STANDING ORDERS FOR ANTIMICROBIAL THERAPY OF MASS CASUALTY PNEUMONIC AND BUBONIC PLAGUE AND POST-EXPOSURE PROPHYLAXIS TO YERSINIA PESTIS: STREPTOMYCIN, GENTAMICIN, CIPROFLOXACIN, DOXYCYCLINE, AND CHLORAMPHENICOL

Purpose: To reduce the morbidity and mortality from Y. pestis infection by providing treatment and post-exposure prophylaxis with streptomycin, gentamicin, ciprofloxacin, doxycycline, or chloramphenicol.

Policy: These standing orders allow eligible healthcare providers to treat persons exposed to Y. pestis.

Indications, Contraindications, Precautions, Special Populations, and Side Effects: The dose and safety precautions for these drugs can change over time. Clinicians should seek the most current and comprehensive product information before using these drugs as treatment or prophylaxis for plague.
<table>
<thead>
<tr>
<th>Indications</th>
<th>Streptomycin</th>
<th>Gentamicin</th>
<th>Ciprofloxacin</th>
<th>Doxycycline</th>
<th>Chloramphenicol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persons infected or exposed to aerosolized Y. pestis.</td>
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<tr>
<td>Contraindications</td>
<td>Hypersensitivity to streptomycin or other aminoglycosides. Pregnancy.</td>
<td>Hypersensitivity to gentamicin or other aminoglycosides. Pregnancy.</td>
<td>Allergy to ciprofloxacin or other quinolone medicine (e.g., norfloxacin, ofloxacin, nalidixic acid). Concurrent administration with tizanidine.</td>
<td>Hypersensitivity to tetracyclines. Concurrent use of tetracycline and methoxyflurane (methyl ether) may result in fatal renal toxicity.</td>
<td>Contraindicated if another drug can be used instead.</td>
</tr>
<tr>
<td>Precautions</td>
<td>Renal insufficiency. Baseline and periodic caloric stimulation tests and audiometric tests are advisable with extended streptomycin therapy. Co-administration of ethacrynic acid, furosemide, mannitol and possibly other diuretics. Use of drug may allow for overgrowth of nonsusceptible organisms, including fungi.</td>
<td>Renal insufficiency. Use with caution in patients with pre-existing vertigo, tinnitus, or hearing loss; hypocalcemia; neuromuscular disorders; and renal insufficiency. Prolonged use may result in fungal or bacterial superinfection.</td>
<td>Chronic renal or liver disease, myasthenia gravis, history of seizures or stroke, breastfeeding, pregnancy, pyrosis, joint or tendon disease, unusual bleeding or bruising. Avoid direct sunlight and alcohol. Women may be at increased risk for yeast infections. Ciprofloxacin may increase the effects of caffeine and theophylline.</td>
<td>Breastfeeding or pregnant women, liver disease, kidney disease, pyrosis, infants less than 6 months of age. Avoid direct sunlight. If using oral contraceptives, use alternative forms of birth control during and 1 week after taking doxycycline. Women may be at increased risk for yeast infections.</td>
<td>Breastfeeding or pregnant women, liver disease, kidney disease, porphyria.</td>
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<tr>
<td>Special Populations</td>
<td>Pregnancy Risk Factor D: crosses placenta and may cause total irreversible congenital.</td>
<td>Pregnancy Risk Factor D: crosses the placenta and may cause total irreversible bilateral.</td>
<td>Children: Typically, fluoroquinolones are not used in children less than 18 years of age, however,</td>
<td>Children: Doxycycline is not typically used in children less than 9 years of age, however, it is</td>
<td>Pregnant and Nursing Women: may cross placental barrier leading to gray baby syndrome.</td>
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<tr>
<td>Side Effects</td>
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</table>
| Deafness | Pregnancy Women: Readily crosses placental barrier and may cause fetal harm. Nursing Women: excreted in breast milk.  
Infants: CNS depression with stupor, flaccidity and occasionally coma and deep respiratory depression has been observed when dosage has exceeded recommended limits. |
| Congenital deafness | Nursing Women: excreted in breast milk.  
Nursing Women: excreted in breast milk. |
| Risk/benefit comparison | regarding plague infection indicates use. Children under the age of 18 years may experience joint pain. If this occurs, a doctor must be consulted immediately. |
| Indicated if antibiotic susceptibility testing, limited drugs supplies or adverse reactions precludes ciprofloxacin usage. Children less than 8 years of age may experience teeth staining. Premature infants may experience temporary bone growth delay. |
| Neuritis | (Neonates and infants). Excreted in breast milk. Plasma levels of chloramphenicol must be monitored in neonates and in patients with abnormal liver function. It is recommended that plasma levels be monitored in all children under the age of 4, the elderly and patients with renal failure. |

