anaplasma species that cause anaplasmosis, which is the most common form of anaplasmosis in ruminants like camels and cattle. Anaplasmosis is a serious disease that causes large financial losses, especially in subtropical and tropical regions (Omer, Elfehid et al. 2021). Anaplasma species were thought to be parasites until genetic studies showed that they are rickettsial bacterial pathogens that belong to the Anaplasmataceae family (Dumler, Barbet et al. 2001). Sir Arnold Theiler developed the term "yellow bag" or "gall sickness" in 1910 (Theiler and Therapeutics 1910, Kocan, de la Fuente et al. 2010). A disease of ruminants in tropical and subtropical regions, as well as many temperate ones, began to be widely recognized after Theiler's studies. At least 20 species of ticks transmit Anaplasma (Marchette and Stiller 2018); although Rhipicephalus (Boophilus) microplus is the primary transmission agent (Aubry, Geale et al. 2011, Marchette and Stiller 2018). Other modes of transmission include biting insects or fomites contaminated with blood. Because it lacks a normal cell wall and is unable to synthesize lipopolysaccharide and peptidoglycan, this rickettsial bacterium is more closely resembles to protozoa (Brayton, Kappmeyer et al. 2005). Infections with Anaplasma are more prevalent in cattle than in buffaloes (Rajput, Hu et al. 2005). There are approximately 20 different types of ticks involved in the disease's dissemination, which is the primary mode of transmission (Marchette and Stiller 2018). The, Rhipicephalus, Hyalomma Ixodes, Dermacentor and Boophilus species of ticks are of importance, as well as numerous more ticks (Estrada-Pena, D'Amico et al. 2017). Anaplasmosis is more frequent during the hot, humid, and rainy seasons because of the high quantity of ticks (El-Metenawy 2000). Hemorrickettsial disease anaemia is prevalent in subtropical and tropical regions of the globe (Iqbal, Mukhtar et al. 2019). One of the most frequent bovine hemoparasitic diseases in Pakistan, with a prevalence of 4–75.6%, is this parasitic disease (Khan, Zahoor et al. 2004). The livestock and cattle population in Khyber Pakhtunkhwa are suffering from a serious health issue (Ali et al. 2019).

Anaplasmosis

The obligatory intra-erythrocytic bacteria of the genus Anaplasma cause anaplasmosis, more often known as gall sickness, in ruminants. Other ruminants, such as water bison, buffaloes, antelopes from Africa, and various deer species, may also get infected and suffer from chronic sickness. One of the most common causes of anaplasmosis is the transmission of newly formed erythrocytes by ticks and biting flies, as well as surgical equipment like needles and dehorning and castration equipment. Subtropical and Tropical regions (40 N–32 S) across the world, including central and South America, United States, southern Europe, Africa, Asia, and Australia, are known to harbor anaplasmosis cases (Khamesipour, Dida et al., 2018). The absence of a typical cell wall and the inability to synthesize lipopolysaccharide and peptidoglycan make this rickettsial organism more closely connected to protozoa (Brayton, Kappmeyer et al. 2005). Infections with Anaplasma are more common in cattle than in buffaloes (Rajput, Hu et al. 2005). Increased hemolytic anaemia, in addition to jaundice, decreased milk production, fever, abortion, hyperexcitability, and rare occurrences of quick mortality are also symptoms of the condition (Gay, Hinchcliff et al. 2000).

Taxonomic classification of Anaplasma bacteria

Within the order of Rickettsiales, considerable reorganizational modifications were achieved in 2001. As a consequence, certain bacterial genera were renamed as the new names for the Ehrlichiaceae, and certain bacterial genera had their classifications changed as a consequence (Dumler, Barbet et al. 2001). They belong to the Prokaryote kingdom, and Anaplasmataceae is their genus. When Sir Arnold Theiler discovered that "marginal spots" seen in stained erythrocytes of ill cattle were causal agents for a particular disease, he created the genus Anaplasma in 1910 (Theiler and Therapeutics 1910; Theiler 1911).

