Tularemia in Children and Adolescents

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Tularemia colloquially also referred to as "rabbit fever," "wild hare disease," or "deerfly fever" is a rare zoonotic disease caused by the Gram-negative bacterium *Francisella tularensis*. The wide spectrum of clinical presentations depending on the mode of acquisition and the responsible subspecies constitutes a major challenge for clinicians. This review aims to provide a summary of the current knowledge on tularemia epidemiology, clinical presentation, diagnostics, therapy, treatment, and prophylaxis in children and adolescents.

EPIDEMIOLOGY

Francisella tularensis, a small (0.2 µm in diameter) Gram-negative coccobacillus, has been recognized as a human pathogen since the early 20th century. The name of the bacterium renders homage to the major contribution of scientist Edward Francis to improve knowledge of this infection and its etiologic agent. It is a highly virulent, facultative intracellular, nonspore forming, strict aerobe. Due to its high resilience, the bacterium may persist over prolonged periods in water and soil.[1] The classification as category A bioterrorism agent is accounted for by its characteristics including its low-infectious dose, its potential for easy dissemination by aerosols and high-associated mortality,[2] the latter being particularly relevant to subspecies *tularensis* (type A).

F. tularensis comprises 4 subspecies widely differing in their geographic distribution and virulence: *tularensis* (type A), *holarctica* (type B), *mediasiatica*, and *novicida.* The majority of infections in humans and animals are caused by *F. tularensis* subspecies *tularensis* and *F. tularensis* subspecies *holarctica.* Tularemia occurs throughout North America, Europe, the Middle, and East Asia; however, it is not endemic in the tropics or the southern hemisphere.[1] It is a notifiable disease in most European countries and the United States.[1,2] *F. tularensis* subspecies *tularensis* is the most virulent and is mainly found in North America where it accounts for a more severe disease spectrum and a higher fatality rate compared with the other subspecies.[1] Tularemia has been reported in all US states except Hawaii. In 2018, the overall incidence was 0.07 per 100 000 residents, with Arkansas, Oklahoma, Kansas, Missouri, and South Dakota as hotspots. The less virulent subspecies *holarctic*a is predominantly found in Europe and Asia, usually triggering a mild, subclinical disease. *F. tularensis* subspecies *mediasiatica* has been isolated primarily in central Asian republics. *F. tularensis* subspecies *novicida* is much rarer and found worldwide.[1]

According to the surveillance report of the European Centre For Disease Prevention and Control (ECDC), the incidence in 18 countries was 0.07 cases per 100 000 population in 2018.[3] Cyprus, Greece, Iceland, Ireland, Latvia, Luxembourg, Macedonia, Malta, and the United Kingdom are free of endemic tularemia, with only rare imported cases reported. In eastern Europe and especially in the Balkan region, there are nidi of tularemia often leading to several annual case reports.[2] Larger outbreaks have been reported in Kosovo and Turkey.[1,2] Scandinavian countries usually report the majority of infections (in 2018, Norway and Sweden accounted for 45% of the cases).[2,3] Some European countries have reported a substantial increasing trend (eg, 4-fold in Switzerland and 10-fold in Sweden) of tularemia cases in the past 10–30 years. Underlying factors for this development could include increased awareness and higher sensitivity in diagnostics but also a true increase of bacterial colonization of ticks and rodents. Further east, cases are reported from Israel, Iran, Mongolia, China, and Japan.[4]

TRANSMISSION

Transmission to humans can occur from arthropod bites, direct contact with infected animals, ingestion of contaminated food or water (typically private wells) or from