Nephrotoxicity, neuromuscular blockade, respiratory paralysis, and neurotoxicity. Vestibular ototoxicity (nausea, vomiting, vertigo), rash, fever, facial paresthesia, urticaria, angioneurotic edema, and eosinophilia. Less frequent:: cochlear ototoxicity (deafness), exfoliative dermatitis, anaphylaxis, azotemia, leucopenia, amebiasis, thrombocytopenia, pancytopenia, hemolytic anemia, and muscular weakness.  
Nephrotoxicity, neuromuscular blockade, respiratory paralysis, and neurotoxicity. Skin itching and reddening, agranulocytosis allergic reaction, anorexia, burning, drowsiness, dyspnea, enterococcal erythema, edema, granulocytopenia headache, increased LFT, cramps, nausea, photosensitivity, pseudomotor cerebri, increased salivation, thrombocytopenia, tremor, vomiting, weakness, weight loss.  
Nausea, vomiting, diarrhea, fatigue, dizziness, headache, pain in arms or legs, vision changes, restlessness, ringing of ears, mental changes, or photosensitivity/phototoxicity.  
Nausea, vomiting, diarrhea, dark urine, jaundice, sore throat, fever, unusual bleeding or bruising, fatigue, white patches in mouth.  
Nausea, vomiting, diarrhea, glossitis, stomatitis, headache, mental alterations, bone marrow depression, gray baby syndrome, blood dyscrasias (e.g., aplastic anemia, hypoplastic anemia, thrombocytopenia, pancytopenia, and granulocytopenia), optic and peripheral neuritis.
Plague Infection Associated with a Mass Casualty Event Criteria (Table 1 and 2):

• Successful medical management is related to early use of antibiotics and aggressive use of supportive care.

• Optimally, persons diagnosed with pneumonic and bubonic plague should initially receive intravenous antibiotics. However, in a mass casualty setting this may not be feasible and an oral only regiment must be utilized.

• Pregnant women should receive ciprofloxacin in usual adult dosages as part of combination therapy for treatment of pneumonic and bubonic plague.

• Doxycycline should not be used if meningitis is suspected because it does not adequately penetrate the blood brain barrier.

• Antibiotic treatment of bubonic plague is the same as therapy for pneumonic plague. Usually buboes will recede without intervention, but if they become fluctuant or secondarily infected, they may need incision and drainage.

Yersinia Pestis Post-Exposure Prophylaxis (PEP) Criteria (Table 2):

• PEP is not indicated for health care and mortuary workers if they use standard precautions (airborne if indicated).

• Ciprofloxacin and doxycycline should be used as first-line PEP.

• Any potentially exposed persons in the affected community in whom a temperature of 38.5°C or higher or a new cough develops should be evaluated and placed on appropriate parenteral therapy (if available) for presumptive pneumonic plague if PEP was not taken.

• Persons who have close contact with a patient with pneumonic plague who has not received at least 48 hours of appropriate antibiotic therapy should receive antibiotic postexposure prophylaxis. Since transmission occurs through respiratory droplets, close contact is defined as contact at less than 2 meters.

• Persons who develop fever or cough while receiving antibiotic prophylaxis should be evaluated immediately for pneumonic plague and treated appropriately if plague is suspected.

Medical Emergency or Anaphylaxis: Written emergency medical protocols, as well as equipment and medications, must be available at administration site. Anaphylaxis includes rash, difficulty breathing, swollen tongue or throat, itchiness of throat, and collapse.

Dosage Information: See Table 1 for recommended therapy for plague infection and recommended post-exposure prophylaxis in a mass casualty setting (Table 2). Chloramphenicol is only available as an injectable in the United States.

Table 3 and 4 provide simplified pediatric dosing by weight for ciprofloxacin and doxycycline respectively when used for treatment of plague. For more information regarding doxycycline crushing and administration visit: http://www.fda.gov/downloads/Drugs/EmergencyPreparedness/BioterrorismandDrugPreparedness/UCM131006.pdf.
This protocol shall remain in effect for all persons infected or exposed to *Y. pestis* until rescinded.