History

Anaplasma species were thought to be parasites until genetic studies showed that they are rickettsial bacterial pathogens that belong to the Anaplasmataceae family (Dumler, Barbet et al. 2001). Sir Arnold Theiler coined the term "yellow bag" to describe gall illness in 1910

(Theiler and Therapeutics 1910, Kocan, de la Fuente et al. 2010). Salmon and Smith found inclusion in calf erythrocytes in 1894, which was the first time anyone had heard of *A. marginale*. Sir Arnold Theiler discovered bacteria in the erythrocytes of South African cattle in 1910 and published the first comprehensive description of the organism (Kocan, De la Fuente et al. 2003). *A. marginale* and *A. centrale* are two separate subspecies of erythrocytes, with the latter more prone to developing "marginal points" in calves' erythrocytes. This sub-specie was shown to be slight dangerous to domesticated animals than others (Kocan, De la Fuente et al. 2003). Animal-pathogenic anaplasmosis species like *A. ovis*, A. platys (currently called E. platys), and *A. bovis* were discovered in the following years (Harvey, Simpson et al. 1978, Kuttler 1984). Human anaplasmosis (HGA) was detected for the first time in the United States in 1994 following years of investigation (Tylewska-Wierzbanowska, Chmielewski et al. 2001).

Europe has seen tick fever instances in calves, lambs, and goats since 1780. However, despite the fact that the cause of this ailment has yet to be discovered, the symptom description is quite similar. By discovering tick fever in small ruminants and thereafter in dogs, the disease of anaplasmosis has been revolutionized. Animals perished from the sickness on occasion, although its cause was unknown. Major reorganizational changes occurred within the Rickettsiales order in 2001. Some bacterial genera, as well as their families, were reclassified as a result of this reorganization (Dumler, Barbet et al. 2001). 150 years after the initial report, the sickness was ultimately identified to a bacterium, E. phagocytophila (now known as *A. phagocytophilum*) (Jenkins, Fallowfield et al. 2001).

After considerable investigation, it was discovered that anaplasmosis may infect people; the first instance of HGA was discovered in the US in 1994. There is an *A. phagocytophilum* agent that caused it (a human granulocytic anaplasmosis agent that was initially defined as a granulocytic ehrlichiosis agent) (Dumler et al., 2001). This disease was first identified in Europe in 1996 in Slovenia (Petrovec et al., 1997), and was first reported in Poland in 2001 Tylewska-Wierzbanowska and colleagues.

Types / Taxonomy

Anaplasma marginale

Anaplasma marginale is a tick-borne intraerythrocytic pathogen that infects just its particular host. Most often, infected hosts are ruminants, such as cattle (Kocan, de la Fuente et al. 2010, Zhang, Lv et al. 2016). Biting flies and the majority of tick species transmit the parasite either physiologically or mechanically. Fever, generalised sadness, loss of weight, developing anaemia, and icterus are all symptoms of A. marginale illness (Fereig, Mohamed et al. 2017). It is the most virulent species worldwide, causing epidemics more often than other anaplasmosis species, which is the most common tick-borne haemorickettsial illness (Atif, Khan et al. 2013). It is the most hazardous species, is an intraerythrocytic parasite that produces mild to severe epidemics in small ruminants (George, Bhandari et al. 2017).

Anaplasma centrale

Anaplasma centrale is found in the red blood cells of ruminants, mainly in cattle. It creates concentrations in the cell's center, as opposed to *A. marginale*. This bacterium may be found all over the world. Despite differences in appearance and virulence, *A. centrale* and *A. marginale* are closely related. *A. centrale* is the most common cause of minor anemia in cow infections (Rajput, Hu et al. 2005). A. centrale, according to Theiler, is less harmful to cattle than A. marginale, however it may sometimes produce resistance to the latter. As a consequence, it is used to develop live vaccine strains that give immune protection against bovine anaplasmosis. This vaccine is manufactured in Israel, Australia, Latin America, and Africa (Kocan, De la Fuente et al. 2003).

Anaplasma bovis

Anaplasma bovis is a bacterium that belongs to the Anaplasma genus, the Anaplasmataceae family, and the Rickettsiales order. It was identified in 1936 while researching Theileria sp. transmission (Brouqui, Parola et al. 2007). It is recognized as a tick-borne pathogen in buffalo and cattle and, more importantly, has a deleterious effect on cow output (Dumler, Barbet et al. 2001). *A. bovis*, like other members of its family, is an obligate intracellular bacterium that lives inside cells and may spread to other cells throughout the body. Anaplasma bovis is passed from ticks to vertebrates through the bit of ticks that are infected with it (Brouqui, Parola et al. 2007). So, vertebrates are important to their lifetime. Recently, *A. bovis* was also found in mosquitoes, but the particular roles they play in maintaining and transmitting the disease aren't clear (Guo, Tian et al. 2016).

