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Tiny Pathogen, Big Problem: 2025 Updates in the Treatment and Prevention of Tularemia

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1



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2



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Presentation Objectives

- Describe the epidemiology, transmission routes, and clinical manifestations of tularemia (Pharmacist)
- Discuss the classification of tularemia as a Tier 1 Select Agent with bioterrorism potential and it's implications for emergency preparedness (Pharmacist)
- Evaluate first-line and alternative antimicrobial treatment options for tularemia (Pharmacist)
- Explain the difference between treatment and prophylaxis medications (Pharmacy Technician)
- Identify first-line antimicrobial agents recommended for tularemia treatment and post-exposure prophylaxis (Pharmacy Technician)

3



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"Rabbit Fever"

- Other names include:
 - Market's Men Disease
 - Meat-Cutter's Disease
 - Deer-Fly Fever
 - Water-Rat-Trappers' Disease
 - Glandular Type of Tick Fever



4

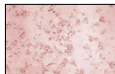


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Tularemia

- Caused by *Francisella tularensis*, an aerobic gram-negative bacteria
 - Initially confused for *Yersinia pestis*
- First described in 1910s in Tulare County, CA
- Associated with a massive die-off of ground-squirrels
- Now known to be transmitted by arthropods, air, food, or water
 - Dog tick (aka wood tick) can spread by rabbits & rodents that are infected or carrying ticks
 - Complex host distribution, including >250 wildlife animal species
- Seen in the media in recent years for exposures in Martha's Vineyard, associated with inhalation of particles during outdoor landscaping



5



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A Quote from Early Study

It is so highly contagious that after it's discovery the Medical Research Council of England stated in 1922, that occupational infection is:

"...an accident which seems... to befall practically all laboratory workers who attempt the cultivation."

6

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How Tularemia Spreads

- Tick and deer fly bites
 - American dog tick, Rocky Mountain wood tick, lone star tick
 - Not transmitted by the same ticks that spreads Lyme disease
- Skin contact with infected animals
- Drinking contaminated water
- Inhaling contaminated aerosols or agricultural and landscaping dust
- Laboratory exposure
- Bioterrorism risk of spread



www.cdc.gov/eid/content/vol14/1403/tularemia.htm



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Tularemia: An Interesting Case



Morbidity and Mortality Weekly Report (MMWR)

Notes from the Field. Tularemia Associated with Harbor Seal Necropsy
— Kitsap County, Washington, October 2023

Weekly / August 22, 2024 / 73(33):751–752

What is added by this report?

In 2023, tularemia occurred in a wildlife volunteer after exposure to a deceased, infected harbor seal, the first known report of tularemia acquired through contact with a marine mammal, and the first detection of *F. tularensis* in a marine mammal.

What are the implications for public health practice?

Health care providers, public health investigators, and persons working with marine wildlife need to be aware of the potential risk for tularemia and other zoonotic diseases associated with harbor seal contact and adhere to established safety protocols.



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Fun Side-Bar: “Seal Finger”

- First described in 1907
- Caused by *Mycoplasma* species
- Associated with close contact to seals
- Patients present with localized swelling, erythema, and pain
- May also occur after exposure to cats or bears
- Treated with doxycycline or moxifloxacin



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Occupational Exposure of Tularemia

KEY POINTS

- People can get tularemia through occupational exposures.
- People who work in a microbiological laboratory and veterinary or other animal care may have higher risk of infection with *Francisella tularensis* compared to those in human healthcare, where the risk is generally lower.
- Appropriate precautions to decrease risk of tularemia through occupational exposure are important in all settings.

<https://www.fsfh.org/occupational-exposure-tularemia>



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Preventing Exposure

- Insect repellents
- Wearing gloves if handling sick or dead animals
- Avoid mowing over dead animals
- Occupational precautions



www.fsps.org/2019/09/2019-annual-meeting/ | [History.com/shows/alone](http://history.com/shows/alone)

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F. tularensis Outbreaks & as a Biologic Weapon