Approved by:

[Signature]

Chief Medical Executive
Michigan Department of Community Health

[Signature]

Frederick A. Johansen, M.D., M.P.H.
Medical Director

11/8/2011
8-7-12
**Table 1. Recommendations From the Working Group on Civilian Biodefense for Preferred Treatment of *Y. pestis* infection.**

<table>
<thead>
<tr>
<th>Category</th>
<th>Therapy</th>
</tr>
</thead>
</table>
| **Adults** | Preferred choices:  
Streptomycin: 1g IM twice daily  
Gentamicin: 5 mg/kg IM or IV once daily or 2 mg/kg loading dose followed by 1.7 mg/kg IM or IV three times daily  
Alternative choices:  
Doxycycline, 100 mg IV twice daily or 200 mg IV once daily  
Ciprofloxacin, 400 mg IV twice daily  
Chloramphenicol, 25 mg/kg IV 4 times daily |
|          | Duration: 10 days |
| **Children** | Preferred choices:  
Streptomycin: 15 mg/kg IM twice daily (maximum daily dose 2 g)  
Gentamicin: 2.5 mg/kg IM or IV three times daily  
Alternative choices:  
Doxycycline:  
≥45 kg: same as adult  
<45 kg: 2.2 mg/kg IV twice daily (maximum daily dose 200 mg/dl)  
Ciprofloxacin: 15 mg/kg IV twice daily  
Chloramphenicol: 25 mg/kg IV 4 times daily |
|          | Duration: 10 days |
| **Pregnant Women** | Preferred choices:  
Gentamicin: 5 mg/kg IM or IV once daily or 2 mg/kg loading dose followed by 1.7 mg/kg IM or IV three times daily  
Alternative choices:  
Doxycycline, 100 mg IV twice daily or 200 mg IV once daily  
Ciprofloxacin, 400 mg IV twice daily |
|          | Duration: 10 days |

Abbreviations: IM intramuscularly; IV intravenously

* These are consensus recommendations of the Working Group on Civilian Biodefense and are not necessarily approved by the U.S. Food and Drug Administration. See "Therapy" section for explanations. One antimicrobial agent should be selected. Therapy should continue for 10 days. Oral therapy should be substituted when the patient’s condition improves. IM indicates intramuscularly; IV indicates intravenously.
† Aminoglycosides must be adjusted according to renal function. Evidence suggests that gentamicin, 5 mg/kg IM or IV once daily, would be efficacious in children, although this is not yet widely accepted clinical practice. Neonates up to 1 week of age and premature infants should receive gentamicin, 2.5 mg/kg IV twice a day.
‡ Other fluoroquinolones can be substituted at doses appropriate for age. Ciprofloxacin dosage should not exceed 1 g/d in children.
§ Concentration should be maintained between 5 and 20 μg/mL. Concentrations greater than 25 μg/mL can cause reversible bone marrow suppression.
|| In children, ciprofloxacin dose should not exceed 1g/d, and chloramphenicol should not exceed 4g/d.
# Duration of treatment of plague in mass casualty setting is 10 days. Duration of postexposure prophylaxis to prevent plague infection is 7 days.
** Tetracycline could be substituted for doxycycline.
†† Children younger than 2 years should not receive chloramphenicol. Oral formulation available only outside the U.S.

Table 2. Recommendations From the Working Group on Civilian Biodefense for Treatment of Plague in the Mass Casualty Setting and for Post-Exposure Prophylaxis to Y. pestis.

<table>
<thead>
<tr>
<th>Category</th>
<th>Preferred Oral Therapy</th>
<th>Alternative Oral Therapy</th>
<th>Duration</th>
</tr>
</thead>
</table>
| Adults   | Doxycycline: 100 mg PO twice daily\(^b\)  
            or  
            Ciprofloxacin: 500 mg PO twice daily\(^c,d\) | Chloramphenicol: 25 mg/kg PO  
            4 times daily\(^e\) | PEP: 7 days  
            or  
            Treatment: 10 days |
| Children | Doxycycline:  
            ≥45 kg: same as adult  
            <45 kg: 2.2 mg/kg PO twice daily\(^b\)  
            or  
            Ciprofloxacin: 20 mg/kg PO twice daily  
            (maximum daily dose, 1 g)\(^d\) | Chloramphenicol: 25 mg/kg PO  
            4 times daily  
            (maximum daily dose, 4 g)\(^f,g\) | PEP: 7 days  
            or  
            Treatment: 10 days |

Abbreviation: PO, orally.

\(^a\)Recommendations were reached by consensus of the Working Group on Civilian Biodefense and may not necessarily be approved by the Food and Drug Administration. Although these recommendations are intended for postexposure prophylaxis, they also can be used for treatment of plague cases in the mass-casualty setting where the number of patients is too great for all patients to receive intravenous antibiotics and oral antibiotics must be substituted (except that treatment should be continued for 10 days instead of 7 days as for prophylaxis).

\(^b\)Tetracycline can be substituted for doxycycline at a dose of 10-25 mg/kg/day divided into 2-4 doses.