Several clinical symptoms, such as elevated fever, weight loss, and reduced milk production, were associated with anaplasmosis in cattle infected with Anaplasma bovis. It sometimes causes abortions and mortality during the severe phase of the illness (Rar, Golovljova et al. 2011). The majority of diseased buffalo and cattle, however, are asymptomatic. Aside from the two ruminants described above, DNA of *A. bovis* has been found in Mongolian gazelles, deer, raccoons, cottontail rabbits, rats, goats, sheep, dogs, wild cats, pigs, Eastern rock sengi, and monkeys all across the globe (Gofton, Waudby et al. 2017). Furthermore, *A. bovis* disease in these animals does not result in scientific signs.

Anaplasma ovis

Anaplasma ovis are obligate intracellular bacterium carried by ticks. This Anaplasma species is thought to be reservoirs in wild ungulates (Kauffmann, Rehbein et al. 2017). Contrary to *A. phagocytophilum*, *A. ovis* causes ovine anaplasmosis and is much more host-specific. This disease mostly affects ovine and caprine red blood cells, but it has also been discovered in wild ungulates such as red and reo deer (Jiménez, Benito et al. 2019).

So far, just a few cases of *A. ovis* infection in humans have been recorded (Chochlakis, Ioannou et al. 2010). Despite its widespread distribution in the Mediterranean basin, Anaplasma ovis has only been identified on a few of occasions in Central Europe and has yet to be discovered in Northern Europe (Stuen 2016). Ticks belonging to the genera Rhipicephalus, Dermacentor, and Hyalomma are assumed to be the vectors of the illness, although there is no fresh evidence to support this theory (Friedhoff 1997).

A. ovis has just been discovered in sheep keds (Melophagus ovinus) (Zhang, Wang et al. 2021). Severe anemia, serious weakness, anorexia, and weight damage are the most common clinical symptoms in sheep, although they only appear when the animals are in poor health (Lacasta, Ferrer et al. 2020). Hemoglobinuria has been documented in a sheep herd in Hungary (Hornok, Elek et al. 2007), and icteric corpses of *A. ovis* positive lambs have recently been recorded in Spain (Lacasta, Ferrer et al. 2020). *A. ovis* produces hemolytic anaemia, which results in a reduction in hemological markers such as RBC, Hb, and PCV in sheep experimentally infected with the disease (Yasini, Khaki et al. 2012).

A. ovis is a worldwide problem, not only in developing nations, according to current studies by a significant number of scientific institutions. The United States, Italy, and Hungary have all reported the presence of these microorganisms (Hornok, Elek et al. 2007). However, it should be emphasized that the restoration of old agricultural methods (pasturage on meadows) may aid in the spread of *A. ovis* in that region. Some experts say that modern climate change has the potential to contribute to the spread of this bacterium.

Anaplasma platys

Anaplasma platys is a gram-negative, intracellular bacterium believed to be spread by Rhipicephalus sanguineus sensu lato brown dog ticks (Ramos, Latrofa et al. 2014). It is usually detected in dogs, although natural infections have been reported in cats, foxes, wild boars, red deer, and goats (Pereira, Parreira et al. 2016). Majority of infected dogs, blood loss may occur, and co-infection with other vector-borne infections deteriorates A. platys infection (Iatta, Sazmand et al. 2021).

Modern vector competence research, on the other hand, seems to provide strong evidence that R. sanguineus sensu stricto is a biological vector of A. platys (Snellgrove, Krapiunaya et al. 2020). This tick is also a vector for Ehrlichia canis, an Anaplasmataceae disease associated with A. platys. Co-infections with A. platys and E. canis are common in dogs (LanzaPerea, Zieger et al., 2014). Clinical signs of A. platys and E. canis infections in dogs can vary from asymptomatic to severe, including high fever, depression, weakness/lethargy, anorexia, lymphadenopathy, splenomegaly, thrombocytopenia, and weight loss (Mylonakis and Theodorou 2017).

Infections with Anaplasma platys may cause petechiae, whereas infections with E. canis can cause nasal bleeding in some dog breeds. Ecchymosis and cyclical changes in platelet counts occur in dogs with A. platys infections, most likely as a result of an infection-related decrease in thrombocytes and a host-induced immune response. While the infection is likely to be spontaneously managed by the canine immune system, the illness-associated immunological suppression and changing platelet levels may have a negative influence on the animal's health.

