WORKSHOP

ANAPLASMA INFECTION AND ANIMAL REPRODUCTION

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Introduction

The genus *Anaplasma* (Rickettsiales: Anaplasmataceae) includes six species of Gram-negative intracellular bacteria (Dumler et al., 2001). *A. phagocytophilum* infects a wide variety of small and large domestic and wild mammals and birds (Woldehiwet, 2010) and causes human granulocytic anaplasmosis (HGA), an emerging disease in the U.S., Europe and Asia, tick-borne fever (TBF) in ruminants and equine and canine anaplasmosis (Stuen, 2007; Woldehiwet, 2010; Nieder et al., 2012). Some species such *Sus scrofa* are susceptible to infection with *A. phagocytophilum*, but show no clinical signs and their role in pathogen natural cycle is questionable (Galindo et al., 2012; de la Fuente and Gortazar, 2012). Three *Anaplasma* spp. exclusively infect ruminants, *A. marginale, A. marginale ss. centrale* (usually referred to as *A. centrale*), and *A. ovis*. *A. marginale* is the causative agent of bovine anaplasmosis, causing economic losses to cattle industry worldwide and can also infect wildlife (Kocan et al., 2010). Cattle inoculated with the live *A. centrale* vaccine generally experience mild clinical disease and then remain persistently infected but immune for life (Kocan et al., 2010). *A. ovis* is infective for sheep and wild ruminants, but infections are usually asymptomatic (Kocan et al., 2010). Also included in the genus *Anaplasma* are *A. bovis* and *A. platys*, which infect cattle and dogs, respectively. Ixodid ticks transmit all these pathogens, although tick transmissibility of *A. centrale* has been recently questioned (Kocan et al., 2010). For *A. marginale*, mechanical transmission by blood-contaminated fomites and biting insect mouthparts also occur. Transovarial transmission of *Anaplasma* spp. from female ticks to their progeny does not occur. Therefore, ticks must acquire infection during blood feeding and the infectious cycle of these bacteria in nature is dependent upon the presence of infected reservoir hosts.

Anaplasma spp. infection affects gene expression in ticks and vertebrate hosts (Severo et al., 2012; Galindo et al., 2012; Hajdušek et al., 2013), although differences may exist between species (Zivkovic et al., 2009). Furthermore, functional studies of *Anaplasma*-tick interactions have shown how tick genes may affect bacterial infection and transmission (Hajdušek et al., 2013). The effect of pathogen infection on gene expression impact on tick vector capacity, human health, and animal health and production.

Clinical symptoms of *Anaplasma* infection

Bovine anaplasmosis often results in development of mild to severe anemia and icterus without hemoglobinemia and hemoglobinuria. Clinical symptoms may include fever, weight loss, lethargy, icterus, and often death in animals over 2 years old (Kocan et al., 2010). In sheep, cattle and horses, TBF is accompanied by fever, pyemia in lambs,

respiratory signs in cattle and secondary infections that appear days after animals are introduced to tick-infested pastures (Woldehiwet, 2010). A drop in milk yield is another clinical sign in dairy cattle. The severe leukopenia and especially the prolonged neutropenia that accompanies the disease are also good indicators of TBF. Equine and canine infections are characterized by fever, depression, anorexia, leukopenia, and thrombocytopenia (Dumler et al., 2005). In most cases, treatment with antibiotics and supportive therapies usually make a complete recovery.

Effect of *Anaplasma* infection on animal reproduction

The effect of *Anaplasma* infection on animal reproduction has not been fully characterized. Abortion is one of the clinical symptoms associated with bovine anaplasmosis (Kocan et al., 2010). In some cases of TBF abortions may occur, especially when pregnant ewes or cows are moved to tick-infested pastures during the last stages of their pregnancy (Woldehiwet, 2010). Recently, an 8-year-old alpaca infected with *A. phagocytophilum* was reported with fever, anorexia, edema, ascites, and premature parturition (Tinkler et al., 2012).

Another effect of *Anaplasma* infection on animal reproduction that has been reported for *A. marginale* in cattle (Zaugg, 1985; Guglielmone et al., 1995; Bock et al., 2003; Aubry and Geale, 2011) and for *A. phagocytophilum* in humans and cattle (Pusterla et al., 1997; Horowitz et al., 1998; Dhand et al, 2007; Henniger et al., 2013; Reppert et al., 2013) is the possibility for intrauterine or transplacental pathogen transmission, which may result in newborn depression and death.

Conclusions

The impact of *Anaplasma* infection on animal reproduction has not been characterized in detail. Limited information is available for *A. marginale* and *A. phagocytophilum* but absent for other *Anaplasma* species. Infected animals are found in tick-free pastures or high altitude pasturing where ticks would not be present, suggesting that transplacental transmission may be an important means of spread of these pathogens in many host species (Guglielmone et al., 1995; Stuen and Bergstrom, 2001).

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References

Aubry P, Geale DW. A review of bovine anaplasmosis. Transbound. Emerg. Dis. 2011; 58: 1-30.

