PEER REVIEWED

Current Challenges of the Management and Epidemiology of Bovine Anaplasmosis

Katherine M. Kocan[1], *PhD;* **José de la Fuente**[1,3], *PhD;* **Douglas L. Step**[2], *DVM, DACVIM;*
Edmour F. Blouin[1], *PhD;* **Johann F. Coetzee**[4], *BVSc, Cert CHP, PhD, DACVCP, DVM;*
Katharine M. Simpson[2], *DVM;* **Suzanne G. Genova**[2], *DVM;* **Melanie J. Boileau**[2], *DVM, MS, DACVIM*
[1]*Department of Veterinary Pathobiology, Center for Veterinary Health Sciences, Oklahoma State University, Stillwater, OK 74078, USA*
[2]*Department of Veterinary Clinical Sciences, Center for Veterinary Health Sciences, Oklahoma State University, Stillwater, OK 74078, USA*
[3]*Instituto de Investigación en Recursos Cinegéticos IREC (CSIC-UCLM-JCCM), Ronda de Toledo s/n, 13005 Ciudad Real, Spain*
[4]*Veterinary Clinical Sciences, Kansas State University, Manhattan, KS 66502, USA*
Corresponding author: Katherine M. Kocan, Department of Veterinary Pathobiology, 250 McElroy Hall, Center for Veterinary Health Sciences, Oklahoma State University, Stillwater, OK 74078-2007, E-mail: Katherine.Kocan@okstate.edu, Phone: (405) 744-7271; FAX: (405) 744-5275

Abstract

Bovine anaplasmosis, caused by the intracellular rickettsia *Anaplasma marginale,* is endemic in several areas of the United States and has continued to impact cattle production. While considerable research has been done over the past several decades, control strategies for anaplasmosis have advanced minimally since the first anaplasmosis vaccine was marketed in the US in the 1960s. However, these research findings have continued to contribute to our overall understanding of the complexity of bovine anaplasmosis. With the advent of molecular biology, host/pathogen interactions are currently better defined and the classification of *Anaplasma* has been reorganized to include several organisms in addition to those that are host-specific for ruminants. In this review, the current status of anaplasmosis is discussed with the aim of providing insight to bovine practitioners on the future challenges for the management, diagnosis, and control of bovine anaplasmosis. This review focuses on updated information on the classification of the genus *Anaplasma* and related organisms, the developmental cycle of *A. marginale* in cattle and ticks, the role of male ticks in transmission of anaplasmosis, the diversity of *A. marginale* strains, the wildlife reservoirs of *A. marginale*, and the potential influence of climate change on the epidemiology of this serious disease. A second review will follow which focuses on current issues related to diagnosis and control of bovine anaplasmosis. Overall, the goal of these reviews is to provide an understanding of the current status of research and knowledge of bovine anaplasmosis and provide veterinarians answers to frequently asked questions.

Key words: *Anaplasma marginale*, bovine anaplasmosis, rickettsia, cattle, *Anaplasma phagocytophilum*

Résumé

L'anaplasmose bovine, qui est causée par la rickettsie intracellulaire *Anaplasma marginale,* est endémique dans plusieurs régions des États-Unis et continue toujours d'affecter les bovins. Bien qu'il y ait eu des progrès de recherche considérables depuis les dernières décennies, les stratégies de contrôle de l'anaplasmose n'ont que bien peu évoluées depuis la mise en marché du premier vaccin aux États-Unis dans les années soixante. Néanmoins, ces travaux continuent toujours à contribuer à notre compréhension de la complexité de l'anaplasmose bovine. Avec les percées récentes en biologie moléculaire, les interactions entre hôtes et pathogènes sont présentement mieux définies et la classification d'*Anaplasma* a été réorganisée afin d'inclure plusieurs organismes autre que ceux rattachés spécifiquement aux ruminants. Dans cette analyse documentaire, le statut actuel de l'anaplasmose est discuté afin d'éclairer les médecins vétérinaires en pratique bovine sur les défis futurs concernant la gestion, le diagnostic et le contrôle de l'anaplasmose bovine. Cette analyse documentaire donne une information à jour sur la classification du genre *Anaplasma* et d'autres organismes apparentés, le cycle de développement de *A. marginale* chez les bovins et les tiques, le rôle des tiques mâles dans la transmission de l'anaplasmose et l'influence potentielle des changements climatiques dans l'épidémiologie de cette sérieuse maladie. Une seconde analyse documentaire suivra se penchant sur

les problèmes de l'heure associés au diagnostic et au contrôle de l'anaplasmose bovine. Le but général de ces analyses documentaires est de permettre de mieux comprendre l'état actuel des travaux de recherche et des connaissances sur l'anaplasmose bovine et de fournir aux praticiens des réponses à leurs fréquentes questions.

