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1091 8.6.20 Francisella tularensis infection review of the literature in the last 10 years. Int J Infect Dis, 14 Suppl 3, e242–5. Medeiros I, Saconato H (2001). Antibiotic prophylaxis for mammalian bites. Cochrane Database Syst Rev, 2, CD001738. Morgan MS (2005). The hospital management of animal bites. J Infect, 61, 1–10. Talan DA, et al. (1999). Bacteriologic analysis of infected dog and cat bites. N Engl J Med, 340, 85–92. Wilson BA, Ho M (2013). Pasteurella multocida: from zoonosis to cel- lular microbiology. Clin Microbiol Rev, 26, 631–55. 8.6.20 Francisella tularensis infection Petra C.F. Oyston ESSENTIALS Fransicella tularensis is a small Gram-negative coccobacillus that circulates in small rodents, rabbits, and hares, most frequently in Scandinavia, northern North America, Japan, and Russia. Clinical presentation depends on the route of infection. Most commonly this follows the bite of an infected arthropod vector, resulting in ulceroglandular tularaemia. The most acute and life-threatening dis- ease, respiratory or pneumonic tularaemia, arises following inhal- ation of infectious aerosols or dusts. The organism is highly fastidious, requiring rich media for isolation and specialized reagents for posi- tive identification; most cases are diagnosed serologically. Treatment is with supportive care and antibiotics (usually ciprofloxacin, doxy- cycline, or gentamicin). There is no vaccine. Historical perspective Francisella tularensis was first isolated during an outbreak of a plague-like disease in rodents in California in 1911. Since then it has been recognized as a zoonotic infection of humans capable of causing significant morbidity or death. Human infection occurs following contact with infected animals or invertebrate vectors. It is also called Francis' disease, deer fly fever, rabbit fever, water-rat trappers' disease, wild hare disease (yato-byo), and Ohara's disease. It is highly infectious by the aerosol route and, as such, has been of concern as a biological threat agent. Aetiology, genetics, pathogenesis, and pathology The genus Francisella includes two species, Francisella tularensis and Francisella philomiragia. F. tularensis is a small (0.2–0.5 μm × 0.7–1.0 μm) Gram-negative coccobacillus that is nonmotile and an obligate aerobe. The four subspecies of F. tularensis are: F. tularensis subsp. tularensis (also called F. tularensis type A or F. neoarctica); F. tularensis subsp. holarctica (also called F. tularensis type B); F. tula- rensis subsp. novicida and F. tularensis subsp. mediastica. Molecular typing methods have identified distinct genotypes of F. tularensis subsp. tularensis that differ in their grographic location and viru- lence. Most human and animal infections are caused by F. tularensis subsp.

tularensis and F. tularensis subsp. holoarctica. Human dis- ease has also been reported with F. tularensis subsp. novicida and F. philomiragia. F. tularensis can infect a variety of hosts including humans to cause tularaemia. An intracellular pathogen, it is one of the most highly infectious bacteria known with an infectious dose in hu- mans as low as 10 bacteria by the inhalational route. It multiplies to high levels within macrophages, and mutants unable to multiply in macrophages are avirulent. F. tularensis susbp. tularensis causes more severe infections than F. tularensis susbp. holoarctica. F. tula- rensis susbp. tularensis genotype A1b are more likely to be associated with invasive disease and higher mortality than type A1a, A2, or B. F. tularensis multiplies at the site of inoculation and spreads to the regional lymph nodes and then systemically. An acute inflam- matory reaction with neutrophils, macrophages, and lymphocytes is seen at the site of inoculation, resulting in tissue necrosis and, some- times granuloma formation. F. tularensis is an intracellular pathogen that replicates primarily on host macrophages. Macrophage uptake occurs by an unusual process called 'looping phagoyctosis' that in- volves symmetric and spacious pseudopod loops. Once ingested, phagosome maturation and phagosome–lysosome fusion are im- paired resulting in organism escape and multiplication in the cytosol. Similar events occur in neutrophils where the organism suppresses oxidative burst and escapes into the cytoplasm. Within the macro- phage cytosol the organisms activate a multimolecular complex, the inflammasone, which leads to the release of proinflammatory cyto- kines and trigger caspase-1 dependent cell death. The virulence of F. tularensis has been correlated with several phenotypic character- istics including capsule formation, lipopolysaccharide, pili, produc- tion of acid phosphatases, and a siderophore. Genomic studies have identified genes in the Francisella pathogenicity island which are in- volved in intracellular survival and animal virulence. Epidemiology F. tularensis is mainly isolated in the northern hemisphere, most frequently in Scandinavia, northern America, Japan, and Russia (100–400 cases/year), but has never been isolated in the United Kingdom. F. tularensis subsp. tularensis accounts for 90% of infec- tions in North America whereas F. tularensis subsp. holarctica in- fections are more common in the rest of the world. The organism infects more than 100 species of wild and domestic vertebrates, such as small rodents, rabbits, hares, squirrels, hamsters, mice, and voles. Outbreaks in human populations frequently mirror outbreaks of disease occurring in wild animals. A wide range of arthropod vec- tors have been implicated in the transmission of the disease within wild animal populations and to humans. Rural populations, espe- cially those individuals who spend periods of time in endemic areas such as farmers, hunters, walkers, and forest workers, are most at risk of contracting tularaemia. Transmission to humans occurs from contact with an infected animal or biting insect. Contaminated meat and water are important environmental sources of the infection