- Tularemia can increase with ecologic disruption and poor sanitation from war
- During WW-II, hundreds of thousands of people in the former Soviet Union developed tularemia from infected rodents
- Tier 1 Select Agent, indicating the greatest risk for use in bioterrorism
 - History of weaponization, stability in the environment, low inoculum
 - Easily stored in dried form, which can cause disease when inhaled
 - Included in weapons stockpiles in the 1950s and 1960s
 - Former Soviet Union scientists purposely developed antibiotic-resistant strains
- WHO predicts release of 50 kg of aerosolized *F. tularensis* in a city with a population of 5M would result in 250K incapacitated persons and 19K deaths, with effects lasting for months
- International treaty in 1972 officially prohibited biological weapons



13

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Signs & Symptoms of Tularemia

- Incubation period: 3-7 days (range 1-21 days)
- Typical clinical pictures:
 1. Ulceroglandular
 2. Glandular
 3. Oculoglandular
 4. Oropharyngeal
 5. Typhoidal (worse outcomes)
 6. Pneumonic (worse outcomes)
- Generalized s/sx:
 - Fever, chills
 - Headache
 - Malaise, fatigue
 - Anorexia
 - Myalgia
 - Chest discomfort, cough
 - Sore throat
 - Vomiting, diarrhea
 - Abdominal pain

14

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Learning About Tularemia Through Gaming



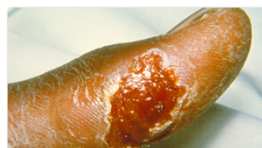
15

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Tularemia: (Ulcer) Glandular Presentation

(Ulcer) Glandular: Usually occurs following a tick or deer fly bite or after handling an infected animal.

- Localized lymphadenopathy
- Cutaneous ulcer at infection site (not always present)



An ulcer on a person's thumb caused by *Francisella tularensis*.

16

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Tularemia: Oculoglandular Presentation



Oculoglandular: Occurs when the bacteria enter through the eye, for example when a person touches their eye after handling infectious material.

- Photophobia
- Excessive lacrimation
- Conjunctivitis
- Preauricular, submandibular and cervical lymphadenopathy

17

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Tularemia: Other Presentations

Oropharyngeal

- Occurs after eating/drinking contaminated food/water
 - Severe throat pain
 - Exudative pharyngitis or tonsillitis
 - Cervical, periparotid, and/or retropharyngeal lymphadenopathy

Pneumonic

- Occurs after breathing dusts or aerosols containing the bacteria or secondary to other untreated forms of tularemia
 - Cough (dry or productive)
 - Substernal tightness
 - Pleuritic chest pain
 - Hilar adenopathy, infiltrate, or pleural effusion may be present on chest imaging

Typhoidal

- Characterized by any combination of the general symptoms, without localizing symptoms of other specific presentations

18

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Tularemia: Testing & Diagnosis

- Providers who expect *F. tularensis* should inform the lab to prevent exposure
- There are 3 subspecies
 - F. tularensis tularensis* (type A), associated with severe disease
 - F. tularensis holarctica* (type B)
 - F. tularensis mediasiatica* (not found in humans, yet)
- Specimens from various body sites
- Serologic testing
 - CDC provides robust guidance on testing:

Diagnostic considerations for serologic testing

What is the timing of the IgM and IgG antibody response to *F. tularensis* infection?

What are the clinical implications?

Do serologic cross-reactions occur on *F. tularensis* antibody testing?

When is it useful to repeat serologic testing for *F. tularensis*?

19

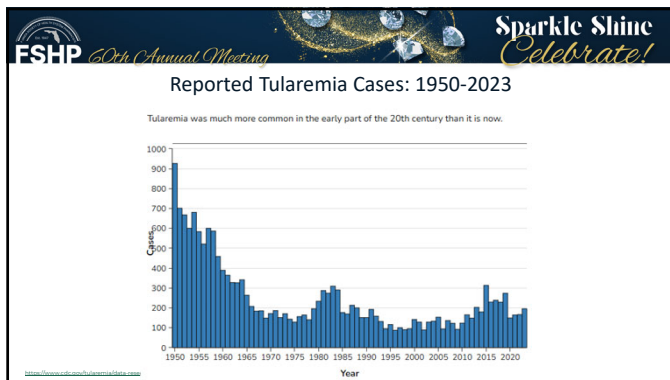
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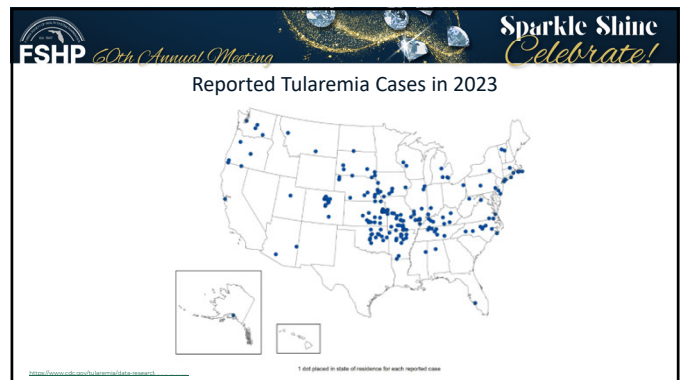
Tularemia Reporting