Introduction

Bovine anaplasmosis, caused by the intracellular rickettsia *Anaplasma marginale*, is presently considered to be the only major tick-borne disease in the United States (US) that impacts cattle production.[42] Although bovine anaplasmosis has been reported in a majority of states, the disease is endemic in south central and southeastern Gulf and northwestern states. *A. marginale* is considered to be host-specific for cattle. While selected ruminants may serve as reservoirs of infection, clinical disease occurs predominantly in cattle.

The dynamics of *A. marginale* are more complex than other tick transmitted diseases of cattle because transmission occurs either biologically by ticks, in which the *A. marginale* multiplies and then is transmitted to cattle during tick feeding, or mechanically by any means of transfer of infective organisms. These include blood-contaminated mouthparts of biting flies and instruments frequently used in veterinary practice, such as needles, ear tag applicators, castration instruments, and dehorning equipment.[38,40,42] In some geographic areas where tick vectors are absent or are unable to transmit local *A. marginale* strains, mechanical transmission may be the only means of transmitting *A. marginale*.

Even though bovine anaplasmosis is a well recognized disease, the epidemiology of anaplasmosis is complex and not well understood. Factors that lead to anaplasmosis outbreaks are ill-defined, and these factors are likely to vary among geographic areas in the US.

Considerable research on *A. marginale* has been conducted over the past several decades. The collective findings of this research have contributed markedly to our current understanding of the biology of the pathogen and its relationship with cattle and tick hosts, as well as the epidemiology of the disease. Despite this newfound knowledge, control strategies for anaplasmosis have advanced minimally since the first anaplasmosis vaccine was marketed in the 1960s. Because anaplasmosis is not a reportable disease in most states, the economic impact of this disease on cattle production has been difficult to estimate. The more recently quoted estimate of $300 million annual loss to cattle production (likely now higher) was re-calculated in 1990, and is an inflation-adjusted amount based on a 1973 report[55] in which anaplasmosis was estimated to cost cattle producers $100 million annually. However, lack of ongoing information on the incidence of anaplasmosis and its economic impact on cattle production does not allow for accurate assessment of production losses incurred by the cattle industry in the US.

This review will provide updated information on the classification of the genus *Anaplasma* and related organisms, the developmental cycle of *A. marginale* in cattle and ticks, the role of male ticks in transmission of anaplasmosis, current information on wildlife reservoirs of *A. marginale*, and the potential influence of climate changes on the epidemiology of the disease. The second review currently in preparation will address current issues related to diagnosis and control of bovine anaplasmosis. The authors hope this information will serve as an update and provide answers to questions frequently asked by bovine practitioners and producers.

Current Classification of the Genus *Anaplasma* and Relationship of Newly Added Organisms to *A. marginale*

The classification that contains the causative agent of bovine anaplasmosis, *Anaplasma marginale*, has recently undergone considerable revision. The order Rickettsiales, which includes the genus *Anaplasma*, was reorganized by Dumler *et al* in 2001,[22] and the genus *Anaplasma* now contains the original pathogens that infect ruminants, as well as organisms that infect other vertebrates. Notably, *A. phagocytophilum,* causative agent of human granulocytic anaplasmosis (HGA), was added to this genus. Although *A. marginale* and *A. phagocytophilum* have a genetically-based similarity that warrants their placement in the same taxon, these organisms are markedly different in their biology as described below. *A. phagocytophilum* infections alone could result in clinical disease in cattle, but disease may more likely occur with concurrent infections of *A. marginale* or other hemoparasites. However, at present *A. phagocytophilum* has not been reported to be a disease problem in cattle in the US. Bovine anaplasmosis, caused by *A. marginale*, and human anaplasmosis are separate and distinctly different diseases and only *A. phagocytophilum* is infective for humans.

