Clinical manifestations and the epidemiology of tularemia

Klinička slika i epidemiologija tularemije

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Abstract. *Francisella tularensis*, the etiological agent of tularemia, was first recognized as a human pathogen more than 100 years ago. For several decades after its discovery, tularemia was a common disease in Soviet Union, the USA, and in certain parts of Eastern Europe but its importance in these countries has declined. In contrast, during the last decades, the disease has been emerging in several areas in the world, *e.g.*, in Turkey, Kosovo, and Spain, and the largest number of cases in Europe have consistently been recorded in Sweden and Finland. The various forms of clinical manifestations are reviewed and their occurrences in various parts of the world described. Currently used antibiotic regimens are also described.

Key words: Clinical manifestations; epidemiology; *Francisella*; treatment; tularemia

Sažetak. Bakterija *Francisella tularensis* je uzročnik tularemije, a kao humani patogen prepoznata je prije više od 100 godina. Nekoliko desetljeća nakon otkrića tularemija je bila česta diljem Sovjetskog Saveza, SAD-a te u istočnoj Europi, no bolest se u tim područjima javlja sve rjeđe. No, u posljednje vrijeme tularemija se pojavljuje u različitim dijelovima svijeta, uključujući Tursku, Kosovo i Španjolsku, a najučestalija je diljem Švedske i Finske. U ovom radu opisani su različiti klinički oblici tularemije te njihova pojavnost diljem svijeta. Također su opisani antibiotici koji se koriste u liječenju tularemije.

Ključne riječi: epidemiologija; *Francisella;* klinička slika; liječenje; tularemija

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THE EPIDEMIOLOGY OF TULAREMIA

Francisella tularensis has been recognized as a human pathogen since the beginning of the 20th century and the etiological agent of the zoonotic disease tularemia. The disease has been reported from many countries of the Northern Hemisphere, but it is a rare pathogen in most countries. The rarity of tularemia and the high contagiousness of the pathogen have resulted in a limited experience of *F. tularensis* by most clinical laboratories.

F. tularensis subsp. *tularensis* has been classified by the CDC as a category A select agent (potential biological weapon).

First recognized as a plague-like disease of rodents, the first human tularemia cases in the United States were reported already in 1914[1]. It was named after Tulare County in California where the disease was endemic among rodents. It soon was obvious that the disease was common in the United States and also in other parts of the world, and during the 1920's, Japanese and Russian researchers also described tularemia for the first time. The number of tularemia cases in the United States and Soviet Union peaked during World War II but declined thereafter[2,3]. *F. tularensis* has been considered as a potential biological weapon starting from the 1940's and it was one of the agents given highest priority in the United States and Soviet Union during the Cold War[4]. Today, *F. tularensis* is one of six agents designated as a Tier-1 Select Agent by the US Centers for Disease Control and Prevention, *i.e.*, biological agents considered to have the highest "potential to pose a severe threat to public health and safety" (http://www.selectagents.gov/SelectAgentsandToxinsList.html).

For very long, endemic foci have existed in Russia, Kazakhstan and Turkmenistan[5,6] as well as in Finland and Sweden[7]. In the former Soviet Union, the total numbers of cases have decreased significantly and since 1990, have varied between 50 to 150 cases annually[7,8]. Cases are reported every year from many countries in Eastern Europe, but it is a rare disease in continental Western Europe

although several extensive outbreaks have occurred since 1996 in Spain[9]. Other regions with significant outbreaks as well as endemic regions have been in Turkey, Finland, Sweden and Kosovo. Many of the out breaks have been substantial and encompassed several hundreds of cases[10-13]. Tularemia had never been reported in Kosovo before 1999, when patients presented with fever, pharyngitis and lymphadenopathy[12]. More than 500 cases were serologically confirmed from most regions of Kosovo, except in the far north, during the period 1999-2002. A majority of the cases presented as the oropharyngeal form and, accordingly, the outbreak was found to be food- and water-related[12]. After this outbreak, the number of cases in Kosovo has been lower, 25-237, but it still represents an average annual incidence of 5.2/100,000, the highest in Europe during the period[14]. This is significantly higher than in neighboring countries, such as Serbia and Croatia. In the former country, the average number of annual cases during the period 2006-2012 was 19 and in the latter country 3. In Croatia, the highest number of reported cases, 29, occurred in 1999 (http://data.euro.who.int/cisid/).

Turkey has been the country in the world with the highest number of annual cases during the last decade. For example, during the period from 2009 to 2012, annual numbers ranged from 428 to 2151[10]. In Europe, the highest total numbers were reported from Sweden. During a period of 29 years, 1984-2012, a total of 4,830 cases were recorded and the incidence was 10-fold higher during the second half of the period, with an average incidence of 2.47/100,000[11]. Peak annual incidences are extremely high in endemic regions in Sweden, ranging from 400 – 920/100,000[11].