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airborne spread of contaminated materials.[4] Transmission from human-to-human has never been reported. The different routes of acquisition of infection account for the wide range of clinical manifestations (Table 1). *F. tularensis* infects a broad spectrum of domestic (including dogs, cattle, sheep) and wild vertebrates and invertebrates. Lagomorphs (eg, rabbits and hares) and rodents are deemed to be the prime reservoir vertebrates as they may develop high bacteremia, facilitating transmission to diverse vectors.[2] Vectors involved in transmission are blood-feeding arthropods such as ticks, flies, and mosquitoes, which have either previously fed on an infected animal or, alternatively, in case of mosquitoes, have been infected in the larval stage during their aquatic life-cycle.[2,4] While ticks play a dominant role as vectors in the United States and in large parts of Europe, most of the tularemia cases in the Scandinavian countries are mosquito transmitted.[1,2] The seasonal pattern of human tularemia cases, which primarily occur during summer (peaking in August) is due to the higher risk of exposure to ticks and mosquito bites.[2,3] In contrast, water-borne tularemia outbreaks, such as the one reported in Turkey, occur mostly during the autumn and winter months.[2,5] The degree of landscape fragmentation due to urbanization and the contemporaneous reduction of biodiversity may influence the epidemiology of the disease by altering the ratio of hosts versus low or non-competent hosts. In highly fragmented landscapes, big wildlife like deer, which are less vulnerable to *F. tularensis* infection, are much less frequent in comparison to highly susceptible small rodents. This leads to a diminished pathogen dilution effect and in turn elevates the vector competence of the ticks and thus the probability of disease transmission.[6,7] This together with the effects of global warming, which favors the geographic spread and reproduction rate of insect vectors will probably lead to a further increase in tularemia cases in the future.[8]

PATHOGENESIS AND CLINICAL PRESENTATION

Human inoculation can result through skin, conjunctiva, and mucous membranes. Initially, the pathogen spreads to regional lymph nodes, where it may cause the formation of granulomas and caseous-type necroses, mimicking tuberculosis. Systemic dissemination may occur due to lymphohematogenous spread, potentially causing septicemia.[4] *F. tularensis* is a facultative intracellular organism replicating primarily within macrophages.[1,4] Humoral response develops around 2 weeks after onset of the disease; however, antibodies play a rather minor role in the elimination of the bacteria. Recovery from infection is mainly dependent on the cell-mediated immunity. Factors underlying the higher virulence of *F. tularensis* subspecies *tularensis* compared with the other subspecies are not yet identified.[4]

After a typically short incubation period of 3–5 days (range: 1–21), there is an onset of nonspecific, flu-like symptoms such as fever, chills, malaise, headache, myalgia, and arthralgia.[4] Dependent on the route of acquisition, there are 6 major clinical forms as summarized in Table 1.

Ulceroglandular and glandular disease are the most commonly observed forms in children and adults.[2] A retrospective study performed in Arkansas showed that children more frequently presented with glandular disease compared with adults, in whom the ulceroglandular form was the most common presentation.[9] This observation however may be skewed as in children the frequency of head (Fig. 1), neck, and inguinal regions

TABLE 1. Tularemia Syndromes, Ways of Transmission, Signs and Symptoms, Differential Diagnosis and Treatment[2,4]

Clinical Form	Transmission	Signs and Symptoms	Differential Diagnosis
Ulceroglandular	Vector-borne (arthropod bites) or direct animal contact (insignificant skin break)	Evolution of papulopustular, eschar, and ulcerative lesion at site of inoculation with regional lymphadenopathy (painful)	Infectious: Cat scratch disease (*B. henselae*), pasteurellosis, mycobacteriosis, toxoplasmosis, nocardiosis, actinomycosis, rickettsiosis, anthrax, plague, streptococcal, or staphylococcal skin lesions/lymphadenitis Noninfectious: malignancy (eg, lymphoma)
Glandular	Vector-borne (arthropod bites) or direct animal contact (insignificant skin break)	Painful regional lymphadenopathy in the absence of a visible skin ulcer	See ulceroglandular
Oculoglandular	Eye-rubbing with contaminated fingers or by exposure to contaminated dust/aerosols	Unilateral conjunctivitis with pain, swelling of the eyelids, increased lacrimation, and photophobia. Small, sharply defined, yellowish nodules and ulcers on the palpebral conjunctivae, painful preauricular lymphadenopathy (Parinaud complex)	Cat scratch disease (*B. henselae*), sporotrichiosis, tuberculosis, syphilis
Oropharyngeal	Ingestion of contaminated food or water	Exudative pharyngitis, tonsillitis, usually unilateral cervical lymphadenopathy	Streptococcal pharyngitis, infectious mononucleosis, adenoviral infection, diphtheria
Pneumonic	Inhalation of contaminated aerosol or hematogenous spread to the lung	Respiratory symptoms or nonspecific clinical picture with fever and general symptoms; radiologic findings may include infiltrates, pleuritis, and hilar lymphadenopathy. May be associated with typhoidal type	Infectious: typical and atypical pneumonias, psittacosis, influenza, tuberculosis, pulmonary mycoses, pneumonic plague, coxiella infection/Q fever, brucellosis, leptospirosis Noninfectious: Lymphoma, sarcoidosis
Typhoidal	Any portal of entry (children more often with ingestion of contaminated food or water)	Systemic febrile disease (eg, presenting as fever of unknown origin) with general, unspecific symptoms. Pharyngeal pain without localized signs, no skin lesions, or prominent regional adenopathy. Diarrhea possible	Salmonellosis, brucellosis, coxiellosis, culture-negative endocarditis, viral illness, rickettsiosis

