TULAREMIA

AUGUST 2005

Outline

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By law, health care providers must report suspected or confirmed Tularemia to the local health department immediately (within 1 hr).

Even a single case of Tularemia is considered an outbreak and is a public health emergency.

To report: call SFDPH communicable disease control (24/7 Tel: 415-554-2830).

Upon receipt, SFDPH will initiate the public health response and can facilitate lab testing.

AGENT

Tularemia is a zoonotic disease caused by *Franciscella tularensis*, a non-sporulating, non-motile, aerobic gram-negative coccobacillus. The organism has a thin, lipid-rich capsule. It grows on commercial blood culture media, but does not grow reliably on most other standard media. *F. tularensis* strains are generally resistant to beta-lactam antibiotics. Organisms can persist for long periods of time in water, mud, and decaying animal carcasses.

There are several subspecies of *F. tularensis*. The most common naturally occurring isolate in the USA is the subspecies *tularensis* (type A), which typically results in a more severe illness. *F. tularensis* is a facultative intracellular pathogen that multiplies predominantly within macrophages. Its virulence factors are not well characterized.

EPIDEMIOLOGY

Tularemia as a Biological Weapon

Weaponized *F. tularensis* was developed and stockpiled by the US military, though the supply was destroyed in the 1970's. The Soviet Union is reported to have developed antibiotic- and vaccine-resistant strains of weaponized *F. tularensis.*

The most likely form of intentional release for *F. tularensis* organisms would be via infectious aerosols. An aerosol release is likely to cause several clinical syndromes:

- Primary pneumonic tularemia in the majority of patients
- Nonspecific febrile illness of varying severity (i.e. typhoidal tularemia) in some
- Oculoglandular tularemia could occur from eye contamination
- Glandular or ulceroglandular disease following exposure of broken skin to infectious aerosols
- Oropharyngeal disease also could occur through inhalation of organisms

An intentional outbreak of tularemia would be expected to have the following features:

- **Short incubation period (shorter incubation correlates with virulence of the infecting strain, and in a bioterrorist attack a highly virulent strain is likely)**
- **Illness onset 3 to 5 days after the initial release (range 1-14 days)**
- **Outbreak in an urban area, where naturally occurring tularemia is not endemic**
- **Patients lack risk factors for tularemia exposure (e.g. outdoor field work or recreational activity, contact with tissues of potentially infected animals).**

In the event of a bioterrorist attack, use of *F. tularensis* strains with enhanced virulence or antimicrobial resistance may be encountered.

Naturally Occurring Tularemia

The natural reservoirs for *F. tularensis* are small and medium-sized mammals. In the USA these are primarily lagomorphs (rabbits, hares) but may include aquatic rodents (beaver, muskrats), field voles, water and wood rats, and squirrels. Humans, other mammalian species (e.g. cats, dogs, cattle), and some species of birds, fish, and amphibians are incidental hosts.

The primary vectors for infection in the USA are ticks (dog ticks, wood ticks) and flies such as the deerfly. Humans have become infected by several mechanisms:

- Bites by infected arthropods (majority of cases)
- Handling of infectious animal tissues or fluids, during for example hunting or butchering
- Ingestion of contaminated food or water
- Inhalation of infectious aerosols, including dust from contaminated hay and aerosols generated by lawn mowing and brush cutting
- Exposure in the laboratory setting during specimen handling

Nationwide, reported cases have declined from about 2,000 annually during the 1930s, to a mean of 124 per year during the 1990's. Most cases have occurred in rural or semi-rural environments, during the summer months. In California, there were 21 total cases reported during the period 1994-2003, and just one of these was in San Francisco.

In 2002, tularemia was responsible for a die-off of several hundred prairie dogs caught in the wild in South Dakota and then commercially distributed widely throughout the USA. One human case occurred in an animal handler who cared for the infected animals.

In 2003, low levels of *F. tularensis* were identified in a biodetection air-monitoring system in Houston, Texas. No human cases occurred. An investigation supported contamination of the filters by naturally occurring *F. tularensis* organisms, although the environmental reservoir was not definitively identified.

CLINICAL FEATURES

Human tularemia occurs in 6 recognized forms, determined primarily by route of infection. Clinically, tularemia can range from a mild infection to a severe life-threatening illness. Overall case-fatality rates have declined from 7% in the pre-antibiotic era to approximately 2% currently. Mortality was historically much higher with pulmonic infection. Most patients respond rapidly to appropriate antibiotic therapy, with fever and generalized symptoms improving in 24-48 hours. Recognition of tularemia as a potential etiologic agent is critical, as poor outcomes have been associated with delays in seeking care and/or instituting effective antimicrobial treatment.

