

**DEPARTMENT OF HUMAN SERVICES
PUBLIC HEALTH DIVISION
ACUTE AND COMMUNICABLE DISEASE PROGRAM**

**Model Standing Order for
Plague Prophylaxis**

I. ORDER

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

Signature, Health Officer

Date

II. Persons for whom prophylaxis may be ordered

1. Persons who have a confirmed or highly suspect exposure to *Yersinia pestis*, as determined by the local Health Officer;
2. Persons in a group for which the state Health Officer has activated the Health and Medical Annex (Annex F) of the State of Oregon Emergency Operations Plan.

July 20, 2006

Table 1

Recommendations for Treatment of Patients With Plague in a Mass Casualty Setting and for Postexposure Prophylaxis^a	
Adults	<p>Preferred choices Doxycycline, 100 mg orally twice daily^b Ciprofloxacin, 500 mg orally twice daily^c</p> <p>Alternative choice Chloramphenicol, 25mg/kg orally 4 times daily^{d, e}</p>
Pregnant women^f	<p>Preferred choices Doxycycline, 100 mg orally twice daily^b Ciprofloxacin, 500 mg orally twice daily^c</p> <p>Alternative choice Chloramphenicol, 25 mg/kg orally 4 times daily^{d, e}</p>
Children^g	<p>Preferred choices Doxycycline,^b If ≥45 kg, give adult dosage If <45 kg, then give 2.2 mg/kg (1 mg/lb) orally twice daily</p> <p>Ciprofloxacin, 20 mg/kg orally twice daily^c</p> <p>Alternative choice Chloramphenicol, 25 mg/kg orally 4 times daily^{d, e}</p>
<p>^a These are consensus recommendations of the Working Group on Civilian Biodefense and are not necessarily approved by the Food and Drug Administration. See the “Therapy” section of Inglesby, et al. for explanations. One antimicrobial agent should be selected. Duration of postexposure prophylaxis is 7 days.</p> <p>^b Tetracycline could be substituted for doxycycline.</p> <p>^c Other fluoroquinolones can be substituted at doses appropriate for age. Ciprofloxacin dosage should not exceed 1 g/d in children.</p> <p>^d Concentration should be maintained between 5 and 20 µg/mL. Concentrations greater than 25 µg/mL can cause reversible bone marrow suppression.</p> <p>^e Children younger than 2 years should not receive chloramphenicol. Oral formulation available only outside the United States.</p> <p>^f Refer to the “Management of Special Groups” section of Inglesby, et al., for details and for discussion of breastfeeding women.</p> <p>^g Refer to the “Management of Special Groups” section of Inglesby, et al., for details. In children, ciprofloxacin dose should not exceed 1 g/d; chloramphenicol should not exceed 4 g/d. Children younger than 2 years should not receive chloramphenicol.</p>	

Reference:

Inglesby TV, Dennis DT, et al. Plague as a Biological Weapon: Medical and Public Health Management. JAMA 2000; 283:2281-90.

Plague Postexposure Prophylaxis

Drug selection and dosing information for patients requiring postexposure prophylaxis or preventive treatment after exposure to *Yersinia pestis*, the bacterium that causes plague, 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 postexposure prophylaxis for prevention of plague after intentional exposure to *Y. pestis* is doxycycline.¹ All patients who have been potentially exposed to *Y. pestis* should receive a 7-day course of drug therapy.

Recommendations for antimicrobial prophylactic treatment with efficacy against plague are conditioned by balancing risks associated with treatment against those posed by pneumonic plague. 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 these antimicrobials in the treating of pneumonic plague infection substantially outweigh the risks. The Working Group specifically recommends doxycycline as the first choice antibiotic for postexposure prophylaxis.¹ If the child is unable to take doxycycline or the medication is unavailable, ciprofloxacin would be recommended.

To prevent serious medical consequences associated with hypersensitivity reactions and drug interactions, The Oregon Department of Human Services recommends that patients 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.

Plague Postexposure Prophylaxis
Doxycycline Designated as Primary Drug

The Working Group on Civilian Biodefense recommends the use of doxycycline as the first choice antibiotic for postexposure prophylaxis; other recommended antibiotics are noted in Table 1 of this document. All patients to receive postexposure 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); 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 7-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

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 breastfeeding?

The tetracycline class of antibiotics has been associated with fetal toxicity including retarded skeletal growth. However, a large case-control study of congenital abnormalities showed that doxycycline use in pregnancy presented little teratogenic risk to the fetus. Liver toxicity has been reported in pregnant women following large doses of intravenous tetracycline (no longer sold in the United States), but it has also been reported following oral administration of tetracycline to non-pregnant individuals. Balancing the risks of pneumonic plague with those associated with doxycycline use in pregnancy, the Working Group recommends that pregnant women receive doxycycline for postexposure prophylaxis.¹ If the woman is unable to take doxycycline or the medication is unavailable, ciprofloxacin should be recommended.

