OREGON HEALTH AUTHORITY
PUBLIC HEALTH DIVISION
ACUTE AND COMMUNICABLE DISEASE PREVENTION SECTION

Tularemia Prophylaxis

I. OREGON MODEL PROTOCOL

1. Follow the nursing assessment of individuals presenting for prophylactic treatment to a known or potentially harmful biological agent.
2. Provide patient information about tularemia and the preventive antibiotics prior to administration, answering any questions
3. Dispense antibiotic prophylaxis in accordance with prophylactic treatment guidelines (Table 1) and within the restrictions of the guidelines of the Strategic National Stockpile program.

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Signature, Health Officer Date

II. Persons for whom prophylaxis may be dispensed

The World Health Organization recommends post-exposure prophylaxis in the following settings:

1. Exposure of laboratory personnel to *Francisella tularensis* in the absence of proper infection control measures;

2. Exposure to an aerosolized release of *Francisella tularensis*.

Table 1

Recommendations for Treatment of Patients with Tularemia in a Mass Casualty Setting and for Post-exposure Prophylaxis [a]	
Adults	**Preferred Choices** Doxycycline, 100 mg orally twice daily Ciprofloxacin, 500 mg orally twice daily [b]
Children	**Preferred Choices** Doxycycline; if ≥45 kg, give 100 mg orally twice daily; Doxycycline, if <45 kg, give 2.2 mg/kg orally twice daily; Ciprofloxacin, 10–15 mg/kg orally twice daily [c]
Pregnant women	**Preferred Choices** Ciprofloxacin, 500 mg orally twice daily [b] Doxycycline, 100 mg orally twice daily

[a] One antibiotic, appropriate for patient age, should be chosen from among alternatives. The duration of all recommended therapies in Table 1 is 14 days.
[b] Not a US Food and Drug Administration–approved use.
[c] Ciprofloxacin dosage should not exceed 1g/d in children.

Reference:
CDC. 2005. Abstract: "Consensus statement: Tularemia as a Biological Weapon: Medical and Public Health Management. Dennis DT, Inglesby TV, et al. Tularemia as a biological weapon. JAMA 2001; 285: 2763-73.

Tularemia Postexposure Prophylaxis

Drug selection and dosing information for patients requiring prophylaxis after exposure to *Francisella tularensis*, the bacterium that causes tularemia, are outlined in this document. Recommendations follow those of the Working Group on Civilian Biodefense.[1]

Until antibiotic susceptibility results of the implicated strain are available, initial therapy for prophylaxis after exposure to *F. tularensis* is doxycycline or ciprofloxacin.[1] Following an intentional release, public health officials of the Oregon Health Authority will designate which of these two drugs will be the primary drug to use for prophylaxis. All people who have been potentially exposed to *F. tularensis* should receive a 14-day course of drug therapy.

To prevent serious medical consequences associated with hypersensitivity reactions and drug interactions, the Oregon Health Authority recommends that people be medically evaluated as described in this document prior to dispensing. In the event that this is not possible due to extreme time constraints, following a non-medical model may be necessary.

Tularemia Post-Exposure Prophylaxis
Doxycycline Designated as Primary Drug

All persons to receive post-exposure prophylaxis start in the "express" line. Anyone answering "yes" to any of the following questions should be routed to a medical screener for evaluation.

1. **Has the patient ever had an allergic reaction to any medication in the tetracycline class?**

   Allergic reactions may include: hives, redness of the skin, rash, difficulty breathing, or worsening of lupus after taking one of the tetracycline class drugs, including demeclocycline (Declomycin®); doxycycline (Adoxa®, Bio-Tab®, Doryx®, Doxy®, Monodox®, Periostat®, Vibra-Tabs®, Vibramycin®); minocycline (Arestin®, Dynacin®, Minocin®, Vectrin®); oxytetracycline (Terak®, Terra-Cortril®, Terramycin®, Urobiotic-®250®); or tetracycline (Achromycin V®, Sumycin®, Topicycline®, Helidac).[2,3]

   Patients who are allergic to any medication in the tetracycline class should be referred to a medical screener and receive another form of therapy such as ciprofloxacin.