Treatment (children and adults):
Severe tularemia (requiring hospitalization), eg, typhoidal and pneumonic:
(1)Gentamicin*: 5–7.5 mg/kg/dose o.d., IV or IM
(2)Combination of gentamicin* IV and ciprofloxacin PO or IV
(*or alternative aminoglycoside, eg, amikacin)
Mild tularemia, eg, ulceroglandular, glandular:
(1)Ciprofloxacin: 15 mg/kg/dose b.i.d. PO (maximum daily dose: 1 g), adults 500 mg b.i.d.
(2)Doxycycline (>8 y): 2.0 mg/kg/dose b.i.d. PO (maximum daily dose 200 mg), adults 100 mg b.i.d.
Mode and duration of therapy:
Switch from IV to oral as soon as clinical improvement and tolerating fluids. Treatment duration: 10-14 days (doxycycline 14–21 days).

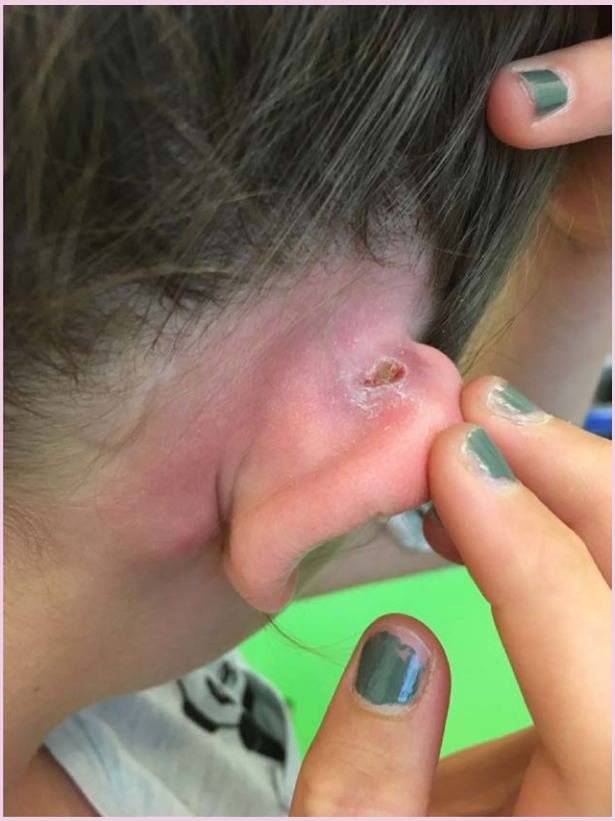

FIGURE 1. Ulceroglandular tularemia after a tick bite in an adolescent girl. Ulcer posterior helix (site of tick bite) with localized posterior auricular lymphadenopathy.

as primary sites of infection is high. It is likely that the ulcerations in these areas are missed or may have already resolved by the time tularemia is diagnosed. While the oropharyngeal form is infrequently observed in most parts of Europe and the United States, it is common in Norway, South-East Europe, and Turkey.[1,2] Tularemia is considered to be underreported, particularly in Europe, and, therefore, one can assume that milder disease caused by *holarctica* (type B strain) can also be self-limiting.[2]

The age distribution shows tularemia cases peaking at around 45–60 years and single peaks in the pediatric age group. These are mainly associated with participation in outdoor activities.[3]