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 plague 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 postexposure prophylaxis to prevent plague infection is 7 days.

Plague Postexposure Prophylaxis
Ciprofloxacin Designated as Primary Drug

All people to receive postexposure 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, Ocuflax); oxolinic acid; pefloxacin (Peflacin); 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.

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

Although fluoroquinolones have been used to treat serious infections in children, some concern exists that fluoroquinolones may cause arthropathy in children. No comparative studies assessing efficacy or safety of alternative treatment strategies for plague in children has been or can be performed. Given these considerations, the Working Group recommends that children in a mass casualty setting or for postexposure prophylaxis be given doxycycline. Alternatives such as Ciprofloxacin are listed in Table 1 of this document.¹

People weighing less than 73 pounds (33 kilograms) should be referred to a medical screener to be weighed. If Ciprofloxacin is used, they will receive the appropriate dose of Ciprofloxacin for their weight. Patients less than 73 pounds (33 kilograms) should receive a 7-day supply of ciprofloxacin, and take 10-15 mg/kg by mouth every 12 hours, as described in Table 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 breastfeeding?

The Working Group recommends that pregnant women receive oral doxycycline for mass casualty treatment or postexposure prophylaxis. If the patient is unable to take doxycycline or the medication is unavailable, ciprofloxacin or other fluoroquinolones would be recommended in the mass-casualty setting. In breastfeeding women, the mother and infant should receive the same antibiotic based on what is safe and effective for the infant: doxycycline in a mass-casualty setting. Fluoroquinolones would be the recommended alternative.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 healthcare 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 4⁴ to determine the dose of ciprofloxacin required for patients with kidney problems when creatinine clearance is known or can be determined. Give all patients a 7-day supply of medication.

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 or over-the-counter antacids or anti-inflammatory drugs?

People 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 plague 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 7 days, as described in Table 1.

References

1. Inglesby TV, Dennis DT, Henderson DA, et al. Plague as a biological weapon: medical and public health management. Working Group on Civilian Biodefense. *JAMA* 2000;283:2281-2290.
2. Vibramycin Package Insert. New York: Pfizer Inc., 2001.
3. Sweetman S. *Martindale: The Complete Drug Reference*. 33rd ed. Great Britain: Pharmaceutical Press, 2002.
4. Lacy CF, Armstrong LL, Goldman MP, et al. *Drug Information Handbook 2000-2001*. 8th ed: Lexi Comp, 2000.

Attachment 1 Tetracycline Drug Interactions¹

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, butobarbital, 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	Coadministration 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 [®]) treatment for hyperlipidemia	Coadministration may decrease or delay the absorption of tetracyclines, therefore decreasing the serum concentrations.	Adjust the tetracycline dose if needed.
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.

¹ Adapted from Drug Facts and Comparison, 2004 Edition.

Other Drug	Effect	Recommendation
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.
Urinary alkalinizers (e.g., sodium lactate, potassium citrate)	Coadministration 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.
Contraceptives, oral	Tetracyclines may interfere with the enterohepatic recirculation of certain contraceptive steroids, leading to reduced efficacy. Although infrequently reported, contraceptive failure is possible.	Counsel patient regarding use of alternative contraceptives while taking tetracyclines.
Digoxin (Lanoxin [®] , Lanoxicaps [®]) cardiac glycoside	Coadministration 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 coadministration of tetracyclines.	Avoid concomitant use.

Other Drug	Effect	Recommendation
Methoxyflurane (Penthrane [®]) general anesthetic	Coadministration may enhance the risk for renal toxicity; deaths have been reported.	Do not coadminister.
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.
Theophylline (various brand names) bronchodilator	The incidence of adverse reactions to theophyllines may be increased.	Monitor theophylline levels and adjust dose as needed.

Attachment 2

Ciprofloxacin Drug Interactions²

Other Drug	Effect	Recommendation
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%.
Sucralfate (Carafate [®]) ulcer treatment	Decreased GI absorption of quinolones.	Avoid simultaneous use; administer sucralfate \geq 6 hours after the quinolone.
Iron salts	GI absorption of certain quinolones may be decreased by formation of an iron-quinolone complex.	Avoid coadministration of these drugs.
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.
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.	

² Adapted from Drug Facts and Comparison, 2004 Edition.

Other Drug	Effect	Recommendation
Probenecid Gout treatment	Diminished urinary excretion of the quinolones have been reported during concomitant administration with probenecid.	Due to the interaction between probenecid and ciprofloxacin, probenecid should be temporarily stopped.
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 been observed.	Monitor prothrombin times when given concomitantly.
NSAIDs Nonsteroidal anti-inflammatory drugs	Concurrent administration of NSAIDs with a quinolone may increase the risk of CNS stimulation and convulsive seizures.	
Dairy products	Reduce the absorption of ciprofloxacin.	Ciprofloxacin should not be taken with dairy products.