The number of tularemia cases has dramatically decreased in certain areas of the world, as aforementioned, it has been evident in Russia and the US. The annual number of human cases in these countries does not exceed a few hundred and this is only a small proportion compared to the peak incidences of the disease in the 1940's. In the US, > 2,000 cases were recorded in 1939 and in Soviet Union, annual number of cases during World War II were likely > 100,000[2,15]. Although the latter, extreme numbers were to a large ex-

tent depending on special conditions during the war, in both countries, areas that once were considered endemic have experienced dramatic decreases of tularemia.

The aforementioned, much changing, increasing and decreasing, epidemiological patterns of tularemia in many parts of the world are not well understood, but it is likely that ongoing climate change, both global and regional, are important drivers. Factors such as changing temperatures and precipitation patterns, together with changes in vector occurrences, are probably important for the occurrence of tularemia. In fact, it has been demonstrated that the occurrence of tularemia in an endemic area in Sweden was possible to model based on a set of environmental variables together with mosquito prevalence. In fact, it was hypothesized that if the quality of the environmental variables as well as the algorithms were improved, it would be possible to forecast tularemia outbreaks in real-time[16]. In addition, it is likely that human behavior in certain instances is also a driver for outbreaks of tularemia. The most clear-cut examples are the extreme outbreaks during World War II in Soviet Union but also in Kosovo 1999[2,12]. The deterioration of hygienic conditions together with rapid increases of rodent populations are probable reason for the outbreaks. There are, however, possible that other human activities in more subtle ways affect tularemia. One example is the spread of the disease due to commercial sale of hares in the US when the disease was introduced in New England and most likely, the endemic focus at Martha's Vineyard is a result of such importation from the Midwest[17]. Another example of human activities leading to the spread of tularemia is an outbreak among entrapped prairie dogs in Texas. Some of the infected prairie dogs were also shipped to the Czech Republic and Japan[18].

CLINICAL PRESENTATIONS OF TULAREMIA

After an incubation period of usually 3-5 days, onset is often rather abrupt with flu-like symptoms such as fever, chills, malaise, sore throat, and headache[19,20]. Other clinical manifestations are highly dependent on the route of entrance. Infection acquired through skin or mucous mem-

branes results in the ulceroglandular form. In most parts of the world, this is the predominant form of the disease[7,21-23]. It normally results from arthropod bites, in most parts of the world, ticks, but, notably, in Scandinavia by mosquito bites. Rarely, it may be transmitted by direct contact with infected animals. Although there is not so much direct evidence for ticks being the most important vector transmitting tularemia, the epidemiological evidence is strong[24]. Also, there are very few studies showing that mosquitoes harbor *F. tularensis*, but epidemiological data indicate that mosquitoes are the predominant vectors responsible for transmission during outbreaks of tularemia in Scandinavia[25].

The ulceroglandular form presents with a primary ulcer at the site of the arthropod bite, surrounded by inflammation, and eventually prominent enlargement of the draining lymph nodes. The ulcer may be inconspicuous and heals within at most a week. It may be mistaken for a normal tick or mosquito bite. The term glandular tularemia refers to a similar clinical presentation, although there is no primary skin lesion. In Scandinavia and most parts of the world, more than 90% of cases are represented by the ulceroglandular and glandular forms[7,21-23]. The oculoglandular form is likely transmitted via physical inoculation, *e.g.*, via the patient's fingers and presents with conjunctivitis and preauricular lymph node enlargement. If appropriate antibiotic therapy is not instituted within 7-10 days, the lymph node enlargement may become very prominent and suppuration may result in 30-40% of cases[26].

The oropharyngeal form of tularemia results from the intake of contaminated food or water and presents with exudative stomatitis and pharyngitis, often with tonsillar involvement and a very marked regional, often unilateral, neck lymphadenitis[26]. Today, this is an uncommon form of the disease in most parts of the world with one striking exception, Turkey. For example, during the period 2005-2009, it was reported that almost all of 1091 cases presented as the oropharyngeal form[10]. Presumably, the spread is due to poorly protected water sources that may become contaminated by dead rodents. A similar scenario was suggested to have caused the aforemen-

tioned outbreak of tularemia in Kosovo 1999[12]. Despite that proximity to lakes and rivers is a strong risk factor for tularemia in Sweden[11], there have been very few cases of oropharyngeal tularemia in Scandinavia. A review summarized 127 cases that occurred in Finland from 1967 until 1983 but the source of infection was unknown in a majority of cases[27]. There has been only known outbreak of water-borne disease in Sweden involving 9 individuals and contaminated well water was the likely source[28].

Vector-borne transmission of *Francisella* is responsible for high incidence of tularemia in continental part of Europe, and due to global warming there are speculation that the tularemia cases will be in increase.

