Tularemia

Subjects: Pathology
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Francisella tularensis (Ft) is the etiological agent of tularemia, a disease known for over 100 years in the northern hemisphere. Ft includes four subspecies, of which two are the etiologic agents of tularemia: Ft subsp. *tularensis* (Ftt) and Ft subsp. *holarctica* (Fth), mainly distributed in North America and the whole northern hemisphere, respectively.

Keywords: Francisella tularensis

1. Historical Background of *Francisella tularensis* and Tularemia

Ft (originally named *Bacterium tularense*) was first isolated in 1911 by McCoy and Chapin in Tulare County (CA, USA), during an investigation of a epizootic pseudoplague in ground squirrels[1][2]. This bacterium was isolated from humans in 1912 by Werry and Lamb from a patient suffering from deer fly fever[3]. In 1921, Francis proposed the name tularemia for the disease caused by Ft[4]. In 1924, Parker and Spencer isolated the bacterium from the tick species *Dermacentor andersoni* and demonstrated this arthropod species' role as an Ft vector[5]. The genus name *Francisella* and species name *tularensis* were proposed in 1947 to honor Edward Francis[6].

2. Francisella tularensis

Ft is a Gram-negative, coccobacillus shaped, facultative intracellular bacteria. This species includes four subspecies distinguishable by their geographical distribution[7][8]. The most virulent subspecies are Ftt (type A) and Fth (type B), representing the etiological agents of tularemia[9][10]. The third subspecies, *mediasiatica,* has never been associated with human infections[11][12]. Finally, Ft subsp. *novicida* (Ftn) living in aquatic biotopes generally affects immunocompromised people and is used as a laboratory model due to its low virulence[13][14].

Ft was classified by the CDC in 2002 as a biological weapon category A[15] because of its high virulence and the possibility of inducing fatal pneumonia by aerosol diffusion[16]. Indeed, 10 CFU of this bacterium can cause infection in humans[15]. No tularemia vaccine is currently authorized for human use. In the past, tularemia vaccines were mainly developed to protect human populations from Ft as a biological weapon. The live vaccine strain (LVS) of Ft has been extensively used for this purpose but then abandoned because of significant side effects and low efficacy in preventing type A tularemia[10].

Ft is a zoonotic agent with a large animal reservoir (mammals, fish, amphibians, birds, reptiles). Lagomorphs (wild hares and rabbits) and small rodents (mice, voles, gerbils, lemmings, coypu, etc.) are the primary sources of human infections[3][10]. Humans can be infected through different ways, such as direct contact with infected animals, inhalation of contaminated dust, ingestion of contaminated food, contact with or ingestion of contaminated water, and arthropod bites (mainly the ticks Ixodidae)[17].

3. Tularemia Geographical Distribution

Tularemia is mainly distributed in the Northern Hemisphere of the globe[18]. In Europe, Scandinavia (Sweden and Finland) is a primary endemic area, followed by the Balkans, particularly Kosovo[19][20]. Hungary and the European part of Turkey (Thrace) also record high incidences, followed by Slovakia, the Czech Republic, Serbia, Bulgaria, Norway, Germany, Spain, Poland, Georgia, and France[6][20][21][22]. In Asia, Russia, China, Japan, Kazakhstan, and Turkmenistan are endemic areas of tularemia. Northern America is also an endemic area for tularemia (mainly Ftt), with Canada and the United States recording several human infections every year and occasional outbreaks. In the United States, most human tularemia cases are reported in central states, Arkansas, Oklahoma, South Dakota, Kansas, and Missouri[20]. The subspecies *holarctica* has recently been detected in southern Australia, causing human infections after bites from possums[23]. Tularemia is classically absent in the United Kingdom, Iceland, Africa, South America, and Antarctica[20].

4. Tularemia, the Disease

Tularemia usually manifests in humans by a flu-like syndrome occurring on average 3 to 5 days after infection, with a maximum incubation period of two weeks[6][10][24]. Then, the disease classically progresses to one of the six clinical forms (sometimes combined), depending on the route of contamination. The ulceroglandular form manifests by a skin lesion at the inoculation site of bacteria and regional lymphadenopathy. The glandular form manifests by regional lymphadenopathy without skin lesions. The oculoglandular form corresponds to the bacterium inoculation through the conjunctiva. It corresponds to conjunctivitis with satellite lymphadenopathy. The oropharyngeal form occurs after oral contamination. It corresponds to pharyngitis with submandibular or cervical lymphadenopathy. The pneumonic form is triggered by the bacteria's inhalation and corresponds to acute, subacute, or even chronic pneumonia. Finally, the typhoidal form manifests by severe sepsis usually associated with neurological signs (confusion) and Ft bacteremia. These two last systemic infections are the most severe forms of tularemia[10].

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