Pneumonic Tularemia

Pneumonic tularemia occurs after inhalation of the organism, or as the result of secondary hematogenous spread to the lung. The infectious dose is thought to be as low as 10 organisms. It is only rarely acquired naturally, but is associated with the most severe disease. Pneumonic tularemia would present as a non-specific febrile illness with progression to pleuropneumonitis and systemic infection.

PNEUMONIC TULAREMIA: CLINICAL FEATURES	
Incubation Period	3-5 days (range 1-14 days)
Signs & Symptoms	• Initial presentation as atypical community-acquired pneumonia (CAP) unresponsive to typical antibiotic therapy for CAP • Illness may progress rapidly to severe disease OR may be indolent with progressive debilitation over several months • Prominent symptoms: abrupt onset of fever, nonproductive cough, dyspnea, pleuritic chest pain, myalgias • Hilar adenopathy, pleural effusion, pleural adhesions, bronchiolitis, and/or pharyngitis may be present • Nausea, vomiting, diarrhea may occur • 20% may have generalized maculopapular rash with progression to pustules or erythema-nodosum type rash
Complications	• Severe pneumonia • Lung abscess or cavitary lesions • Respiratory failure, ARDS • Sepsis
Laboratory Findings	• Lobar, segmental, or subsegmental opacities on CXR, often with pleural involvement • Leukocytosis; differential may be normal • Liver enzymes and/or CK may be abnormal • Sputum gram stain is often not helpful

Glandular and Ulceroglandular Tularemia

Glandular and ulceroglandular tularemia account for the majority of naturally-occurring cases of tularemia. In both these forms, organisms enter the skin through the bite of infective arthropods,

direct contact with infectious materials (such as contaminated carcasses), or percutaneous inoculation with a sharp object (such as a bone fragment from a contaminated carcass).

In the ulceroglandular form, an ulcer is formed at the site of inoculation, with subsequent lymphadenopathy in the proximal draining lymph nodes. Occasionally, lymphadenopathy occurs without an ulcer leading to the designation of glandular disease.

GLANDULAR AND ULCEROGLANDULAR TULAREMIA: CLINICAL FEATURES	
Incubation Period	3-5 days (range 1-14 days)
Signs & Symptoms	• Ulceroglandular form – begins as local painful cutaneous lesion at inoculation site (papule that ulcerates in a few days) • Glandular form – no cutaneous lesion • Tender regional lymphadenopathy • Fever, chills, malaise, myalgias, arthralgias, headache, anorexia, GI symptoms are common • Lymphadenopathy may persist for months
Complications	• Lymph node suppuration • Secondary pneumonia • Hematogenous spread to other organs • Sepsis
Laboratory Findings	• Leukocytosis; differential may be normal • Liver enzymes and/or CK may be abnormal

Oculoglandular Tularemia

In oculoglandular tularemia, organisms gain entry via the conjunctiva. Oculoglandular tularemia might occur in a bioterrorist setting as a result of an aerosol exposure or from direct or indirect contact with contaminated water or food. Organisms spread from the conjunctiva to the preauricular, submandibular, or cervical lymph nodes, where they cause focal necrosis and lesions similar to those noted with ulceroglandular tularemia.

After an incubation period of 3-5 (range 1-14) days, oculoglandular tularemia presents as a painful "red eye" with purulent exudation and painful preauricular and/or cervical lymphadenopathy. Additional signs and symptoms may include photophobia, lacrimation, itching, local edema, and changes in visual acuity. There is a potential for lymph node suppuration, hematogenous dissemination, and development of sepsis.

Laboratory values are generally unremarkable, and gram stain of conjunctival scrapings may or may not demonstrate organisms.

Oropharyngeal Tularemia

Oropharyngeal or gastrointestinal tularemia occurs via ingestion of contaminated food, undercooked meat, contaminated water or droplets, and oral inoculation from the hands after contact with contaminated material.
After an incubation period of 3-5 (range 1-14) days, oropharyngeal tularemia presents either as acute pharyngitis with cervical lymphadenopathy or as ulcerative gastrointestinal lesions with abdominal pain, diarrhea, nausea, vomiting, mesenteric lymphadenopathy and gastrointestinal bleeding. Severity can range from mild diarrhea to overwhelming ulceration with frank gastrointestinal bleeding and sepsis. A large inoculum (approximately 100,000,000 organisms) is required to transmit disease orally. There is a potential for lymph node suppuration, hematogenous dissemination, and development of sepsis.

Laboratory values are generally unremarkable, although leukocytosis may be present.

Typhoidal Tularemia

Typhoidal (septicemic) tularemia is an acute, nonspecific febrile illness associated with *F. tularensis* that is not associated with prominent lymphadenopathy.