Anaplasma phagocytophilum

Anaplasma phagocytophilum causes human, horse, and canine granulocytic anaplasmosis (Chvostá, Pitalská et al. 2018). Several *A. phagocytophilum* genetic variations have been identified in free-living and domestic animals in Europe (Földvári, Jahfari et al. 2014). Ixodes ricinus is the most common genotype in Europe, but other species of Ixodes are thought to be involved in the transmission of this disease. Ixodes persulcatus transmits the pathogen in Eastern Europe and temperate Asia, whereas Ixodes scapularis and Ixodes pacificus transmit it in North America (Jahfari, Coipan et al. 2014, Jaarsma, Sprong et al. 2019). When it comes to transmitting gram-negative TBPs (such as *A. phagocytophilum*), the ecology of Ixodes species vectors and reservoir vertebrate hosts determines their ecological niche (Jaarsma, Sprong et al. 2019). Several molecular marker analyses demonstrated the presence of several genetic variations in *A. phagocytophilum*. Furthermore, some degree of host specificity has been documented for the various genetic variations at both the tick and vertebrate host levels (Kauffmann, Rehbein et al. 2017). *A. phagocytophilum's* genetic structure and complicated epidemiology are similar to the variety of genospecies in the Borrelia burgdorferi sensu lato complex (Jaarsma, Sprong et al. 2019). There are no significant differences in the robustness and consistency of genetic variant categorization in A. phagocytophilum using groEL as compared to methods that use the 16S-rDNA gene sequence, the ankA and the msp4 gene sequences (Battilani, De Arcangeli et al. 2017). There have been eight distinct genetic clusters, separated into four ecotypes based on their geographic distribution and their relationship with vertebrate or vector species, found by Jaarsma et al. via the DNA sequence of a groEL fragment as the basis for their research. (Jaarsma, Sprong et al. 2019).

Table 1. Pathogens characteristic of the genus *Anaplasma*

Etiological agent		Disease			
before 2001	**After 2001**		**Vector**	**Infected host**	**Infected cell**
Ehrlichia bovis	*Anaplasma bovis*	Bovine anaplasmosis	*Haemaphysalis* sp.*Rhipicephalus* sp.*Amblyomma* sp.	ruminants farming, small mammals	Monocytes
Anaplasma ovis	*Anaplasma ovis*	Bovine anaplasmosis	*Dermacentor* sp.	small ruminants (goats, sheep)	Red blood cells
Anaplasma marginale	*Anaplasma marginale*	Bovine anaplasmosis	*Ixodes* sp.*Dermacentor* sp.	ruminants farming	Red blood cells
Anaplasma centrale	*Anaplasma centrale*	Bovine anaplasmosis	*Ixodes* sp.*Haemaphysalis* sp.	ruminants farming	Red blood cells
E. equiE. phagocytophila Czynnik HE	*Anaplasma phagocytophilum* (HGA agent)	HGA anaplasmosis	*Ixodes* sp.*Dermacentor* sp.	small ruminants forming and humans, wild, horses, dogs,	Granulocyte
E. platys	*Anaplasma platys*	Canine cyclic thrombocytopenia	*Rhipicephalus sanguineus*	Dogs	Platelets

Tick morphology and behavior

Ticks are the world's most lethal arthropod disease vectors, second only to mosquitoes in vector competence (Benelli, Maggi et al. 2017). Ehrlichiosis, Lyme disease, anaplasmosis, Powassan virus, piroplasmosis and Rocky Mountain spotted fever are all illnesses transmitted by ticks. (Ebani, Rocchigiani et al. 2017). About 900 different species of ticks may be found in the two major families of Argasidae and Ixodidae, as well as one in the Nutalliellidae, which only has one specie (*Nuttalliella namaqua*, Bredford) (Guglielmone, Robbins et al. 2014). Hard ticks, also known as Ixodidae, are the most prevalent vectors of human parasitism. However, Argasidae, sometimes known as soft ticks, do bite people sometimes (Dantas-Torres and Otranto 2016). There are a wide range of tick species that vary from location to region and often infect animals as reservoir hosts for a variety of disease pathogens (Piesman and Eisen 2008).