The reclassification of the order Rickettsiales was based upon genetic analyses of 16S rRNA, groESL, and surface protein genes. Organisms of this taxon were then assigned to one of two families: Anaplasmataceae and Rickettsiaceae.[22] Among the organisms of the Family Anaplasmataceae, the phylogenetic analyses consistently supported formation of four genetically distinct groups: (1) *Anaplasma*, (2) *Ehrlichia*, (3) *Wolbachia*, and (4) *Neorickettsia.*[22] Although both families contain obligate intracellular rickettsia, organisms assigned to the family Rickettsiaceae grow freely within the cytoplasm of eukaryotic cells, while organisms placed in the family Anaplasmataceae are found exclusively within membrane-bound vacuoles in the host cell cytoplasm.

Furthermore, almost all organisms assigned to the family Anaplasmataceae multiply in both vertebrate and invertebrate (primarily tick or trematode) hosts.

After this recent reclassification, the genus *Anaplasma* continues to include the three species of *Anaplasma* which exclusively infect ruminants: *A. marginale* (the type species), *A. marginale ss. centrale* (referred to herein as *A. centrale*), and *A. ovis,* and several additional organisms were reclassified into this genus (Table 1). *Anaplasma centrale,* originally described in South Africa, does not naturally occur in the United States, is less pathogenic for cattle, and is used as a live vaccine in Israel, Africa, and South America (as reviewed by Bock[1]). Cattle inoculated with the live *A. centrale* vaccine generally experience mild clinical disease and then remain persistently infected but immune to clinical disease for life. Recent research demonstrated that *A. centrale* is not transmissible by ticks,[71] and therefore imported ticks are not likely to be a source of *A. centrale* for introduction into the US. *Anaplasma ovis,* a pathogen infective for domestic and wild sheep, has not been reported to infect or establish persistent infection in cattle (reviewed by Kocan *et al*[42]). Therefore, commingling of sheep or goats infected with *A. ovis* with cattle should not pose a risk to cattle.

A. phagocytophilum, which represents three pathogens now recognized as the same agent (*Ehrlichia equi, E. phagocytophila,* and the previously unnamed causative agent of human granulocytic ehrlichiosis), was also added to the genus *Anaplasma.* In contrast to *A. marginale, A. phagocytophilum* has a wide host range and infects a wide variety of small and large mammals, including cattle and humans. The potential for many mammals to become infected and serve as reservoirs and a source of infection for ticks may eventually contribute to the emergence and establishment of *A. phagocytophilum* as a zoonotic disease.

Also included in the genus *Anaplasma* are *A. bovis* (formerly *E. bovis*), *A. platys* (formerly *E. platys*), and *Aegyptianella pullorum,* while other species of *Aegyptionaella* remain molecularly undefined[65] and have yet to be placed in their proper taxon (Table 1).

Anaplasma phagocytophilum and its Potential as an Emerging Pathogen of Cattle

Anaplasma phagocytophilum infects humans, as well as a wide range of small and large mammals, and HGA is considered an emerging disease of humans in the US. Human granulocytic anaplasmosis was first described in the US in 1994 and subsequently was reported in Europe and South and North America. Since this time, *A. phagocytophilum* has become a predominant form of anaplasmosis and is among the most common tick-borne pathogens in the US and Europe.[54,59] In hu-

Table 1. Current classification of the genus *Anaplasma.*

Order Rickettsiales	
Family Anaplasmataceae: Obligate intracellular bacteria that replicate with membrane-derived vacuoles in the cytoplasm of eukaryotic host cells.	
Genus *Anaplasma*	
***Anaplasma* species**	**Host(s)**
Anaplasma marginale (type species)	Cattle
Anaplasma centrale (Less pathogenic than *A. marginale*; used as a live vaccine in Israel, Africa, and South America)	Cattle
Anaplasma ovis	Sheep, goats
Anaplasma bovis (formerly *Ehrlichia bovis*)	Cattle
Anaplasma phagocytophilum (formerly Ehrlichia phagocytophilum, E. equi, HGE agent)	Wide host range: small mammals, ruminants, horses, birds, cats, dogs, humans (causes HGA, human granulocytic anaplasmosis)
Anaplasma platys (formerly *Ehrlichia platys*)	Dogs
Aegyptianella pullorum, (With other *Aegyptianella* species remaining molecularly undefined)	Birds

mans, HGA is characterized clinically by fever, headache, myalgia, and malaise. Clinicopathologic findings include leukopenia, thrombocytopenia, and elevated levels of C-reactive protein and liver transaminases, both of which are evidence of hepatic injury (reviewed by Carlyon and Fikrig[5]). Although the disease is usually self-limiting, severe complications can result, including prolonged fever, shock, seizures, pneumonitis, acute renal failure, hemorrhage, rhabdomyolysis, and opportunistic infections that may result in death (reviewed by Carlyon and Fikrig[22]).