Tularemia is a reportable disease, meaning the law requires reporting to public health authorities

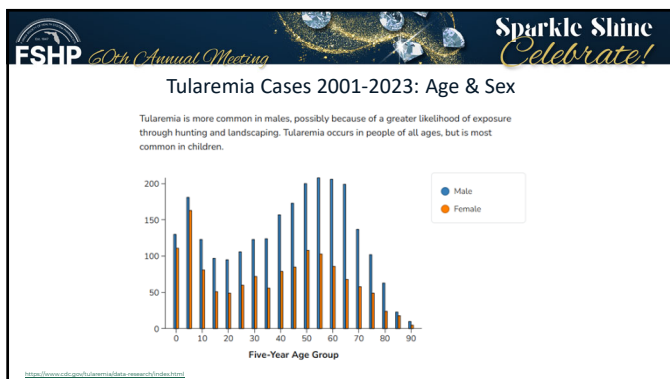
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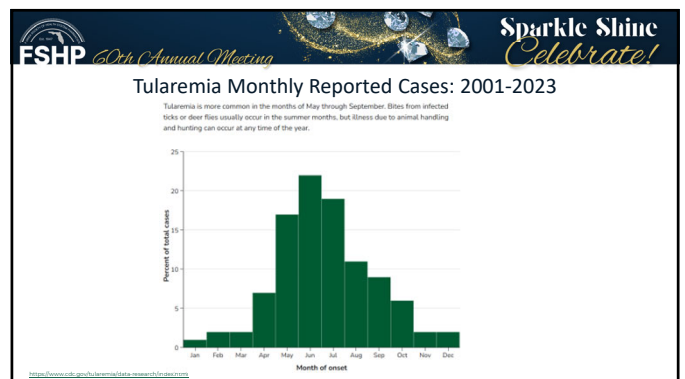
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22



23



24




Managing Potential Occupational Tularemia Exposure

- Time since exposure
 - Fever watch may be performed if incubation period (~7 days) already passed
- Type of exposure (low- vs high-risk)
 - High risk includes:
 - Working with cultures outside a biosafety cabinet
 - Bites from infected animals
 - Needlesticks, scalpel wounds
 - Mucous membrane exposures during necropsies
 - Aerosol-generating procedures on cultures or tissues without PPE
- Personal preference and risk tolerance

http://www.cdc.gov/ncez/occupational/occupational_tularemia.htm



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Tularemia & Antimicrobials

- Many antibiotics have been studied, including:
 - Fluoroquinolones
 - Aminoglycosides
 - Tetracyclines
 - Macrolides
 - Chloramphenicol
- CDC provides tables on treatment and prophylaxis
 - Ciprofloxacin, levofloxacin, gentamicin, and doxycycline make repeat appearances
 - Take note of whether recommendations are for bioterrorism response and/or naturally acquired infection



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Tularemia Prevention

- No vaccines available for PEP or PrEP
- CDC recommendations for PEP in adults:

Population	Category	Antimicrobial class	Antimicrobial	Dosage	Duration (days)
Adults aged ≥18 yrs	First-line	Fluoroquinolone	Ciprofloxacin	500 mg every 12 hrs orally	7
			Levofloxacin	500 mg every 24 hrs orally	7
		Tetracycline	Doxycycline	100 mg every 12 hrs orally	10-14
	Alternative	Fluoroquinolone	Moxifloxacin*	400 mg every 24 hrs orally	7
			Ofloxacin†	400 mg every 12 hrs orally	7
		Tetracycline	Minocycline	100 mg every 12 hrs orally	10-14
			Tetracycline	500 mg every 6 hrs orally	10-14
		Macrolide	Azithromycin (for Type A and susceptible Type B biovars)‡	500 mg every 24 hrs orally	10