Principally, children and adults show a similar clinical picture.[10] Some minor differences may be identified as documented in different studies: Uhari et al[11] reported a relative increase in degree of severity in type B tularemia in children in Scandinavia, probably due to a considerable delay of diagnosis and administration of antibiotics. Gozel et al,[10] on the other hand, observed a significantly higher occurrence of erythema, tenderness, and fluctuation of enlarged lymph nodes in the adult group compared with the pediatric group with oropharyngeal tularemia in Turkey. Rarely, the mild tularemia forms (glandular/ulceroglandular) may evolve into disseminated disease spreading to other organs (spleen, liver, lung, brain). Unusual manifestations of tularemia include pericarditis, appendicitis, peritonitis, liver abscess, cerebellitis with ataxia, meningitis, encephalitis, osteomyelitis, rhabdomyolysis, and venous thrombosis. The differential diagnosis of tularemia is broad and varies among the different clinical syndromes (Table 1). Thus, patients often initially receive an inadequate therapy (mostly β-lactams) before the correct diagnosis being made.[5]

DIAGNOSIS

Laboratory work-up for tularemia is often nonspecific, with a moderate increase of inflammatory markers.[5,10] The gold standard for the indirect diagnosis of tularemia (2–4 weeks after symptom onset) involves serologic tests. Both, agglutination and enzyme-immuno assays (ELISA and Western blot analysis) show high sensitivity and specificity.[2,4] A single positive titer of 1:160 or higher is regarded as supportive of the diagnosis in an acute setting.[10] Seroconversion or a greater than 4-fold increase in antibody titer between serum samples taken in the acute, and the convalescent phase are defined as confirmatory. Despite the high specificity, there is a potential of serologic cross-reactions (eg, with Brucella or Legionella) occurring usually at a low, nondiagnostic level.[2,4] Molecular detection of *F. tularensis* DNA in appropriate clinical specimens (eg, lymph node aspirates or samples from skin ulcers) is the gold standard test for an early diagnosis in the acute phase.[2] Whole blood polymerase chain reaction via GeneXpert systems are becoming a promising additional diagnostic tool. Due to the high clonality of the genome, polymerase chain reaction targets for subspecies identification are hard to find. Most labs refrain from molecular subtyping due to the limited clinical relevance of the results. Bacterial cultures are not part of the routine diagnostic test since it is significantly less sensitive than above methods and bears the risk of laboratory infection. Many laboratories now use tularemia-specific immunochromatographic test based on the detection of anti-*F. tularensis* lipopolysaccharide antibodies as a fast screening test before confirmation with agglutination and enzyme-immuno-assays (ELISA and Western blot analysis).

TREATMENT

Early diagnosis and the prompt administration of appropriate antimicrobial therapy (Table 1) are crucial for successful disease management without long-term morbidity or treatment failure.[5,10] Aminoglycosides are well-established first-line antimicrobials recommended for both children and adults particularly with systemic disease, which may require hospital admission. In severe cases, a combination of an aminoglycoside with ciprofloxacin is recommended. In Europe, fluoroquinolones are used successfully in the out-patient setting to treat localized mild syndromes caused by *F. tularensis* type B also in children. Relapses are very rare. Doxycycline is also considered a treatment option in adults and in children older than 8 years.[5] There have been reports of relapses in patients receiving doxycycline, however, findings of different studies could not reach a consensus. The potential higher relapse rates and the bacteriostatic nature of this antimicrobial agent are the underlying basis for the recommendation of a minimum therapy duration of 14–21 days.[5] In the available literature, there is a lack of robust comparative data regarding the efficacy of the different drug regimens, making it an important research field for future studies. For post exposure prophylaxis (eg, bioterrorism), ciprofloxacin is recommended for 14 days.

Beta-lactams (includings cephalosporines), clindamycin, daptomycin, linezolid, and rifampicin are not effective treatment options. Despite in vitro susceptibility of *F.t. tularensis* (type A) organisms, erythromycin

is not a reliable antimicrobial due to the resistance of the *F.t. holarctica* B.12 clade, which is prevalent in Northern Europe. As expected of an organism with a highly clonal genome, there has been no report of naturally occurring antibiotic resistance of *F. tularensis.*

COMPLICATIONS AND TREATMENT FAILURE

In glandular or ulceroglandular disease, suppuration is a common complication. Tezer et al[5] showed a significant association between a treatment delay of ≥16 days and spontaneous suppuration. The same study also reported that the use of doxycycline, and female sex were contributing risk factors for suppuration and treatment failure in children. Oz et al[12] found that an adequate treatment delay of more than 3 weeks resulted in a rate of abscess formation as high as 62%, compared with 38% when therapy was initiated earlier. Other complications include secondary skin manifestations such as erythema nodosum, erythema multiforme, or papular lesions, which are reported in up to 50% in some case series, including an analysis of 50 children as part of an outbreak of *Holarctica*-type Tularemia in Northern Finland. These skin reactions were often misdiagnosed as reaction to medication or varicella infection.[13]