TYPHOIDAL TULAREMIA: CLINICAL FEATURES	
Incubation Period	3-5 days (range 1-14 days)
Signs & Symptoms	• Fever, chills, malaise, weakness, myalgias, arthralgias • Prostration, dehydration • GI symptoms (watery diarrhea, vomiting, abdominal pain) • Skin findings may include generalized maculopapular rash with progression to pustules or erythema-nodosum type rash
Complications	• Secondary pneumonia (50-80%) • Hematogenous spread to other organs – osteomyelitis, pericarditis, peritonitis, endocarditis, meningitis • Sepsis • Rhabdomyolysis • Renal failure • Debilitating illness lasting several months
Laboratory Findings	• Leukocytosis; differential may be normal • Liver enzymes and/or CK may be abnormal • Sterile pyuria may occur

DIFFERENTIAL DIAGNOSIS

A high index of suspicion is required to diagnose tularemia as there are no readily available rapid and specific confirmatory tests. In addition, the various forms of tularemia can have a nonspecific appearance and/or resemble a wide range of much more common illnesses.

Pneumonic Tularemia: Differential

Key features that could help identify intentional aerosol release of tularemia:

- **Cluster of acute, severe respiratory illness in an urban, non-agricultural setting**
- **Unexpected, severe respiratory illness in otherwise healthy persons**
- **Findings of atypical pneumonia, pleuritis, and hilar lymphadenopathy**
- **Community-acquired atypical pneumonia unresponsive to typical antimicrobials**

Other conditions to consider:

- Community-acquired bacterial pneumonia (*Mycoplasma, Staph, Strep, Haemophilus, Klebsiella, Moraxella)*
- *Chlamydia psittaci* or *pneumoniae*
- Inhalational anthrax
- Pneumonic plague
- Q fever
- Tuberculosis
- Fungal pulmonary disease (histoplasmosis, coccidiodomycosis)
- Viral pneumonia (influenza, hantavirus, RSV, CMV)

Glandular Tularemia: Differential

- Bubonic plague
- Cat-scratch disease
- Mycobacterial infection
- Sporotrichosis
- *Staph* or *Strep* Adenitis
- Chancroid
- Lymphogranuloma venereum
- Primary genital herpes
- Syphilis

Ulceroglandular Tularemia: Differential

- Anthrax
- Pasteurella infections
- Primary syphilis
- Rat-bite fever
- Rickettsial pox
- Scrub typhus
- *Staph* or *Strep* cellulitis
- Orf virus

Oculoglandular Tularemia: Differential

- Adenoviral infection
- Cat-scratch disease
- Coccidiodomycosis
- Herpes simplex or Herpes zoster
- Pyogenic bacterial infections
- Sporotrichosis
- Syphilis
- Tuberculosis

Oropharyngeal Tularemia: Differential

- *Strep* pharyngitis
- GI anthrax
- Diphtheria
- Infectious mononucleosis
- Adenoviral infection

Typhoidal Tularemia: Differential

- Brucellosis
- Disseminated mycobacterial or fungal infection
- Endocarditis
- Leptospirosis
- Malaria
- Q fever
- Typhoid fever
- Meningococcemia
- Septicemic plague
- Septicemia caused by other gram-negative bacteria
- *Staph* or *Strep* toxic shock syndrome
- Rocky Mountain spotted fever
- Ehrlichiosis

LABORATORY DIAGNOSIS

The diagnosis of tularemia requires a high index of suspicion since the disease often presents with non-specific symptoms. Since the organism is hard to isolate, diagnosis often rests on serologic evidence of infection in a patient with a compatible clinical syndrome.

If you consider testing for Tularemia, you should:

- **IMMEDIATELY notify SFDPH Communicable Disease Control (24/7 Tel: 415-554-2830) to facilitate specimen processing and public health response.**
- **Notify the lab that Tularemia is suspected, as F. tularensis may pose a risk to lab personnel.**

Antibody detection assays include tube agglutination, microagglutination, and ELISA. Significant antibodies appear around the end of the 2nd week of illness, peak at 4-5 weeks, and can persist indefinitely. A single titer of $\geq$1:160 (by tube agglutination) or $\geq$1:128 (by microagglutination) is a presumptive positive; a four-fold rise in titer is required for definitive serologic diagnosis.

Gram's staining of specimens may be of little value, as *F. tularensis* is a small, weakly staining pleomorphic gram-negative coccobaccilus that cannot readily be distinguished from the background. Culture and isolation of *F. tularensis* are difficult and often not fruitful. Some strains may require up to a week to develop visible colonies, especially if the patient has been placed on bacteriostatic antibiotic therapy. A positive DFA test on a culture isolate confirms the identification.

TREATMENT AND PROPHYLAXIS

These recommendations are current as of this document date. SFDPH will provide periodic updates as needed and situational guidance in response to events (www.sfdph.org/cdcp).

