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Review Article

Tick-Borne Fever (*Anaplasma phagocytophilum* Infection) in Sheep – A Review

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Abstract

Ticks may transmit pathogens to ruminants worldwide, creating diseases such as anaplasmosis, babesiosis, ehrlichiosis and theileriosis. In Europe, the most important tick vector is *Ixodes ricinus* and the most widespread tick-borne infection in animals is *Anaplasma phagocytophilum*. This infection causes tick-borne fever (TBF) in ruminants, a disease which may not only cause suboptimal growth, but may also have severe economic and welfare challenges in the sheep industry. In this review, different aspects of *A. phagocytophilum* infection in sheep will be presented.

INTRODUCTION

Several tick-borne infections occur in ruminants, such as anaplasmosis, babesiosis, ehrlichiosis and theileriosis [1,2]. In Europe, the most widespread tick-borne infection in animals is the bacterium *Anaplasma phagocytophilum* [3], causing the disease tick-borne fever (TBF) in ruminants. In the UK, it has been estimated that more than 300 000 lambs get tick pyaemia each year [4], and that up to 30% of TBF-infected lambs may develop crippling lameness and paralysis following secondary infections. Most of these lambs die or have a low economic value [5]. TBF has also for centuries been one of the main scourges for the sheep industry in Norway, and it has been estimated that more than 300 000 lambs are infected annually [6]. The review will present updated information on *A. phagocytophilum* infection in sheep.

TICK-BORNE FEVER

Species

Anaplasma phagocytophilum (formerly *Ehrlichia phagocytophila*) is an obligate intracellular bacteria in the family *Anaplasmataceae* that primarily infects phagocytes [7]. *A. phagocytophilum* appears to be a generalist, infecting a wide range of animals including humans, whereas multiple genetic variants of the bacterium have for instance been characterized in sheep [8].

Distribution

The bacterium is widespread in areas with *Ixodes* ticks, especially in *I. ricinus* areas of Europe [9], whereas severe *A. phagocytophilum* infection in sheep seems to occur mainly in northern areas. However, TBF seems to be rare or an unnoticed disease on other continents, although the bacterium have been detected in several ticks species. The reason for this is unknown, but may be due to different grazing management, unawareness or lack of surveillance and diagnostic tools, host species, breeds and variants of the bacterium involved [9]. The infection in humans was first reported in the US in 1994 [10].

Transmission

Already in 1932, the hard-bodied tick *I. ricinus* was shown to transmit *A. phagocytophilum* in sheep. This tick has later been found to be the main vector of *A. phagocytophilum* in Europe [11,12]. Besides *Ixodes* sp. ticks, *A. phagocytophilum* has also been found in other ticks species, such as ticks within the genera *Dermacentor* and *Rhiplicephalus* [13], but the epidemiological importance of these findings remains to be determined. In addition, mechanical transmission by flies, mosquitoes or even needles may not be totally excluded [12].

Transmission of *A. phagocytophilum* from vector to host occurs generally 24 hours after tick attachment, although transmission can also occur before [14]. The bacteria survive through the moulting process of *I. ricinus*, i.e. transstadial transmission takes place [15]. However, transovarial transmission of *A. phagocytophilum* has not yet been verified.

The possibility of co-feeding transmission in *Ixodes* ticks may occur, but has to be elucidated further [16,17], i.e. uninfected ticks acquiring a non-systemic infection by feeding in time and space with infected ticks on the same host. In general, transmission efficiency may be influenced by several factors, such as the number of feeding ticks, tick species, possible co-feeding transmission, variants of *A. phagocytophilum* involved

and the degree of acquired anti-tick resistance [9].

Other transmission routes may also occur. During the acute phase of the infection, oral and intrauterine transmission of *A. phagocytophilum* has been demonstrated in newborn calves and perinatal infection in one newborn lamb [18-20]. In addition, intrauterine infection in sheep may occur during the persistent phase of the infection (Stuen, unpublished results). However, the epidemiological importance of these results remains to be evaluated.

