Travel Medicine and Infectious Disease (2014) 12, 609–616

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevierhealth.com/journals/tmid

REVIEW

An overview: Tularemia and travel medicine

Aysegul Ulu-Kilic [a], Mehmet Doganay [a,b,*]

[a] Department of Infectious Diseases, Faculty of Medicine, Erciyes University, Kayseri, Turkey
[b] Zoonoses Working Group of International Society of Chemotherapy (ZWG-ISC), United Kingdom

Received 20 February 2014; received in revised form 13 August 2014; accepted 9 October 2014
Available online 18 October 2014

KEYWORDS
Tularemia;
Travel;
Francisella tularensis

Summary Tularemia is a bacterial zoonotic infection. The disease is endemic in most parts of the world, has been reported through the northern hemisphere between 30 and 71° N latitude. *Francisella tularensis* causes infection in a wide range of vertebrates (rodents, lagomorphs) and invertebrates (ticks, mosquitoes and other arthropods). Humans can acquire this infection through several routes including; a bite from an infected tick, deerfly or mosquito, contact with an infected animal or its dead body. It can also be spread to human by drinking contaminated water or breathing contaminated dirt or aerosol. Clinical manifestation of this disease varies depending on the biotype, inoculum and port of entry. Infection is potentially life threatening, but can effectively be treated with antibiotics. Travelers visiting rural and agricultural areas in endemic countries may be at greater risk. Appropriate clothing and use of insect repellants is essential to prevent tick borne illness. Travelers also should be aware of food and waterborne disease; avoid consuming potentially contaminated water and uncooked meat. Physicians should be aware of any clinical presentation of tularemia in the patients returning from endemic areas.

1. Introduction

Tularemia is an infectious bacterial disease that is also known as deerfly fever, rabbit fever and Ohara's fever. The causative agent; *Francisella tularensis*; is a gram-negative, facultative intracellular bacterium. Currently, there are four biotypes or subspecies of this bacterium that are recognized with different virulence characteristics. The disease affects a wide range of host species and human transmission occurs by several routes. Most commonly, humans come into contact with this infection by skin contact which leads to the ulceroglandular form of the disease [1,2].

As the true prevalence of Tularemia is underestimated due to the lack of knowledge about the disease, in some parts of the world the disease is endemic with cases mainly reported throughout the northern hemisphere. The clinical diagnosis mainly relies on clinical suspicion and should be considered in patients with an epidemiological link. As Tularemia often has mild symptoms, many cases go unreported. The disease is extremely rare in travelers, but the

* Corresponding author. Department of Infectious Diseases, Faculty of Medicine, Erciyes University, Kayseri, Turkey.
E-mail addresses: draysegululuu@yahoo.co.uk (A. Ulu-Kilic), mdoganay@erciyes.edu.tr (M. Doganay).

http://dx.doi.org/10.1016/j.tmaid.2014.10.007
1477-8939/

incidence may be underestimated and unreported. The risk for travelers is generally low but those visiting rural and agricultural areas may be at greater risk.

In this paper, current literature on microbiology, ecoepidemiology, diagnosis and treatment of tularemia was reviewed and considered. The literature review emphasized that the risky areas and risk factors for travelers and preventive measures for this disease. Evaluation of the risks and regional data were presented to healthcare workers so that they could advice travelers.

2. Microbiological characteristics

The bacterium was first isolated in 1911 by Mc Coy and Chapin in Tulare country, California. They named the causative agent isolated from ground squirrels as *Bacterium tularense* [3]. The genus was named as *Francisella* after Edward Francis who first defined bacteriology, pathogenesis and epidemiology of bacterium. *F. tularensis* is a small (0.2—0.5 μm × 0.7—1.0 μm), gram negative, intracellular bacterium. It is a pleomorphic, non-motile coccobacillus and highly virulent pathogen capable to cause an infection with only 10—50 bacteria.