Treatment

The treatment of choice for all forms of tularemia is streptomycin. Gentamicin, which is more widely available, is an acceptable alternative. Tetracycline and chloramphenicol have been used to

treat tularemia, however as these drugs are bacteriostatic, relapses occur more often than with the aminoglycosides. Bioterrorist use of an *F. tularensis* strain resistant to conventional antibiotic therapy is of concern and should be considered, particularly if patients deteriorate despite early initiation of antibiotic therapy.

TABLE 1. TREATMENT OF TULAREMIA IN THE CONTAINED CASUALTY SETTING	
Patient Category	**Therapy Recommendation***
Adults: **Preferred Choices**	Streptomycin, 1 gm IM BID for 10 days‡†§ ***OR*** Gentamicin, 5 mg/kg IM or IV QD for 10 days‡†
Adults: **Alternative Choices**	Doxycycline, 100 mg IV BID for 14-21 days† ***OR*** Chloramphenicol, 15 mg/kg IV QID for 14-21 days** ***OR*** Ciprofloxacin, 400 mg IV BID for 10 days†
Children: **Preferred Choices**	Streptomycin, 15 mg/kg IM BID (max 2 gm/day) for 10 days‡ ***OR*** Gentamicin, 2.5 mg/kg IM or IV TID for 10 days‡
Children: **Alternative Choices**	Doxycycline, >45 kg, give adult dosage for 14-21 days <45 kg, give 2.2 mg/kg IV BID for 14-21 days ***OR*** Chloramphenicol, 15 mg/kg IV QID for 14-21 days** ***OR*** Ciprofloxacin, 15 mg/kg IV BID (max 1 gm/day) for 10 days

* These treatment recommendations reflect those of the Working Group on Civilian Biodefense and may not necessarily be approved by the Food and Drug Administration.
† Acceptable for pregnant women.
§ Streptomycin is not as acceptable as gentamicin for use in pregnant women because irreversible deafness in children exposed in utero has been reported with streptomycin use.
‡ Aminoglycosides must be adjusted according to renal function.
** Concentration should be maintained between 5 and 20 цg/mL; concentrations >25 цg/mL can cause reversible bone marrow suppression.

Source: Working Group on Civilian Biodefense. Dennis DT, JAMA 2001 285(21):2763-2773.

Supportive care of patients is also critical, including fluid management and hemodynamic monitoring as indicated. Some patients may require intensive care with respiratory support owing to complications of gram-negative sepsis.

In a contained casualty setting where the medical care delivery system can effectively manage the number of patients, parenteral antibiotics should be administered **(Table 1, above)**. Therapy may be switched to oral antimicrobials when clinically indicated.

In a mass casualty setting where the medical care delivery system is not able to meet the demands for patient care, use of oral antibiotics may be necessary **(Table 2, below)**.

TABLE 2. TREATMENT OF TULAREMIA IN THE MASS CASUALTY SETTING AND FOR POST-EXPOSURE PROPHYLAXIS*	
Patient Category	**Therapy Recommendation***
Adults (Including Pregnant Women)	Doxycycline, 100 mg PO BID for 14 days‡ ***OR*** Ciprofloxacin, 500 mg PO BID for 14 day‡
Children	Doxycycline, >45 kg, give adult dosage for 14 days <45 kg, give 2.2 mg/kg PO BID for 14 days ***OR*** Ciprofloxacin, 15 mg/kg PO BID (max 1 gm/day) for 10 days
* These treatment recommendations reflect those of the Working Group on Civilian Biodefense and may not necessarily be approved by the Food and Drug Administration. ‡ Although fetal toxicity may occur with doxycycline use, the Working Group recommended doxycycline or ciprofloxacin for postexposure prophylaxis of pregnant women or for treatment of infection of pregnant women in the mass casualty setting.	
Source: Working Group on Civilian Biodefense. Dennis DT, JAMA 2001 285(21):2763-2773.	

Post-Exposure Prophylaxis

Antibiotic prophylaxis should begin as soon as possible and preferably within 24 hours after exposure to an infectious aerosol containing *F. tularensis* **(Table 2)**. Post-exposure prophylactic antibiotic treatment of close contacts of tularemia patients is not recommended since human-to-human transmission of *F tularensis* is not known to occur.

Vaccination

A live, attenuated vaccine was used in the USA until recently to protect laboratory workers at high risk for *F. tularensis* exposure. However the vaccine currently is unavailable and is under review by the FDA.

INFECTION CONTROL*

These recommendations are current as of this document date. SFDPH will provide periodic updates as needed and situational guidance in response to events (www.sfdph.org/cdcp).

Person-to-person transmission of tularemia has not been documented; therefore, **Standard Precautions** are considered adequate for patients with tularemia.

Commercially available bleach or a 1:10 dilution of household bleach and water is considered adequate for disinfecting contaminated surfaces. After direct exposure to powder or liquid aerosols containing *F. tularensis*, body surfaces and clothing should be washed with soap and water.

* For description of Precautions, see Chapter on Infection Control

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