2. **Does the patient weight less than 99 pounds (45 kilograms)?**

   Patients weighing less than 99 pounds (45 kilograms), should be referred to a medical screener to be weighed. They will receive a 14-day supply of doxycycline, 2.2 mg/kg (as described in Table 2) by mouth every 12 hours.

Table 2

Weight (lbs)	Weight (kg)	Dose (mg)	Available Dosage Forms of Doxycycline				
			20 mg tablet	50mg tablet or capsule	100mg tablet* or capsule	25mg/5mL suspension*	50mg/5mL syrup
5-10	2-5	10				2 mL	1 mL
11-20	6-9	20	1			4 mL	2 mL
21-30	10-14	30				6 mL	3 mL
31-40	15-19	40	2			8 mL	4 mL
41-50	20-22	50		1	½	10 mL	5 mL
51-60	23-27	60	3			12 mL	6 mL
61-70	28-32	70				14 mL	7 mL
71-80	33-36	80	4			16 mL	8 mL
81-90	37-41	90				18 mL	9 mL
91-100	≥ 42	100	5	2	1	20 mL	10 mL

*Dosage Forms available through the CDC National Pharmaceutical Stockpile Program

Reference: CDC. 2005. Abstract: "Consensus statement: Tularemia as a Biological Weapon: Medical and Public Health Management. Dennis DT, Inglesby TV, et al. Tularemia as a biological weapon. JAMA 2001; 285: 2763-73.

3. Is the patient younger than 9 years?

Doxycycline and other tetracyclines are not normally recommended for children and pregnant women due to the risk of dental staining of the primary teeth, concerns about possible depressed bone growth, defective dental enamel, and rare liver toxicity. Therefore, children and pregnant and lactating women will not normally receive doxycycline.

Due to the risk of teeth discoloration associated with tetracyclines, children without a quinolone allergy, who have not received all of their permanent teeth, should be prescribed ciprofloxacin. Since the age at which a child obtains his/her permanent teeth varies, it is possible for children under the age of 9 years to receive doxycycline. The parent or guardian of the child should be asked whether the child has a full set of permanent teeth.

4. Is the patient pregnant or breast-feeding?

Doxycycline and other tetracyclines are not normally recommended for children and pregnant women due to the risk of dental staining of the primary teeth, concerns about possible depressed bone growth,

defective dental enamel, and rare liver toxicity. The assessment of the Working Group is that the potential benefits of doxycycline and ciprofloxacin in the prevention and treatment of pneumonic tularemia infection substantially outweigh the risks in pregnant women.[1]

Women who are pregnant or breastfeeding should be referred to a medical screener for counseling regarding these recommendations.

5. **Is the patient taking any prescription medications or over-the-counter antacids or anti-inflammatory drugs?**

   People who are taking any prescription medications or over-the-counter antacids or anti-inflammatory drugs should be referred to a medical screener for review of the patient's medical and drug history, as these drugs can have interactions with antibiotics used for tularemia prophylaxis. See Attachment 1 for drug interactions with doxycycline.

6. **Patients answering "no" to all of the above questions.**

   Patients answering "no" to all medical screening questions should receive doxycycline as described in Table 1. Duration of post-exposure prophylaxis to prevent tularemia infection is 14 days.

Tularemia Post-Exposure Prophylaxis: Ciprofloxacin Designated as Primary Drug

All people to receive post-exposure prophylaxis start in the "express" line. Anyone answering "yes" to any of the following questions should be routed to a medical screener for evaluation.

1. **Has the patient ever had an allergic reaction to any medication in the quinolone class?**

   Allergic reactions may include: difficulty breathing, rash, itching, hives, yellowing of the eyes or skin, swelling of the face or neck, cardiovascular collapse, loss of consciousness, hepatic necrosis (death of liver cells), or Stevens-Johnson Disease (a rare but severe skin reaction) after taking a quinolone class drug, including: acrosoxacin or rosoxacin (Eradacil®); cinoxacin (Cinobac®); ciprofloxacin (Cipro®, Ciloxan®); gatifloxacin (Tequin®); grepafloxacin (Raxar®); levofloxacin (Levaquin®, Quixin®); lomefloxacin (Maxaquin®); moxifloxacin (Avelox®, ABC Pak®); nadifloxacin (Acuatim®); norfloxacin (Chibroxin®, Noroxin®); nalidixic acid (NegGram®); ofloxacin (Floxin®, Ocuflox®); oxolinic acid; pefloxacin (Peflacine®); rufloxacin; sparfloxacin (Zagam®, Respipac®); temafloxacin; trovafloxacin or alatrofloxacin (Trovan®).[3]

   Patients who have had an allergic reaction to any medication in the quinolone class should be referred to a medical screener and receive another form of therapy such as doxycycline.