Clinical expression

The most characteristic symptom of TBF in domestic ruminants is high fever (up to >42°C). Sheep exposed to infected ticks develop clinical signs within 3-14 days. The fever may last for one to two weeks, followed by a severe neutropenia (< 0.7 neutrophils/ml) for 1-2 weeks. However, the fever reaction may vary according to the age of the animals, the variant of *A. phagocytophilum* involved, the host species and immunological status of the host [9]. It has been suggested that primary asymptomatic cases of *A. phagocytophilum* infection may be due either to sheep variants with low virulence or a spill over infection from strains not originally associated with sheep [21].

Other clinical signs are often absent or mild. TBF is seldom fatal unless complicated by other infections. However, TBF causes immunosuppression and makes the sheep vulnerable to secondary infections, such as tick pyaemia caused by *Staphylococcus aureus* infections, and *Bibersteinia* / *Mannheimia* septicaemia. Complications also include abortion, impaired spermatogenesis in rams, reduced weight gain in lambs and a reduced milk yield in dairy animals [4,9,15]. To the author´s knowledge, *A. phagocytophilum* has only caused clinical disease with secondary infections in sheep infected for the first time or when challenged with heterologous variants of high pathogenicity. Although subclinical or unrecognised infection may not lead to overt disease, it may however cause suboptimal growth and production. A chronic *A. phagocytophilum* infection has not yet been confirmed in any species.

Persistence

Another important aspect of this bacterium is that it may cause persistent infection in sheep for several months or even years. *A. phagocytophilum* may therefore be carried from one grazing season to the next and between geographical areas by purchasing infected animals [9,15]. Since transovarial transmission of *A. phagocytophilum* appears to be inefficient in *I. ricinus*, mammalian hosts are presumed to play a crucial role in the maintenance and propagation in nature [22].

The persistence of *A. phagocytophilum* in infected hosts seems to involve a mechanism to escape the immune response. In one report, it was suggested that *Anaplasma* may reside in poorly vascularised connective tissue, where antibodies may have difficulties penetrating [23]. However, antigenic variation has been proposed to be the key feature of this pathogen to allow persistence in mammalian hosts [24,25], whereas *A. phagocytophilum* displace cyclic bacteraemia as periodic peaks containing genetically distinct variants of major surface proteins. The low level of circulating organisms detected between periods of bacteraemia may indicate temporary clearance of infected cells or possible margination of infected granulocytes to endothelial surface [26]. *A. phagocytophilum* has also been found to persist in several other species, such as red deer, dogs, horses and cattle [9,27,28]. The continuance of the infection may differ according to individual variation, *Anaplasma* variants and host species involved [12].

A. phagocytophilum has been found in alveolar macrophages and Kupffer cells, reticuloendothelial cells and tissue macrophages in acutely infected sheep [29-31]. Further investigation is needed to clarify which cells harbour the organism in persistently infected sheep.

Immunity

Earlier experimental studies have shown that the immunity after a primary *A. phagocytophilum* infection varies and that sheep may resist homologous challenge for a period from a few months to more than one year. The degree of protection varies according to the variant of *A. phagocytophilum*, the type and age of the host, and the time and frequency of the challenge [9].

As already mentioned, *A. phagocytophilum* causes immunosuppression up to at least 6 weeks [32]. The mechanism by which *A. phagocytophilum* causes immunosuppression is not clearly understood. It is thought to be related to reduced phagocytosis and diapedesis of infected neutrophils, a reduction in the number of circulating neutrophils and lymphocytes, and the down-regulation of some of their functions [33].

The severe immunosuppression may also be related to the changes in lymphocyte populations. It is possible that reduction in various lymphocyte subsets and changes in the helper (CD4): suppressor (CD8) T cell ratio observed in peripheral blood of sheep infected with *A. phagocytophilum* may affect lymphocyte responses to bacterial or viral antigens [34].