 and outbreaks associated with contaminated water supplies can involve large numbers of cases. Transmission can also occur from airborne spread of contaminated materials such as dust, hay, and water. Airborne transmission was the suspected source of an out- break of pneumonic tularaemia in the United States of America and was associated with lawn mowing or brush cutting. Recent reports of tularaemia have been from Russia (following a sable bite), nor- thern Spain (possibly associated with aerosolized contaminated water), and the United States of America (Utah). Prevention Avoidance of contact with infected animals and vectors reduces the risk of infection. Hunters in particular should wear gloves when skinning dead animals, and meat should be thoroughly cooked be- fore eating. Reducing the risk of inhalation of infectious dusts (e.g. during farming activities in endemic areas) by wearing respiratory protection should be considered. No licensed vaccine is available for prevention of tularaemia. However, concern about

the use of Francisella as a bioterrorism threat has led to continuing efforts to develop a vaccine. Clinical features Tularaemia in humans can occur in several forms depending on the route of infection. Although tularaemia can be a severely debilitating and even fatal disease, especially when caused by viru- lent strains, many cases of disease caused by lower virulence strains go undiagnosed owing to the nonspecific nature of the symptoms. The incubation period is normally 3 to 5 days (range 1–21 days), and patients develop influenza-like symptoms which may be pro- tracted and relapsing if untreated. Infection through skin or mucous membranes Infection through the skin results in ulceroglandular tularaemia (Figs. 8.6.20.1, 8.6.20.2); where no ulcer is reported, this is termed glandular tularaemia. These forms of tularaemia are the most common presentations of the disease and can arise following the bite of an infected vector or through direct contact with the flesh of an infected animal. A lesion develops at the site of infection, often a single papule which turns into an ulcer surrounded by a zone of inflammation. The ulcer is relatively painless and heals within a week. Within 3 to 5 days following infection, the patient develops fever, chills, malaise, headaches, and a sore throat. The local draining lymph nodes become enlarged and painful, like a bubo. Lymphadenopathy can take a significant period to resolve even with treatment, and without treatment suppuration occurs in approximately 30% of patients. Symmetrical rashes have been attrib- uted to hypersensitivity (Fig. 8.6.20.3). Less commonly, infection can occur through the conjunctiva. This is termed oculoglandular tularaemia and arises following direct contamination of the eye (e.g. through rubbing the eyes after skin- ning an infected rabbit). The patient develops conjunctivitis in the infected eye, swollen eyelids, and a purulent discharge. Untreated, the infection can spread to the local lymph nodes, in a similar way to ulceroglandular tularaemia. Ingestion of infected meat can result in oropharyngeal (Fig. 8.6.20.4) or gastrointestinal tularaemia. Ulcers, pharyngitis, and swollen cervical lymph nodes develop, and a yellow-white pseudomembrane might be seen in oropharyngeal tularaemia. Gastrointestinal tularaemia can range from a mild but persistent diarrhoea to an acute fatal disease with extensive ulceration of the bowel, depending on the size of the infecting dose. Any of the aforementioned infections can disseminate and pro- gress to systemic disease without the appearance of swollen lymph nodes or ulcers. This is termed typhoidal tularaemia. Severe compli- cations might also occur, such as septic shock. Infection through inhalation Inhalation of F. tularensis results in respiratory or pneumonic tu- laraemia. Pneumonia can also arise following haematogenous spread in other forms of tularaemia. Symptoms can be variable and depend on the virulence of the strain involved. Infection with the most highly virulent strains can have a case fatality rate of up to 30% if untreated, but antibiotic therapy reduces this to approxi- mately 2%. Presentation can range from a mild pneumonia to an Fig. 8.6.20.1 Hands in a case of ulcero-(cutano-)glandular tularaemia. Courtesy of A Berglund, Fallund, Sweden. Fig. 8.6.20.2 Inguinal lymphadenopathy in ulceroglandular tularaemia. Courtesy of A Berglund, Fallund, Sweden.