2. **Does the patient weigh less than 73 pounds (33 kilograms)?**

   Ciprofloxacin and other quinolones are not normally recommended in children due to the risk of arthropathy. This recommendation is based on studies in animals. Data in humans have not confirmed this risk.[1]

   People weighing less than 73 pounds (33 kilograms) should be referred to a medical screener, where they will receive a 14-day supply of ciprofloxacin (10-15 mg/kg by mouth every 12 hours) based on their weight as described in Table 1 and 3. Ciprofloxacin dosage should not exceed 1 g/day in children.

   Table 3 purposely reflects more than one dose for a particular weight to permit flexibility in dosing based upon the products that are available at the time of dispensing. These doses are within the recommended ranges for ciprofloxacin: 10-15 mg/kg.

Table 3

Weight (pounds)	Weight (kilogram)	Dose (mg)	Available Dosage Forms of Ciprofloxacin				
			100mg tablet	250mg tablet	500mg tablet*	250mg/5mL suspension*	500mg/5mL suspension
7-12 lbs	3-5 kg	50 mg PO BID	½	¼		1 mL (1 bottle)	0.5 mL (1 bottle)
13-22 lbs	6-10 kg	100 mg PO BID	1			2 mL (1 bottle)	1 mL (1 bottle)
18-28 lbs	8-13 kg	125 mg PO BID		½	¼	2.5 mL (1 bottle)	1.25 mL (1 bottle)
22-33 lbs	10-15 kg	150 mg PO BID	1½			3 mL (1 bottle)	1.5 mL (1 bottle)
29-44 lbs	13-20 kg	200 mg PO BID	2			4 mL (1 bottle)	2 mL (1 bottle)
36-56 lbs	16-25 kg	250 mg PO BID		1	½	5 mL (1 bottle)	2.5 mL (1 bottle)
55-83 lbs	25-37 kg	375 mg PO BID		1½	¾	7.5 mL (2 bottles)	3.75 mL (1 bottle)
≥73 lbs	≥ 33 kg	500 mg PO BID		2	1	10 mL (2 bottles)	5 mL (1 bottle)

* Dosage Forms available through the CDC National Pharmaceutical Stockpile Program.

3. Is the patient pregnant or breast-feeding?

The assessment of the Working Group is that the potential benefits of ciprofloxacin and doxycycline in the prevention and treatment of pneumonic tularemia infection substantially outweigh the risks in pregnant women.[1]

Women who are pregnant or breastfeeding should be referred to a medical screener for counseling regarding these recommendations.

4. Does the patient have kidney problems?

Patients with kidney problems include those receiving dialysis, with known kidney failure (end-stage renal disease) or who have reduced kidney function. Patients who have chronic kidney infections or kidney stones do not need an adjusted dose, unless they have been told by a health care professional that they have kidney damage.

Patients with kidney problems who weigh less than 73 pounds should be referred to a medical screener.

Give patients ≥73 pounds (33 kilograms) with kidney problems ciprofloxacin 500 mg by mouth ONCE a day, and refer them to a physician for further assessment. Use Table 4[4] to determine the dose of ciprofloxacin required for patients with kidney problems when creatinine clearance is known or can be determined.

Table 4

Kidney Function	Ciprofloxacin Dose
Creatinine Clearance >50 mL/min	**500 mg every 12 hours**
Creatinine Clearance = 30-50 mL/min	**250 mg every 12 hours**
Creatinine Clearance = 5-29 mL/min	**250 mg every 18 hours**
Hemodialysis	**250 mg every 24 hours**

5. Does the patient have a history of seizures or neurologic problems?

People with a history of seizures should avoid use of ciprofloxacin if alternative antibiotics are available. Send to a medical screener to assess for use of doxycycline.

6. Is the patient taking any prescription medications, over-the-counter antacids, anti-inflammatory drugs, or Tizanidine?