Infection of *A. phagocytophilum* in domestic ruminants has long been recognized, and the resulting disease is commonly called tick-borne fever (TBF). Clinical presentations of *A. phagocytophilum* infection have been documented in sheep, goats, cattle, horses, dogs, cats, roe deer, reindeer, and humans.[75,79] Tick-borne fever clinical disease in domestic animals frequently includes fever and inappetence, while laboratory findings may reveal inclusions in neutrophils and severe neutropenia. The disease is rarely fatal unless complicated by concurrent infections. Complications may also include abortions and impaired spermatogenesis. In sheep, the most notable result of *A. phagocytophilum* infection is immune suppression and the predisposition to infection with other pathogens.[75]

Despite sharing a common genus, the biology of *Anaplasma phagocytophilum* differs markedly from *A. marginale*. *Anaplasma phagocytophilum* is transmitted by *Ixodes* spp ticks (*I. scapularis* in central and eastern US and *I. pacificus* in California), but other tick species may subsequently prove to be vectors.[15] Deer are the preferred host for adult *I. scapularis* in the US. While cattle are not considered to be a preferred host for *I. scapularis*, these ticks have been collected from cattle and, in the absence of deer, may feed on other hosts. *Anaplasma phagocytophilum* infections are maintained in nature, in part, by small and medium-sized mammals such as white-footed mice (*Peromyscus leucopus*), raccoons (*Procyon lotor*), and gray squirrels (*Sciurus carolinensis*).[49,60,77] Wild rabbits, birds, and cats have been also implicated in the epidemiology of *A. phagocytophilum*.[7,30,48] Evidence suggests that subclinical persistent infections occur in domestic and wild ruminants, including white-tailed, red, and roe deer.[21,22,61] The clinical and host diversity of *A. phagocytophilum* suggest the presence of strain variation, and genetic differences among these strains do occur, which probably contributes to a limited host range of the *A. phagocytophilum* variants.

While natural infections of *A. phagocytophilum* in cattle have been reported in Switzerland and France,[47,63] outbreaks of TBF in cattle have not been reported in the US. However, bovine practitioners should be aware of the possibility of infections producing clinical disease in cattle, especially when cattle are infected with multiple pathogens resulting in suppression of the immune system. Recent research has demonstrated concurrent infections of *Anaplasma* spp in ruminants and ticks.[15,32,53] The establishment of concurrent *Anaplasma* spp infections in reservoir hosts is likely to increase the risk of pathogen transmission among wildlife and domestic animals, including cattle and humans, thus *A. phagocytophilum* has the potential to be an emerging disease of cattle. Diagnostic tests will need to be developed and validated in the US in the future to differentiate *A. marginale* and *A. phagocytophilum* in cattle. Currently, no such diagnostic tests are available to the practitioner.

Developmental Cycle of *A. marginale* and Clinical Disease in Cattle

Erythrocytes are the only known site of infection of *A. marginale* in cattle. Although Munderloh *et al*[56] recently reported propagation of *A. marginale* in a bovine endothelial cell line, infection of endothelial cells in cattle has not been clearly demonstrated. The clinical signs of bovine anaplasmosis are related erythrocytic infections. Within bovine erythrocytes, membrane bound inclusions, commonly referred to as initial bodies, form which contain from 4-8 rickettsiae, and as many as 70% or more of the erythrocytes may be parasitized during acute infections.[64,66] Clinical disease is directly related to the number of infected erythrocytes. Important to note is that the incubation period of infection (prepatent period) varies with the infective dose and ranges from seven to 60 days, with an average of 28 days, and after infected erythrocytes are detectable the number of parasitized erythrocytes increases geometrically. Infected erythrocytes are subsequently phagocytized by bovine reticuloendothelial cells, resulting in development of mild to severe anemia due to extravascular hemolysis and icterus without hemoglobinemia or hemoglobinuria. Clinical signs may include fever early in the disease process, weight loss, abortion, lethargy, pale mucous membranes, icterus, and often death in animals over two years old.[66] Cattle that survive acute infection develop life-long persistent infections characterized by five to six-week cycles of low level rickettsemia.[26,27,36] Persistently infected or "carrier" cattle are considered to be infected for life and have life-long immunity. Upon challenge-exposure, these persistently infected cattle do not exhibit clinical disease. The potentially long prepatent periods and the cyclic rickettsemias of carrier cattle pose challenges to the diagnosis of *A. marginale* infected cattle, and often require repeated serologic testing in order to confirm infection (in-depth information will be presented in a follow-up paper). Most notably, cattle persistently infected with *A. marginale* serve as the most important reservoir of the pathogen for both infection of ticks and cattle by mechanical transmission through the transfer of infected blood to susceptible cattle.