\(^c\)Acceptable for pregnant women. Although fetal toxicity may occur with doxycycline use and toxic effects on the liver in pregnancy have been noted with the tetracycline class, the working group recommended doxycycline or ciprofloxacin for postexposure prophylaxis of pregnant women or for treatment of infection in the mass-casualty setting.

\(^d\)Other fluoroquinolones may be substituted at dosages appropriate for age.

\(^e\)Trimethoprim-sulfamethoxazole (40 mg sulf/kg/day administered orally in 2 divided doses for 7 days) has been recommended for postexposure prophylaxis in children younger than 8 years old and pregnant women.

\(^f\)Concentration should be maintained between 5 and 20 mcg/mL; concentrations >25 mcg/mL can cause reversible bone marrow suppression. The oral formulation is available only outside the United States.

\(^g\)According to the working group, children younger than 2 years of age should not receive chloramphenicol.
# Table 3: Ciprofloxacin - Pediatric Dosing by Weight for Plague Infection*

<table>
<thead>
<tr>
<th>Weight</th>
<th>Dose (mg)</th>
<th>Suspension</th>
<th>500 mg Tablet Crushed &amp; Mixed 100mg/teaspoon</th>
</tr>
</thead>
<tbody>
<tr>
<td>7-12 lbs/3-5 kg</td>
<td>50 mg PO BID</td>
<td>1 ml twice daily</td>
<td>Use susp.</td>
</tr>
<tr>
<td>13-22 lbs/6-10 kg</td>
<td>100 mg PO BID</td>
<td>2 ml twice daily</td>
<td>Use susp.</td>
</tr>
<tr>
<td>18-28 lbs/8-13 kg</td>
<td>125 mg PO BID</td>
<td>2.5 ml twice daily</td>
<td>1 ¼ teaspoons twice daily</td>
</tr>
<tr>
<td>22-33 lbs/10-15 kg</td>
<td>150 mg PO BID</td>
<td>3 ml twice daily</td>
<td>1 ½ teaspoons twice daily</td>
</tr>
<tr>
<td>29-44 lbs/13-20 kg</td>
<td>200 mg PO BID</td>
<td>4 ml twice daily</td>
<td>2 teaspoons twice daily</td>
</tr>
<tr>
<td>36-56 lbs/16-25 kg</td>
<td>250 mg PO BID</td>
<td>5 ml twice daily</td>
<td>2 ½ teaspoons twice daily</td>
</tr>
<tr>
<td>55-83 lbs/25-37 kg</td>
<td>375 mg PO BID</td>
<td>7.5 ml twice daily</td>
<td>3 ¾ teaspoons twice daily</td>
</tr>
<tr>
<td>≥ 73 lbs/≥ 33 kg</td>
<td>500 mg PO BID</td>
<td>10 ml twice daily</td>
<td>5 teaspoons twice daily</td>
</tr>
</tbody>
</table>

*This chart purposefully reflects more than one dose for a particular weight to permit flexibility in dosing based on the products that are available at the time of dispensing. These doses are within the recommended dosing range of ciprofloxacin 10-15 mg/kg.

# Table 4: Doxycycline - Pediatric Dosing by Weight for Plague Infection**

<table>
<thead>
<tr>
<th>Weight</th>
<th>Dose (mg)</th>
<th>Suspension</th>
<th>100 mg Tablet Crushed &amp; Mixed 25mg/teaspoon</th>
</tr>
</thead>
<tbody>
<tr>
<td>Below 12.5 lbs</td>
<td>12.5 mg twice daily</td>
<td>2.5 ml (1/2 teaspoon twice day)</td>
<td>½ teaspoon mixture twice day</td>
</tr>
<tr>
<td>12.5 – 25 lbs (6-12 kg)</td>
<td>25 mg twice daily</td>
<td>5 ml (1 teaspoon) 2x day</td>
<td>1 teaspoon mixture 2x day</td>
</tr>
<tr>
<td>25 – 50 lbs (12 – 24 kg)</td>
<td>37.5 mg twice daily</td>
<td>7.5 ml (1 ½ teaspoons) 2x day</td>
<td>1½ teaspoon mixture 2x day</td>
</tr>
<tr>
<td>50 – 75 lbs (24 – 36 kg)</td>
<td>50 mg twice daily</td>
<td>10 ml (2 teaspoons) 2x day</td>
<td>2 teaspoons mixture 2x day</td>
</tr>
<tr>
<td>75 – 99 lbs (36 – 45 kg)</td>
<td>75 mg twice daily</td>
<td>15 ml (3 teaspoons) 2x day</td>
<td>3 teaspoons mixture 2x day</td>
</tr>
</tbody>
</table>

**Above 99 lbs (45kg) or >8 years of age (if weight unavailable) use standard adult dosing of 100 mg twice daily.