Investigation has shown that some serum factors are, at least in part, responsible for the immunosuppression associated with TBF in sheep. The concentration of tumour necrosis factor–alpha (TNF-α) and nitrate in ovine sera were significantly increased during infection with *A. phagocytophilum* [34,35]. Recent studies in sheep have identified several cytokines that are induced during infection, such as IFN-γ, IL-β, IL-6, IL-10 and IL-12 [36].

Infection by a human isolate has been shown to prevent the respiratory burst reaction in neutrophils by inhibition of the NADPH oxidase, which also could make the host more susceptible to secondary infections [37]. It has also been speculated that the pathogenesis of anaplasmosis is not caused directly by the organism, but that the injury may be in part host-mediated [31,38,39].

Strains/variants

Based on different genes such as *16S rRNA*, *ankA*, *groESL*, and *msp4*, several genetic variants with high degree of diversity of the bacterium have been found in sheep with a variable degree

of cross-protective immunity [8,9]. In one study, 24 *msp4* gene variants were found in a sheep flock during one grazing season [40]. The reason for this huge amount of *msp4*-gene variants is unknown.

Several *A. phagocytophilum* enzootic cycles between ticks and wild animals in nature have been proposed [8,41,42]. Spillover infection to other hosts may occur commonly. The epidemiology of variants isolated from infected sheep is unknown. According to earlier studies, red deer (*Cervus elaphus*) may act as host for variants of *A. phagocytophilum* known to cause TBF in sheep [43]. However, it should for instance be elucidated if other mammals and/or tick species are involved in the natural transmission cycle of *A. phagocytophilum* variants infecting red deer and sheep. The potential of a vertebrate to function as a reservoir host depends on factors such as the host´s density in the tick habitat and the degree of contact with the actual vector and the host, as well as the level of bacteraemia in the host [12].

Infection with multiple variants of *A. phagocytophilum* in single sheep have been observed, which may be caused by super infection or simultaneous transmission from multiple infected ticks [40,44].

Diagnosis

The clinical diagnosis is based on a sudden onset of very high fever associated with haematological changes and the presence of typical cytoplasmatic inclusions in phagocytes, especially in neutrophils. Microscopy of blood smears taken in the fever period is normally sufficient to confirm the diagnosis. Stained with May-Grünwald Giemsa, the organisms appear as light-blue inclusions. In the acute phase of the infection up to 90% of the neutrophils may be infected [15].

Inoculation of infected blood into susceptible animals was also previously used to confirm the diagnosis. However, a PCR method is now commonly used to identify *A. phagocytophilum* in blood and tissue samples. In addition, cultivation of *A. phagocytophilum* in different tissue cultures has been described [9].

The presence of specific antibodies may support the diagnosis, especially an indirect immunofluorescent antibody (IFA) test is widely used. However, it may be difficult to use the IFA-test to diagnose an acute infection in lambs, since the IFA-titres persist for months after the primary *A. phagocytophilum* infection [9].

At port mortem, an enlarged spleen up to four to five times the normal size often with sub-capsular bleedings, are regarded as indicative of TBF in sheep [15]. No other typical pathological changes in sheep have been described.

Treatment

The safest way to prevent TBF is to avoid tick-infested areas. However, this is often not feasible. In endemic areas, regular dipping or pour-on treatment with pyrethroids against ticks may be necessary [9].

In direct treatment, the drug of choice is tetracycline. However, a 5-day long treatment with oxytetracycline (10 mg/kg per day) was not enough to clear the organism from experimentally *A. phagocytophilum* infected lambs. Data suggest that quinolone antibiotics and rifampin may be alternative drugs for animals and patients with intolerance to tetracycline [9].

Control

The main disease problems associated with TBF are seen in lambs during the first grazing season, and in sheep purchased from tick-free areas and placed on tick-infested pastures for the first time [45]. Problems due to TBF may however differ significantly between neighboring pastures. One reason for this may be due to the variants involved with different virulence and protective immunity [46].