Role of Ticks in Transmission of Bovine Anaplasmosis

Ticks have long been recognized as biological vectors of *A. marginale*.[40] In the US, anaplasmosis is transmitted by *Dermacentor* ticks (*D. andersoni* in western US, *D. variabilis* and *D. albipictus* in other areas of the US). *D. andersoni* and *D. variabilis* are three-host ticks, in which larvae, nymphs, and adult stages feed on separate hosts: larvae and nymphs feed preferentially on small mammals and adults feed on large mammals. *D. albipictus* is a one-host tick, in which all tick stages feed on the same host. *D. variabilis* and *D. andersoni* transmit *A. marginale* from stage to stage (interstadial transmission) or by transfer of male ticks (intrastadial transmission). Once male ticks acquire *A. marginale* infection by feeding on infected cattle, they become persistently infected and, because male ticks are intermittent feeders that transfer readily among cattle, they can repeatedly transmit infection to many cattle.[43,44] Therefore, male ticks may be the main tick vector to transmit *A. marginale* throughout a herd of cattle.

Dermacentor albipictus was implicated in an outbreak of anaplasmosis in western Oklahoma,[25] and may contribute to the epidemiology of anaplasmosis in some areas. Transmission of *A. marginale* to cattle by *D. albipictus* probably occurs most readily by intrastadial transmission by male ticks. *Dermacentor albipictus* has been reported to be a common ectoparasite of moose in Canada.[68] While moose have not been reported to become infected with *A. marginale*, moose may serve as a source of ticks for cattle infestations in areas where moose and cattle share common grazing areas.

Populations of cattle fever ticks, previously reclassified from *Boophilus* to *Rhipicephalus* (*Boophilus*) *microplus* and *R. annulatus*, were declared eradicated from the US in 1943 except for a permanent quarantine or "buffer" zone between Texas and Mexico. However, populations of these ticks have recently expanded,[31] possibly due to tick infestations on deer, elk, nilgai, and other exotic wildlife species that have become established in Texas. Although the major concern with the increase in cattle fever ticks is the reintroduction of Texas cattle fever caused by *Babesia* spp, these tick species also transmit *A. marginale*, and can be co-infected with both pathogens. If populations of *R. microplus* and *R. annulatus* expand and establish populations throughout Texas and other states, these ticks will most likely contribute to an increase in bovine anaplasmosis incidence and prevalence. Although *R. microplus* and *R. annulatus* are one-host ticks and complete their life cycle on an individual animal, transmission of *A. marginale* among cattle could likely occur via male ticks, which may become persistently infected and readily transfer among cattle. A complicating factor in the control of cattle fever ticks has been the selection of acaricide resistant ticks along the border of Mexico and Texas.[51,52,67,74]

The developmental cycle of *A. marginale* in ticks, described in the 1980s and 1990s, is complex and coordinated with the tick feeding cycle.[37,40,42,43] Infected erythrocytes taken into ticks with a blood meal provide the source of *A. marginale* for infection of tick gut cells. After development of the pathogen in tick gut cells, many other tick tissues become infected, including salivary glands (Figure 1), the site from which *A. marginale* is transmitted to cattle during feeding[29] (as reviewed by Kocan[37,39]). At every site of development of *A. marginale* in tick tissues, large colonies form that may contain several hundred organisms. Therefore, even though ticks are small, they may become highly infected with *A. marginale*. Male ticks also develop persistent *A. marginale* infections and, because they are intermittent feeders and readily transfer among cattle, transmission of *A. marginale* by male ticks can be rapidly effected, and male ticks can transmit the pathogen to multiple cattle within a herd or adjacent herds. Under favorable conditions of adequate vegetation and conserved humidity which protect ticks from desiccation, male ticks can persist in the environment for several months to over a year, thereby serving as a reservoir of *A. marginale* in nature. Male ticks are therefore likely to contribute to the epidemiology of anaplasmosis, especially in areas where the tick vector is a one-host tick.