People who are taking any medications or over-the-counter antacids or anti-inflammatory drugs should be referred to a medical screener for the review of the person's medical and drug history, as these drugs can have interactions with antibiotics used for tularemia prophylaxis. See Attachment 2 for drug interactions with ciprofloxacin.

7. People answering "no" to all of the above questions

Patients ≥73 pounds (33 kilograms) should receive ciprofloxacin 500 mg by mouth every 12 hours for 14 days as described in Table 1.

References

1. Dennis DT, Inglesby TV, Henderson DA, et al. Tularemia as a biological weapon: medical and public health management. *JAMA* 2001;285:2763–2773.

2. Vibramycin (doxycycline monohydrate) Package Insert. New York: Pfizer Inc. April 2007. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2008/050006s79,050007s20,050480s42,050533s36lbl.pdf Accessed 27 July 2018.

3. Sweetman S, Martindale C. The Complete Drug Reference. Great Britain; Pharmaceutical Press. 2017

4. Lacy CF, Armstrong LL, Goldman MP, et al. Drug Information Handbook. Hudson, OH; Lexi-Comp. 2017-2018.

5. Drug Facts and Comparisons, 2014, 68th Edition. Lippincott Williams & Wilkins.

Attachment 1 Tetracycline Drug Interactions[1]

Other Drug	Effect	Recommendation
Antacids (containing aluminum, calcium or magnesium salts) Iron salts Zinc salts	Tetracyclines administered with aluminum, calcium, magnesium, iron or zinc salts form an insoluble chelate, thereby decreasing the absorption and serum levels of the tetracycline.	Administer tetracyclines 1 hour before or 2 hours after these agents
Barbiturates – Phenobarbital, amobarbital, aprobarbital, butabarbital, secobarbital (various brand names)	Barbiturates increase the hepatic metabolism of doxycycline, thereby decreasing doxycycline's half-life and serum levels.	Adjust doxycycline dose as needed. Consider using an alternative tetracycline.
Bismuth salts	Co-administration of bismuth salts in liquid formulations may decrease the serum levels of tetracyclines.	Give the bismuth salt 2 hours after the tetracycline.
Carbamazepine (Atretol®, Epitol®, Tegretol®, Carbatrol®) anticonvulsant	Carbamazepine may decrease the half-life and serum levels of doxycycline due to increased hepatic metabolism.	Adjust doxycycline dose as needed. Consider using an alternative tetracycline.
Cholestyramine (LoCHOLEST®, Questran®, Prevalite®) Colestipol (Colestid®) for hyperlipidemia	Co-administration may decrease or delay the absorption of tetracyclines, therefore decreasing the serum concentrations.	Adjust the tetracycline dose if needed.
Contraceptives, oral	Tetracyclines may interfere with circulation of certain contraceptive steroids, Although infrequently reported, contraceptive failure is possible.	Counsel patient regarding use of alternative contraceptives while taking tetracyclines.

[1] Adapted from Drug Facts and Comparisons, 2013, 68th Edition. Lippincott Williams & Wilkins

Attachment 1 (Cont.) Tetracycline Drug Interactions[2]

Other Drug	Effect	Recommendation
Digoxin (Lanoxin®, Lanoxicaps®) cardiac glycoside	Co-administration may result in increased serum levels of digoxin in a small subset of patients (~10%).	Monitor digoxin levels and signs of toxicity.
Insulin	The ability of insulin to produce hypoglycemia may be potentiated.	In diabetic patients, monitor blood glucose concentrations closely and tailor the insulin regimen as needed.
Isotretinoin (Accutane®, Claravis®) acne treatment	Isotretinoin use has been associated with a number of cases of pseudotumor cerebri, some of which involved co-administration of tetracyclines.	Avoid concomitant use.
Methoxyflurane (Penthrane®) general anesthetic	Co-administration may enhance the risk for renal toxicity; deaths have been reported.	Do not co-administer.
Penicillins (various brand names)	The bacteriostatic action of tetracyclines may interfere with the bactericidal activity of penicillins.	Consider avoiding this combination, if at all possible.
Phenytoin (Dilantin®) anticonvulsant	Phenytoin appears to induce the metabolism of doxycycline causing the half-life to be significantly decreased.	Increased doxycycline dosage may be needed.
Rifamycins – Rifampin, rifabutin, rifapentin	Rifamycins appear to induce the metabolism of doxycycline causing the half-life to be significantly decreased.	Increased doxycycline dosage may be needed.