Host density and the weather may have a significant impact on the activity of ticks, which in turn influences the probability of tick-borne illnesses being transmitted to the host (Hubálek, Halouzka et al. 2003). However, ticks' cognitive endogenous elements in host seeking/contacting behaviour are also worth exploring. During host searching, hard ticks

(Ixodidae) conduct a behaviour known as "questing" in order to increase their chances of encountering a suitable mammal host. The tick will crawl up a blade of grass or other similar plant component and then wait with its forelegs spread. When a host passes by, it brushes up against the tick's forelegs, which contain Haller's organ, and the tick grips hold of the host (Randolph and Storey 1999, Perret, Guigoz et al. 2000).

It's difficult to predict exactly how a tick will react to an unfamiliar host. According to research, an increased concentration of CO2 in the air, i.e., exhalations from a host, is a crucial factor affecting the behavior of questing people. Ticks assume an expectant attitude (in passive species) or migrate towards the source of the gas when the concentration of carbon dioxide in the air changes (in active species). The aroma of a host, as well as its body temperature, may have a considerable impact on the tick's decision. Other stimuli that ticks respond to include pheromones, urine, animal noises, and an environmental element called light intensity (Buczek and Magdon, 1999). Stimulating factors differ and define various tick species.

Tick behavior may also be impacted by diurnal and seasonal patterns unique to particular populations. Ambient temperature influences seasonal activity, whereas prospective ambient temperature, host activity, humidity influence and diurnal activity.

Anaplasma bacteria vectors worldwide

The anaplasma-carrying common tick, Ixodes ricinus, is the most common tick in Europe Cafiso, Bazzocchi et al. (2016) use the term "European sheep tick" to refer to Ixodes ricinus. One of the most frequent types of ticks is the arachnid that feeds on blood, the Ixodida order, of the genus Ixodes (Muders 2015). Its parasitic actions on vertebrates, including humans, generate a broad spectrum of pathological alterations, some of which are life-threatening for their victims (swelling, inflammatory disorders of the skin, allergies, and paralysis). There are three distinct hosts for extranidamental ectoparasites such as I. ricinus, which feed on migratory animals in the open and have a three-stage life cycle (Medlock, Hansford et al. 2013). The life cycle of Ixodes ricinus includes all three stages: lymph, larva, and adult (imago). It is a temperate climate-adapted species that exhibits seasonality, or the reliance on the seasons for activity and progression through the life cycle at each stage. In temperate regions, the tick's life cycle may continue for up to three years, but it can live much longer under ideal climatic circumstances (Lindquist 2014). Additionally, studies have indicated that high temperatures and low humidity have a detrimental influence on the lifetime of host-seeking nymphs throughout the warm months of the year, especially when the relative humidity falls below 82% (Ginsberg, Rulison et al. 2014).

In Pakistan, according to Hussain et al. ticks have been identified on cattle, buffalo, and forty diverse species of ticks on goats and sheep. Ticks infesting buffaloes and cattle have been observed in Pakistan as well (2021). A total of two new tick species have been found as a result of this study, which was carried out on tiny ruminants (goats and sheep). The introduction of these two new species has resulted in an increase in the tick fauna in the United States. Ninety-nine tick species present in Pakistan's rural and urban areas have been recognised for the first time, including D. marginatus, Ha.punctata, Rhiphicephalus sanguineus, Rhiphicidephalus microplus, Rhiphicidephalus annulatus, and Hyalomma excavatum, among others (Ramzan *et.,* al.2020). It is possible that this study may result in the discovery of new species in Pakistan. In addition to the ability to transmit harmful infections, these two new species have the potential to wreak enormous economic damage. A number of other species have been discovered in Pakistani cattle. It is necessary to do research on tick species from different locations in Pakistan.

In spite of the fact that DNA testing has shown the existence of Anaplasma and Ehrlichia species in Iranian cattle, the infections' vectors have garnered much less attention than the pathogens themselves. In Iran, until recently, only a few studies examined the presence of Anaplasma and Ehrlichia spp. in ticks, showing that the north of the nation and other regions had infected insects (Tajedin et al. 2016). Because of their ability to transmit diseases like Ehrlichia and Anaplasma, ixodid ticks are vital to their continued existence in the natural world (Han, R. et al., 2019). Since A. marginale has been associated with Hyalomma species, very little study has been done on the idea that these parasites might be involved in the spread of Anaplasma and Ehrlichia species (Shkap et al. 2009). Domestic animals in Baluchistan and Sistan are often infected with Hyalomma, Anaplasma, and Ehrlichia spp.

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