Geographic Diversity of Strains of *Anaplasma marginale*

Prior to the advent of molecular biology, a small number of *A. marginale* strains were recognized based on morphologic characteristics, the geographic area from which they were derived, whether they were cross-protective in cattle, and whether they were infective and transmissible by ticks. For example, most *A. marginale* strains obtained from cattle in Florida were shown to be non-infective for ticks.[10,28,78] Based on this observation,

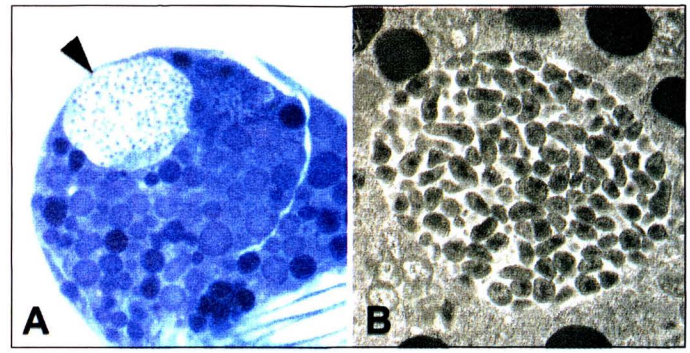

Figure 1. A light (A) and an electron micrograph (B) of colonies of *A. marginale* in salivary gland cells of male *D. variabilis*.

mechanical transmission of anaplasmosis appears to be the major mode of transmission in Florida. A strain from Illinois was also found not to be infective for ticks.[73] Other isolates of *A. marginale* were found not to be cross-protective when used in vaccine trials.[46]

With the advent of molecular biology, several major surface proteins (MSPs) of *A. marginale* were identified and used for phylogenetic analyses of *A. marginale* strains,[16,17,19] as reviewed recently by de la Fuente *et al.*[12,13] Major surface protein 1a, which differs among isolates in molecular weight because of a variable number of tandem 23-31 amino acid repeats, and the genes *msp1α* and *msp4* that encode for the proteins MSP1a and MSP4, were found to be stable genetic markers of *A. marginale* strain identity during multiplication in cattle and ticks.[3,19,20] However, while phylogenetic studies of MSP1a repeat sequences have provided evidence of *A. marginale*-tick co-evolution, these studies did not provide phylogeographic information on a global scale because of the high level of MSP1a genetic diversity. The overall results of these analyses revealed that the diversity of *A. marginale* strains in the US and worldwide was far greater than recognized previously[19,20] (as reviewed by de la Fuente[13]). Within the US, results of these analyses strongly support a southeastern clade or group of related *A. marginale* isolates comprised of isolates from Virginia and Florida. Furthermore, analysis of 16S rDNA fragment sequences from the tick vector *D. variabilis* from various areas of the US was performed and suggested co-evolution of the vector and pathogen.[19] The genetic heterogeneity observed among strains of *A. marginale* within Oklahoma and other endemic regions such as Oregon,[58] could be explained by frequent and sustained cattle movement. In contrast, gene sequences of Australian strains of *A. marginale,* where cattle introductions have been limited, had a 94% similarity.[50]

Recent research demonstrated that maintenance of different genotypes occurs by independent transmission events, due to infection exclusion of *A. marginale* in cattle and ticks in which only one genotype becomes established per animal.[9] Additional research demonstrated the low frequency of cattle infected with two *A. marginale* strains in a cattle herd with high prevalence of infection.[57] The *A. marginale msp1α* genotypes in animals infected with two strains were not closely related, and may reflect a situation similar to the co-infection of *A. centrale/A.marginale* reported in vaccinated cattle in Israel.[72] Overall the importance of these findings helps to explain the mechanism of infection exclusion which results in the maintenance of multiple *A. marginale* isolates in nature.