Tularemia: CDC Treatment Recommendations			
Population	Antimicrobial Class	Antimicrobial Doseage	Duration (Days)
Adults aged ≥18 yrs	Fluoroquinolone	Ciprofloxacin* 400 mg every 8 hrs IV or 750 mg every 12 hrs PO	10
	Levofloxacin	750 mg every 24 hrs IV or PO	10
	Aminoglycoside	Gentamicin** 6 mg/kg every 24 hrs IV or IM*	10
Children aged ≥1 mo. to ≤17 yrs	Doxycycline	200 mg loading dose, then 100 mg every 12 hrs IV or PO	14-21
	Fluoroquinolone	Ciprofloxacin* 10 mg/kg every 8-12 hrs IV (maximum: 400 mg/dose) or 18 mg/kg every 8-12 hrs PO (maximum: 500 mg/dose every 12 hrs)	10
	Levofloxacin	Infants and children aged <5 yrs: 10 mg/kg every 12 hours IV or PO (maximum: 375 mg/dose) Children aged ≥5 yrs and adolescents: 10 mg/kg every 24 hours IV or PO (maximum: 750 mg/dose)	10
Aminoglycoside	Gentamicin**	5-7.5 mg/kg every 24 hrs IV or IM* (mg/kg dose determined by age** upper range can be increased to 9.5 mg/kg based on age and AUC monitoring)	10
	Tetracycline	Doxycycline 4.4 mg/kg loading dose (maximum 200 mg), then 2 mg/kg every 12 hrs IV or PO (maximum: 100 mg/dose)	14-21



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Tularemia Treatment Notes

- Fluoroquinolones
 - Toxicities are concerning
 - Collateral damage to the microbiome
 - Binding oral cations
 - Low cost, widely available
- Aminoglycosides
 - Ototoxicity, nephrotoxicity
 - Inconvenient, more expensive
- Doxycycline
 - Widely available, low cost, relatively well tolerated
 - Longer treatment durations
 - FDA-approved for tularemia (so is streptomycin, tetracycline, and minocycline)
 - Doxycycline has more data than other tetracyclines for tularemia treatment




Mark O'Brien, MD

<https://www.fishbase.org/species/fluorocyclo>

Tularemia Treatment in Pregnancy				
Category	Antimicrobial class	Antimicrobial	Dosage	Duration (days)
First-line	Fluoroquinolone	Ciprofloxacin*	400 mg every 8 hrs IV or 750 mg every 12 hrs orally	10
		Levofloxacin*	750 mg every 24 hrs IV or orally	10
	Aminoglycoside	Gentamicin*	6 mg/kg every 24 hrs IV or IM [§]	10
Alternative	Fluoroquinolone	Moxifloxacin* [§]	400 mg every 24 hrs IV or orally	10
		Ofloxacin* [§]	400 mg every 12 hrs IV or orally	10
	Aminoglycoside	Amikacin*	15 mg/kg every 24 hrs IV or IM [§]	10
		Tobramycin*	6 mg/kg every 24 hrs IV or IM [§]	10
	Tetracycline	Doxycycline	200 mg loading dose, then 100 mg every 12 hrs IV or orally	14-21

31

Tularemia Treatment Considerations

- Severe infection may warrant multiple antibiotics
 - Gentamicin + ciprofloxacin
 - Gentamicin + doxycycline
- Do not use doxycycline monotherapy for severe infection or if delay to treatment by 2 weeks or more
- Adjustments may be required by age, medical history, underlying health condition, pregnancy status, and allergy
 - A fluoroquinolone or gentamicin is first-line for pregnant women

32

Pharmacist's Role In Emergency Preparedness

- Response planning
- Developing guidelines
- Safe medication distribution and handling
- Resource management
- Education and communication
- Training other pharmacy professionals



33

Take Home Points

- Tularemia is rare, but can be a severe and life threatening disease
- Pharmacists and pharmacy technicians should be familiar with key information about prevention and treatment of Tularemia
- CDC and local health departments provide robust resources to support identification and treatment of Tularemia

34

POST-LECTURE QUESTIONS

35

Questions?



36