Four subspecies (*tularensis* - type A, *holarctica* - type B, *mediasiatica*, and *novicida*) of *F. tularensis* differ according to their pathogenicity and geographical distribution. *F. tularensis* subsp. tularensis which is the most virulent is divided in two subpopulations of A.I and A.II [3,4]. *F. tularensis* subsp. *holarctica is clinically significant but less virulent to humans. The difference in virulence is demonstrated in a rabbit model that only one bacterium of F. tularensis* subsp. tularensis *is enough for %100 mortality, while* 10^9 *is required for holarctica* strain [5]. Three biovars of *F. tularensis* subsp. *holarctica* have been described: biovar I (erythromycin susceptible), biovar II (erythromycin resistant), and biovar japonica. *Subsp. mediaasiatica* has similar virulence to *F. tularensis* subsp. *holarctica*. *The other rarely isolated, less virulent type is Francisella novicida which has* been shown to cause disease only in immunocompromised patients [4].

F. tularensis is a highly virulent bacterium which can replicate and survive in macrophage but little is known about the virulence factors of the bacteria. Francisella pathogenicity island (FPI) is found to be responsible for intramacrophage growth. The two proteins (VgrG and IglI) encoded by FPI are secreted into cytosol of infected macrophage and take action in phagosomal escape, intramacrophage growth, inflammasome activation and virulence in mice [6]. *F. tularensis* uses type IV pilli and this surface structure also contribute its virulence [3]. Lipopolysacchride is another surface structural component with a lower toxicity level. Virulent strains of *F. tularensis* have a thick capsule, while avirulent strains have a thinner one.

The Clinical and Laboratory Standards Institute (CLSI) provided antibiotic susceptibility breakpoints for streptomycin, gentamicin, tetracycline, doxycycline, ciprofloxacin, levofloxacin and chloramphenicol. To date, no resistance to these antibiotics has been documented for *F. tularensis* [7]. Erythromycin resistance is used as an epidemiological marker; however, this antibiotic is not recommended for treatment of disease.

3. Ecology of the disease

As Tularemia has a complex ecological cycle in nature, the overall ecology of the disease remains poorly understood. *F. tularensis* causes infection in a wide range of vertebrates (rodents, lagomorphs) and invertebrates (ticks, mosquitoes and other arthropods). There are mainly two cycles of the disease that have been described: terrestrial and aquatic. In the terrestrial cycle rabbits, hares, rodents are the most important mammalian hosts whereas beaver, muskrat and voles are in aquatic cycle [1]. *F. tularensis* subsp. tularensis occurs predominantly in dry environment whereas *F. tularensis* subsp. *holarctica is associated with aquatic habitats*. It has been suggested that the species of protozoan (*Acanthamoeba castellanii*) play a role in aquatic cycle as a reservoir for tularemia [8].

Infection transmission to humans can be by several routes: I) bites by infected arthropods ii) handling of infectious animal tissues or fluids iii) ingestion or direct contact with water, food or soil, iv) inhaling infective aerosols [8].

F. tularensis subsp. tularensis is found in lagomorphs and is generally transmitted to humans via contact with infected animals or by bites from infected insects. *F. tularensis* subsp. *holarctica is isolated mainly from aquatic rodents (beavers, muskrat) and also from voles and hares*. Mosquitoes are considered to be the major vector to transmit *F. tularensis* subsp. *holarctica* to humans [9]. A recent study provided evidence that mosquitoes acquire the bacterium as aquatic larvae and transmit the disease to humans [10]. Subspecies *holarctica* found to be persist in natural waters and sediments in endemic areas [11].

Domestic animals such as sheep and cattle are resistant to infection and develop antibodies; however outbreaks can rarely be seen among sheep during lambing season [12].

Person to person transmission has not been documented.

3.1. Climate change

Climate variations affect vector biology, population as well as behavior of rodents and lagomorphs and consequently transmission of disease to humans [13]. Timing and intensity of outbreaks and geographic distribution of diseases are also associated with the climate. A recent study conducted in certain endemic regions of Sweden found that outbreaks of tularemia was found to be associated with much higher temperatures. The authors used climate change scenario data to predict tularemia outbreak activity. Their results suggested that the increase in temperature during the summer months was associated with prolonged duration of epidemics [14]. Also, another study reported that there was a quantitative correlation of mosquito abundance and human tularemia cases during late summer [15]. A similar study from North America demonstrated that climate changes caused a northward-shift in geographical distribution of diseases [16]. High rainfall affects the abundance of rodent population and subsequent mass death of animals, which has been previously reported to precede tularemia outbreaks in Kosovo [17]. A recent study from Turkey reported that there is a correlation of rain periods and the waterborne tularemia outbreak that occurred between 2010 and 2012 [13].