Despite extensive characterization of the genetic diversity in *A. marginale* geographic strains using MSP sequences, little is known about the biogeography and evolution of *A. marginale* and other *Anaplasma* species. The phylogeography of *A. marginale* MSP1a sequences was recently demonstrated to be associated with world ecological regions (ecoregions), and the evolution of *A. marginale* was found to be linked to ecological traits affecting tick vector performance. Some *A. marginale* strains have evolved under conditions that support the biological transmission of *A. marginale* by *R. microplus* under different ecological conditions which affect the *R. microplus* populations. The evolution of other *A. marginale* strains may be linked to transmission by other tick species or by mechanical transmission in regions where *R. microplus* is currently eradicated.[24]

In summary, these phylogenetic and phylogeographic studies have provided evidence that there appears to be a mechanism for maintaining the diversity of various strains of *A. marginale* in nature. Therefore, the increasing number of geographic strains recognized that vary in genotype, antigenic composition, morphology, and infectivity for ticks most likely has resulted from extensive cattle movement. When cattle movement imports a new *A. marginale* genotype, it can become established and maintained by mechanical and/or biological transmission to susceptible cattle. These results predict that genotypic variation of *A. marginale* strains would be minimal in regions with few cattle/*A. marginale* introductions, while a highly heterogeneous population of *A. marginale* genotypes would be expected to occur in regions with extensive cattle movement, such as Oklahoma and other stocker areas in the US.

The genetic diversity of *A. marginale* strains, as described by use of the genes *msp1α* and *msp4*, constitutes a major challenge for developing vaccines that can protect animals against these diverse isolates. Importantly, vaccine performance may be compromised by the presence of many *A. marginale* strains in a given area because of lack of cross-protection between the *A. marginale* genotype used as vaccine antigen and those genotypes transmitted to cattle in nature.

Epidemiology of Anaplasmosis and the Impact of Wildlife Reservoirs

The epidemiology of anaplasmosis in the US is complex and not well understood. The seroprevalence rates of cattle for *A. marginale* vary widely, and the variability of these rates contributes to the development of geographically stable and unstable enzootic regions. In the US anaplasmosis is enzootic throughout the southern Atlantic states, Gulf Coast states, and several of the midwestern and western states.[55] However, due to the movement of cattle, anaplasmosis has now been reported in almost every state. This wide and increasing distribution is most likely a result of the extensive transport of cattle that are asymptomatic and persistently infected carriers of *A. marginale*. When carrier cattle are imported into any herd or population of cattle,

transmission subsequently can be effected by biological transmission or by mechanical transfer of blood by biting arthropods or blood-contaminated fomites from these carrier cattle to susceptible ones.

Concern about transmission of infectious agents, including *A. marginale*, between wildlife and domestic livestock is increasing, especially in areas where free-ranging wildlife and cattle share common grazing areas.[6] Recent reports have demonstrated that *A. marginale* and *A. phagocytophilum* coexist in certain regions with concurrent infections occurring in ruminants and in ticks.[14,15,18,32,53]

Clinical anaplasmosis occurs in cattle, but in the US other ruminants have been reported to serve as reservoirs of *A. marginale,* including American bison (*Bison bison*), white-tailed deer (*Odocoileus virginianus*), mule deer (*Odocoileus hemionus hemionus*), black-tailed deer (*Odocoileus hemionus columbianus*), and Rocky Mountain elk (*Cervus elaphus nelsoni*),[81] as reviewed by Kuttler.[45] While wild ruminants, particularly mule deer and elk, have been implicated in the epizootiology of bovine anaplasmosis in some regions,[4,33,46,69,81] reinvestigation of wildlife hosts that serve as reservoirs of *A. marginale* using molecular diagnostic tools is needed to define the role of wild ruminants as reservoirs of *A. marginale*. For example, in two recent studies, *A. ovis* rather than *A. marginale* was detected in mule deer,[8,80] raising the question of whether mule deer actually serve as a reservoir host of *A. marginale*. In addition, future research is needed to determine whether mule deer could support coinfections of *A. ovis* and *A. marginale*. The reservoir status of these potential reservoir hosts for *A. marginale* can only be definitively demonstrated by use of molecular diagnostic tests, because serologic tests based on the *A. marginale* major surface protein 5 (MSP5), which is highly conserved, may be cross reactive for *Anaplasma* spp.

Although white-tailed deer in the southeastern US were found experimentally to be susceptible to infection with *A. marginale*, they do not appear to be exposed naturally, even in enzootic areas.[35] In addition, Keel *et al*[35] demonstrated that experimentally-infected white-tailed deer did not develop parasitemia sufficient for mechanical transmission by biting flies. Therefore, while white-tailed deer populations often drive tick populations in much of the US, they do not appear to contribute to the epidemiology of bovine anaplasmosis.

Serologic surveys have incriminated bison in Canada and the US as reservoir hosts for *A. marginale,*[76] and more recently this species was shown to be infected with *A. marginale* and to serve as a host for infection of *Dermacentor* ticks.[11,21,41] Therefore, co-mingling of cattle and bison may not be advisable.