As already mentioned, the infection causes persistence in sheep, and variants may therefore be carried between geographical areas. Ticks may become infected from these carriers and later transfer these variants to susceptible animals. Since infected sheep may show few clinical signs, TBF in flocks with low morbidity and mortality could stay unnoticed for years until severe losses due to secondary infections occur (Stuen, personal information).

Current control strategies are based on the reduction of tick infestation by acaricides at turnout on tick pasture. This is mostly done be dipping or pour-on applications of pyrethroids [9,47]. This treatment has to be repeated several times during the tick season. In the UK, long-acting tetracycline is also used as a prophylactic measure given before animals are moved from tick-free environment into tick-infested pasture [5,48]. However, there is a growing concern about the environmental safety and human health, and the increasing resistance of ticks to pesticides [49].

Another strategy to reduce the losses due to TBF is to infect the lambs as early as possible. However, this practice is only feasible if the lambs are infected immediately after birth (< 2 weeks old), since three to six week old lambs are very susceptible to the infection [9].

Pasture management and habitat modification may reduce the density of ticks and thereafter the occurrence of TBF. The methods include drainage, controlled burning, herbicidal treatment, mechanical clearing of bushes, removal of leaf litter, and in some cases partial removal of the forest canopy [50]. Alteration of the habitat may also change the tick hosts availability. However, the tick abundance can only be reduced by these procedures for a short period, and several procedures have to be repeated periodically and are labour intensive. In addition, sufficient habitat modification is not always feasible and farm animals are always at risk from ticks brought in from surrounding areas, especially if other large animal species use the same pastures.

Biological tick control is an attractive approach to tick management. Studies so far have concentrated of bacteria, entomopathogenic fungi and nematodes [49]. However, the main challenge is to create a sustainable biological control of ticks in the natural habitat.

As already mentioned, recent investigations indicate that there may be natural enzootic cycles among different strains of *A. phagocytophilum*, whereas red deer may serve as hosts for variants involved in TBF in sheep. However, genotyping based on *msp4*-gene sequencing indicates that a clustering of variants with wild ruminants appearing distinct from sheep variants. Management of the cervid population to protect domestic sheep from ticks and tick-borne infection should therefore be further elucidated [43].

A vaccine against *A. phagocytophilum* is not yet available. In order to develop a vaccine, the challenge is to choose the right antigens that are conserved among all variants of *A. phagocytophilum* [51]. The whole genome of human variants of *A. phagocytophilum* has recently been sequenced. However, several sheep variants of the bacterium have to be sequenced in order to do comparative genomics and develop proper recombinant vaccine antigens for future cross-infection studies [52,53].

Vaccines against ticks are also an alternative option. However, only a vaccine against the one-host cattle tick *Rhipicephalus* (*Boophilus*) *microplus* has so far been developed [54]. Control of ticks by vaccination have the advantages of being cost-effective, reducing environmental contamination and prevent the selection of drug-resistant ticks that may result from repeated acaricide applications. Development of vaccines against multiple tick species may be possible using highly conserved tick-protective antigens or by antigens showing immune cross-reaction in different tick species [55].

CONCLUSIONS

A. phagocytophilum epidemiology involves different ecotypes circulating in various hosts species, especially as *Ixodes* ticks feed on a large variety of vertebrates [53]. An active surveillance for *A. phagocytophilum* is therefore necessary in order to identify the real distribution, since strain/variants may exist with various clinical and immunological characteristics between different small ruminant breeds. In addition to welfare aspects, the farmer would also benefit when unrecognised and subclinical infections are revealed and curative and preventive measurements performed.

Climatic change will have an effect on the distribution and establishment of populations of ticks, since climate-warming models predict that several tick species are likely to establish more northern permanent populations [56,57]. In addition, millions of ticks are annually spread by migrating birds, making the possibility for long distance spread of ticks and pathogens, such as *A. phagocytophilum* [58,59].

Development of new recombinant vaccines using comparative genomics and proteomics will continue in progress. Whole genome sequencing is a promising tool to study *A. phagocytophilum* pathogenicity and epidemiology and hopefully in the future help to develop a vaccine for efficient control management.

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