[2] Adapted from Drug Facts and Comparisons, 2013, 68th Edition. Lippincott Williams & Wilkins

Attachment 1 (Cont.) Tetracycline Drug Interactions[3]

Other Drug	Effect	Recommendation
Theophylline (various brand names) bronchodilator	The incidence of adverse reactions to theophyllines may be increased.	Monitor theophylline levels and adjust dose as needed.
Urinary alkalinizers (e.g., sodium lactate, potassium citrate)	Co-administration may result in increased excretion of the tetracyclines and decreased serum levels.	Separate administration by 3 to 4 hours; however, this may not be effective, and an increase in tetracycline dose may be necessary if the pH of the urine remains increased.
Warfarin, (Coumadin®) anticoagulants	The action of oral anticoagulants may be increased because of the elimination of vitamin K-producing gut bacteria by tetracyclines.	Monitor coagulation parameters and adjust anticoagulant dose as needed.

[3] Adapted from Drug Facts and Comparisons, 2013, 68th Edition. Lippincott Williams & Wilkins

Attachment 2 Ciprofloxacin Drug Interactions[4]

Other Drug	Effect	Recommendation
Antacids	Decreased GI absorption of quinolones resulting in decreased serum levels. Bioavailability of ciprofloxacin may be reduced by as much as 90%.	Avoid simultaneous use.
Caffeine	The hepatic metabolism of caffeine is decreased by certain quinolones; therefore, the pharmacologic effects of caffeine may be increased.	
Cyclosporine (various brand names) immunosuppressant	Increased cyclosporine toxicity. The mechanism is unknown.	
Cimetidine (Tagamet®) ulcer treatment	Cimetidine may interfere with the elimination of the fluoroquinolones.	
Dairy products	Reduce the absorption of ciprofloxacin.	Ciprofloxacin should not be taken with dairy products.
Didanosine (Videx®)) Antiretroviral agent	The magnesium and aluminum cations in the buffers present in didanosine tablets decrease the GI absorption of quinolones via chelation.	Avoid simultaneous use.
Iron salts	GI absorption of certain quinolones may be decreased by formation of an iron-quinolone complex.	Avoid co-administration of these drugs.
NSAIDs Nonsteroidal anti-inflammatory drugs	Concurrent administration of NSAIDs with a quinolone may increase the risk of CNS stimulation and convulsive seizures.	

[4] Adapted from Drug Facts and Comparisons, 2013, 68th Edition. Lippincott Williams & Wilkins

Attachment 2 Ciprofloxacin Drug Interactions[5] (Cont.)

Other Drug	Effect	Recommendation
Probenecid Gout treatment	Diminished urinary excretion of the quinolones has been reported during concomitant administration with probenecid.	Due to the interaction between probenecid and ciprofloxacin, probenecid should be temporarily stopped.
Sucralfate (Carafate®) ulcer treatment	Decreased GI absorption of quinolones.	Avoid simultaneous use; administer sucralfate ≥ 6 hours after the quinolone.
Theophylline (various brand names) bronchodilator	Administration of theophylline with ciprofloxacin has decreased theophylline clearance and increased plasma levels and symptoms of toxicity, including seizures.	Use an alternative antibiotic or decrease the dose of theophylline by 50%.
Tizanidine (Zanaflex Capsules™), (Zanaflex® Tablets)	Ciprofloxacin strongly potentiates the action of tizanidine, resulting in low blood pressure and CNS depression. Patients should be advised **not to stop** tizanidine suddenly as rebound hypertension and tachycardia may occur.	Patients requiring tizanidine should use **Doxycycline** whenever possible.
Warfarin, (Coumadin®) anticoagulants	Quinolones decrease the clearance of the R-warfarin, the less active isomer of racemic warfarin. The clearance of the active S-isomer is not affected, and changes in clotting time have not seen observed.	Monitor prothrombin times when given concomitantly.

[5] Adapted from Drug Facts and Comparisons, 2013, 68th Edition. Lippincott Williams & Wilkins