PREVENTION

Currently, there is no tularemia vaccine available. In the 1950s, a vaccine had been developed using the live vaccine strain of *F. tularensis* subspecies *holarctica*.[1,4] However, virulence was retained in animals and protection in humans challenged by aerosolized type A was incomplete. Since the early 2000s, there have been several candidate vaccines (live attenuated) developed but none licensed so far.

Preventive measures mainly comprise behavioral strategies to avoid or reduce exposure to the most common local transmission routes such as proper clothing to prevent insect bites and prompt removal of ticks. Drinking portable water in countries of Eastern Europe and Turkey, where oropharyngeal tularemia is more prevalent, may be advisable.[4] There is no risk of human-to-human transmission. Standard hygiene precautions are adequate for hospitalized patients with tularemia. Whenever tularemia is suspected or proven, laboratory personnel handling the patient's specimen should be notified in advance so that precautions can be taken to minimize exposure to *F. tularensis.*

CONCLUSION

Tularemia should be considered in endemic regions when children develop general flu-like symptoms, lymphadenopathy, or any combination of signs and symptoms corresponding to the different forms of tularemia. To avoid prolonged progression of the disease, treatment failure and the need of surgical intervention, early diagnosis and a prompt initiation of adequate antimicrobial therapy are pivotal. Further research should focus on tools and processes to avoid delayed diagnosis, further evaluation of treatment regimens in children and development of an effective vaccine especially against the more virulent subspecies *tularensis.*

REFERENCES

1. Sjöstedt A. Tularemia: history, epidemiology, pathogen physiology, and clinical manifestations. *Ann N Y Acad Sci.* 2007;1105:1–29.
2. Maurin M, Gyuranecz M. Tularaemia: clinical aspects in Europe. *Lancet Infect Dis.* 2016;16:113–124.
3. European Centre for Disease Prevention and Control. Tularaemia. In: ECDC, ed. *Annual Epidemiological Report for 2018*. Stockholm: ECDC; 2019.
4. Eliasson H, Broman T, Forsman M, et al. Tularemia: current epidemiology and disease management. *Infect Dis Clin North Am.* 2006;20:289–311, ix.
5. Tezer H, Ozkaya-Parlakay A, Aykan H, et al. Tularemia in children, Turkey, September 2009–November 2012. *Emerg Infect Dis*. 2015;20:1–7.
6. Dantas-Torres F. Climate change, biodiversity, ticks and tick-borne diseases: the butterfly effect. *Int J Parasitol Parasites Wildl.* 2015;4:452–461.
7. Wittwer M, Altpeter E, Pilo P, et al. Population genomics of *Francisella tularensis* subsp. holarctica and its implication on the eco-epidemiology of tularemia in Switzerland. *Front Cell Infect Microbiol.* 2018;8:89.
8. Rydén P, Sjöstedt A, Johansson A. Effects of climate change on tularaemia disease activity in Sweden. *Glob Health Action*. 2009;2:1–7.
9. Snowden J, Stovall S. Tularemia: retrospective review of 10 years' experience in Arkansas. *Clin Pediatr (Phila).* 2011;50:64–68.
10. Gozel MG, Engin A, Altuntas EE, et al. Evaluation of clinical and laboratory findings of pediatric and adult patients with oropharyngeal tularemia in Turkey: a combination of surgical drainage and antibiotic therapy increases treatment success. *Jpn J Infect Dis.* 2014;67:295–299.
11. Uhari M, Syrjälä H, Salminen A. Tularemia in children caused by *Francisella tularensis* biovar palaearctica. *Pediatr Infect Dis J.* 1990;9:80–83.
12. Oz F, Eksioglu A, Tanır G, et al. Evaluation of clinical and sonographic features in 55 children with tularemia. *Vector Borne Zoonotic Dis.* 2014;14:571–575.
13. Jounio U, Renko M, Uhari M. An outbreak of holarctica-type tularemia in pediatric patients. *Pediatr Infect Dis J.* 2010;29:160–162.