Wildlife species may be a factor in the epidemiology and spread of anaplasmosis because, as reservoir hosts of *A. marginale*, they could serve as a source of infective blood for mechanical spread by various routes and biological transmission by ticks. On the other hand, factors such as climate, host abundance, tick host diversity, and topography were all shown to impact the epidemiology of *A. marginale.*[23] A recent modeling study conducted in Spain emphasized the importance of host habitat usage which demonstrates conditions for the possible dilution effect of wild boar populations for red deer exposure to *Anaplasma* spp.[23] Tick populations are driven by the availability of hosts, and white-tailed deer are the primary hosts for ticks in many areas of the US, most notably for adult ticks.

Climatic Influence on the Impact of Arthropods and the Transmission of Anaplasmosis

The distribution of anaplasmosis may be expected to continue to change as a result of cattle movement, but also may be impacted in the future by climate change which could affect the movement of the ticks.[34] An example of the validity of such a prediction is a confirmed diagnosis of anaplasmosis in a bison herd in Saskatchewan, Canada, during the summer of 2000.[62] The first reported outbreak of anaplasmosis in Canada occurred in 1971,[2] but that outbreak resulted from mechanical transmission from imported carrier cattle to local ones. Protocols proposed in the Sanitary and Phytosanitary Measures (SPS) and by the Risk Assessment Methodology may be important to control spread of diseases like anaplasmosis in the future global trade market.[70] However, the possible establishment of new tick species may complicate control and prevention efforts when carrier cattle are introduced into an area in which new susceptible species of ticks have become established.

Ticks, and arthropods in general, in the environment have adapted to survive extreme cold temperatures and their populations are not reduced by periods of below freezing temperatures. However, tick survival is dependent on vegetation to promote conservation of humidity and protect them from desiccation. Extreme hot temperatures, coupled with decreased rainfall, typically result in reduction of arthropod populations, at least in a current and following season. However, arthropod populations usually rebound after periods of extreme weather conditions.

Conclusions

Herein, we presented an update of the challenges of the management and epidemiology of bovine anaplasmosis. All of the factors reviewed herein contribute to the increasing complexity, control, and epidemiology of anaplasmosis in the US. Furthermore, the classification of *Anaplasma* has recently been reorganized and now

includes several organisms in addition to those that are host-specific for ruminants.

One of these organisms added to the classification, *A. phagocytophilum,* is an emerging tick-borne pathogen in the US with a wide host range, and may negatively impact cattle health in the future. *A. phagocytophilum* infections alone could result in clinical disease in cattle in the future, but disease may more likely occur with concurrent infections of *A. marginale*, *A. phagocytophilum*, or other bovine hemoparasites. However, at present *A. phagocytophilum* has not been reported to be a disease problem in cattle. Importantly, human anaplasmosis caused by *A. phagocytophilum* and bovine anaplasmosis do not share common features.

In the biological transmission of *A. marginale*, male ticks can contribute to the transmission of anaplasmosis because they become persistently infected and, as intermittent feeders, can transfer among cattle and transmit *A. marginale*. Male ticks are the most likely means of tick transmission by one-host ticks, *D. albipictus* and *Rhipicephalus* (*Boophilus*) spp.

The diversity of *A. marginale* isolates is more completely defined and is far greater than previously known. This genetic diversity, which has most likely resulted from extensive cattle movement, constitutes a major challenge for developing vaccines that are protective against a diverse range of isolates.

Wildlife reservoirs of *A. marginale* may impact the epidemiology of anaplasmosis. The role of deer (white-tailed and mule) as reservoirs of *A. marginale* is not well defined and should be redefined using molecular diagnostic tools. However, bison from both Canada and the US were found to be infected with *A. marginale* strains which proved to be infective for cattle, and the US strain was shown to be transmissible by ticks. Therefore, the commingling of cattle and bison may not be advisable.

Climate change may impact the epidemiology of anaplasmosis by affecting the range of ruminant and tick hosts. While hot, dry summers may reduce the number of arthropods involved in biological or mechanical transmission of *A. marginale*, arthropod populations usually rebound rapidly after extreme weather conditions. Ticks are well-adapted to survive very cold temperatures, which does not impact their populations. Finally, populations of tick species are constantly changing and may inhabit new geographic areas which may contribute to the emergence of tick-borne disease.

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