1093 acute infection with high fever, malaise, chills, cough, delirium, and pulse–temperature dissociation. Radiological examination might reveal parenchymal infiltrates, most commonly in one lobe, and hilar lymphadenopathy can be present. Differential diagnosis Diagnosis of tularaemia is difficult due to the nonspecific nature of most of the symptoms, particularly if the ulcer has already healed. A high index of clinical suspicion is therefore required. Other dis- eases which must be rapidly excluded in patients presenting with acute respiratory distress and fever or influenza-like disease include plague and Q fever (Table 8.6.20.1). Oculoglandular tularaemia can be confused with severe infection caused by a range of viral and bac- terial conjunctival pathogens. Criteria for diagnosis Most cases of tularaemia are diagnosed on the basis of the epidemio- logical and clinical picture. The diagnosis is confirmed serologically and a range of serological tests for the

detection of antibodies against F. tularensis is commercially available. The antibody response peaks at 4–6 weeks, but can be detected from 2 weeks. Routine cultures of specimens such as blood, sputum, pleural fluid, skin lesions, and lymph nodes are frequently negative as the organism is fastidious and requires enriched media and prolonged culture. The micro- biology laboratory should be alerted to the possibility of F. tularensis as it is a biohazard group 3 pathogen and should be processed in a containment level 3 laboratory. Most strains require cystine or cyst- eine for growth and more than 2 days' incubation at 35°C to produce colonies. Some strains grow on conventional media such as choc- olate agar, modified Thayer–Martin medium, or buffered charcoal yeast agar. The organisms are tiny, poorly staining Gram-negative coccobacilli and are oxidase negative, weakly catalase positive, β- lactamase positive, urease negative, and satellite or XV test nega- tive. Polymerase chain reaction and enzyme-linked immunosorbent assay (ELISA) can be used to positively identify the bacteria, both following isolation and in specimens. Such direct detection of the pathogen is useful in patients who are serologically negative (e.g. in the early days of infection). Treatment Antimicrobial therapy should be administered to patients in whom tularaemia is suspected or confirmed. There are no randomized controlled trials comparing the efficacy of different drug regimens. Historically, aminoglycosides have been the drugs of choice for the treatment of tularaemia. Although it is clinically effective, strepto- mycin is rarely used now; gentamicin is a suitable alternative and is usually given for 7 to 14 days. For patients with milder disease, oral therapy with tetracyclines or fluoroquinolones has been recommended. Doxycycline is ef- fective in the treatment of tularaemia and can also be used in chil- dren and pregnant women. Ciprofloxacin has been shown to be highly effective and can be considered the current drug of choice for uncomplicated tularaemia. It has been shown to be effective in treating tularaemia in children and may be suitable for use in preg- nant women. Both tetracyclines and fluorquinolones have been as- sociated with relapse after cessation of treatment. Fig. 8.6.20.3 Hypersensitivity reaction in infection with Francisella tularensis. Courtesy of A Berglund, Fallund, Sweden.
Fig. 8.6.20.4 Oral tularaemia in a case from northern Sweden. Courtesy of A Berglund, Fallund, Sweden. 8.6.20 Francisella tularensis infection

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