The respiratory form of tularemia is often related to farming, presumably due to inhalation of aerosols or dust containing remains from infected animals[25,29]. An unusual mode of transmission has been suggested to be lawn-mowing[30,31]. Symptoms may vary and often presents as a systemic illness with fever but the not necessarily with prominent signs of respiratory disease[20,32]. Respiratory tularemia is generally rare but it has the potential to involve a large number of cases, as seen in Sweden 1966-1967 when > 2,700 cases were reported[32]. Notably, only 10% of the patients had typical pneumonic symptoms. X-ray findings usually reveal lung infiltrates, pleuritis, and often hilar enlargement[29]. Although respiratory tularemia is the most serious form of the disease, in Europe mortality is highly unusual, but in the US, before effective antibiotics were available, a case-fatality rate of > 50% was noted[33]. Today, modern antibiotic regimens have reduced the fatality rate also in the US to less than 2%[4]. The more severe form of disease in the US is due to the presence of a unique *F. tularensis* subspecies, *tularensis*. In addition, this subspecies relatively commonly may cause other severe, clinical manifestations such as rhabdomyolysis and septic shock[34] and gastrointestinal symptoms, such as vomiting, diarrhea and abdominal pain[4].

Typhoidal tularemia describes a clinical presentation with rather severe systemic manifestations but lacking characteristic regional symptoms such as cutaneous or mucosal lesions or regional lymphadenitits[4].

F. TULARENSIS VACCINES

The massive tularemia outbreaks in Soviet Union created a strong impetus for the development of a vaccine and much efforts were devoted to this starting in the 1930's and, eventually, live, attenuated strains that appeared to confer efficient protection were developed (reviewed in[35]). As many as 60 million individuals were immunized with live tularemia vaccines between 1946 and 1960 in the Soviet Union[2]. One of these vaccine strains was transferred to the US and after further passages and characterization, was denoted *F. tularensis* LVS (live vaccine strain)[36]. After introduction of the LVS vaccine in the US, the incidence of laboratory-acquired respiratory tularemia dramatically decreased, whereas the incidence of ulceroglandular tularemia remained unchanged[37]. The vaccine appears to provide good albeit, not complete protection against tularemia, but it is not licensed in Western countries[38].

ANTIBIOTIC TREATMENT

In vitro, *F. tularensis* is susceptible to carbapenems, ceftriazone, ceftazidime, rifampin, and certain macrolides, but their use has not supported by substantial clinical data[21]. Notably, there is widespread natural resistance against erythromycin among many strains of subspecies *holarctica*[39]. Aminoglycosides, tetracyclines, and quinolones show excellent *in vitro* activity against *F. tularensis* strains and are also clinically proven. The best documentation refers to the use of aminoglycosides, gentamicin or streptomycin, and both of which have been the drugs of choice for treatment of tularemia and their efficacy have since long been proven clinically[40-42]. There is also much clinical experience of tetracyclines, in particular doxycycline, however, they are rather often associated with relapses, at least when given in standard doses. More recent microbiological and clinical data show that ciprofloxacin, and possibly other quinolones, may be the preferred choice for oral treatment of tularemia and of mild to moderate forms of tularemia[21,40,43,44].

Streptomycin was the first antibiotic with proven efficacy against tularemia and historical data indicated a very high cure rate[40]. Due to its marked ototoxicity, it is very rarely used today and, in fact, not available in many countries. It is still an option for tularemia meningitis, a very rare form of clinical presentation, in combination with agents showing good penetration into the cerebrospinal fluid. For other forms of tularemia, gentamicin is the recommended form of treatment[42]. There are practical disadvantages of using aminoglycosides, since they require parenteral administration and continuous monitoring of serum levels, therefore, they are the drugs of choice for serious forms of tularemia and in cases where there are no alternative efficacious regimens available, such as treatment of children and pregnant women[44,45]. There is accumulating evidence that ciprofloxacin may be an alternative in the latter two cases[45,46].

There is much experience of the use of tetracyclines for treatment of tularemia, despite their bacteriostatic mode of action. Due to its excellent pharmacokinetic properties, doxycycline is the preferred alternative[21]. Relapses have been reported rather frequently and the recommended dose is therefore twice the standard dose for at least 2 weeks. It is a second line of treatment of uncomplicated forms of ulceroglandular tularemia.

Quinolones demonstrate excellent *in vitro* efficacy against *F. tularensis*, and MIC values are extremely low for all tested *F. tularensis* strains of both subspecies *tularensis* and *holarctica*[39,41,43]. In addition, several studies have demonstrated excellent clinical efficacy for ciprofloxacin[40,46,47], moxifloxacin[48], and levofloxacin[49]. Thus, clinical evidence and microbiological data strongly support that ciprofloxacin and, possibly, moxifloxacin and levofloxacin, are drugs of choice for treatment of uncomplicated tularemia and as a second line of treatment for severe infections[4,44].

Ciprofloxacin may also be a possible alternative for treatment of tularemia in pregnant women and children although there is only limited experience in the former case[45]. Excellent clinical efficacy for treatment of children has been reported[46]. Oral administration of ciprofloxacin, or alternatively doxycycline, is the drug of choice for treatment in a mass casualty setting[4].

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