Bock RE, deVos AJ, Kingston TG, Carter PD. Assessment of a low virulence Australian isolate of *Anaplasma marginale* for pathogenicity, immunogenicity and transmissibility by *Boophilus microplus*. Vet. Parasitol. 2003; 118: 121-131.

de la Fuente J, Gortazar C. Wild boars as hosts of human-pathogenic *Anaplasma phagocytophilum* variants. Emerg. Infect. Dis. 2012; 18: 2094-2095.

Dhand A, Nadelman RB, Aguero-Rosenfeld M, Haddad FA, Stokes DP, Horowitz HW. Human granulocytic anaplasmosis during pregnancy: Case series and literature review. Clin. Inf. Dis. 2007; 45: 589-593.

Dumler JS, Barbet AF, Bekker CPJ, Dasch GA, Palmer GH, Ray SC, Rikihisa Y, Rurangirwa FR. Reorganization of the genera in the families Rickettsiaceae and

Anaplasmataceae in the order Rickettsiales: unification of some species of *Ehrlichia* with *Anaplasma*, *Cowdria* with *Ehrlichia* and *Ehrlichia* with *Neorickettsia*, descriptions of six new species combinations and designation of *Ehrlichia equi* and "HGE agent" as subjective synonyms of *Ehrlichia phagocytophila.* Int J Sys Evol Microbiol 2001; 51:2145-2165.

Dumler JS, Choi KS, Garcia-Garcia JC, Barat NS, Scorpio DG, Garyu JW, Drab DJ, Bakken SB. Human granulocytic anaplasmosis and *Anaplasma phagocytophilum*. Emerg. Infect. Dis. 2005; 11: 1-9.

Galindo RC, Ayllón N, Strašek Smrdel K, Boadella M, Beltrán-Beck B, Mazariegos M, García N, Pérez de la Lastra JM, Avsic-Zupanc T, Kocan KM, Gortazar C, de la Fuente J. Gene expression profile suggests that pigs (*Sus scrofa*) are susceptible to *Anaplasma phagocytophilum* but control infection. Parasites & Vectors 2012; 5: 181.

Guglielmone AA. Epidemiology of babesiosis and anaplasmosis in South and Central America. Vet. Parasitol. 1995; 57: 109-119.

Hajdušek O, Šíma R, Ayllón N, Jalovecká M, Perner J, de la Fuente J, Kopáček P. Interaction of the tick immune system with transmitted pathogens. Front. Microbiol. (Cellular and Infection Microbiology) 2013; in press.

Henniger T, Henniger P, Grossmann T, Distl O, Ganter M, von Loewenich FD. Congenital infection with *Anaplasma phagocytophilum* in a calf in northern Germany. Acta Vet. Scand. 2013; 55: 38.

Horowitz HW, Kilchevsky E, Haber S, Aguero-Rosenfeld M, Kranwinkel R, James EK, Wong SJ, Chu F, Liveris D, Schwartz I. Perinatal transmission of the agent of human granulocytic ehrlichiosis. New England J. Med. 1998; 339: 375-378.

Kocan KM, de la Fuente J, Blouin EF, Coetzee JF, Ewing SA. 2010. The Natural History of *Anaplasma marginale*. Vet. Parasitol. 2010; 167: 95-107.

Nieder M, Silaghi C, Hamel D, Pfister K, Schmäschke R, Pfeffer M. Tick-borne fever caused by *Anaplasma phagocytophilum* in Germany: first laboratory confirmed case in a dairy cattle herd. Tierarztl Prax Ausg G Grosstiere Nutztiere 2012; 40: 101-106.

Pusterla N, Brun U, Wolfensberger C, Lutz H. Intrauterine infection with *Ehlrichia phagocytophila* in a cow. Vet. Rec. 1997; 141: 101-102.

Reppert E, Galindo RC, Breshears MA, Kocan KM, Blouin EF, de la Fuente J. Demonstration of transplacental transmission of a human isolate of *Anaplasma phagocytophilum* in an experimentally infected sheep. Transbound. Emerg. Dis. 2013; in press.

Severo MS, Stephens KD, Kotsyfakis M, Pedra JH. *Anaplasma phagocytophilum*: deceptively simple or simply deceptive? Future Microbiol. 2012; 7: 719-731.

Stuen S. *Anaplasma phagocytophilum* - the most widespread tick-borne infection in animals in Eur. Vet. Res. Com. 2007; 31(Suppl. 1): 79-84.

Stuen S, Bergstrom K. Serological investigation of granulocytic *Ehrlichia* infection in sheep in Norway. Acta Vet. Scand. 2001; 42: 331-338.

Tinkler SH, Firshman AM, Sharkey LC. Premature parturition, edema, and ascites in an alpaca infected with *Anaplasma phagocytophilum*. Can. Vet. J. 2012; 53: 1199-1202.

Woldehiwet Z. The natural history of *Anaplasma phagocytophilum*. Vet. Parasitol. 2010; 167: 108-122.

Zaugg JL. Bovine anaplasmosis: transplacental transmission as it relates to stage of gestation. Am. J. Vet. Res. 1985; 46: 570-572.

Zivkovic Z, Blouin EF, Manzano-Roman R, Almazán C, Naranjo V, Massung RF, Jongejan F, Kocan KM, de la Fuente J. *Anaplasma phagocytophilum* and *A. marginale* elicit different gene expression responses in ticks and cultured tick cells. Comp. Funct. Genomics 2009; 2009: 705034.