PLAGUE PROPHYLAXIS (BIOTERRORISM)

I. DEFINITION:

Plague is caused by *Yersinia pestis*, a gram-negative bacillus. The bacteria maintain their existence in a cycle involving rodents and the fleas that live on them. Plague is a zoonotic disease of rodents that is transmitted to humans and other mammals from the bite of an infected rodent flea. Percutaneous inoculation of the bacteria in humans initiates inflammation of the lymph nodes that drain at the site of the flea bite resulting in bubonic plague, the most common clinical presentation among naturally acquired infections. Symptoms of the disease may be non-specific with sudden onset of fever, chills, malaise, myalgia, nausea, prostration, sore throat and headache. If the bacteria invade the bloodstream, this may lead to septicemic plague or to infection of other organ systems, such as the lungs (pneumonic plague) or meninges (plague meningitis). The clinical presentation is dependent upon how the patient was exposed to the plague bacteria.

II. EPIDEMIOLOGY:

A. The oriental rat flea (*Xenopsylla cheopis*) is the insect vector that has been implicated in the largest number of cases of human bubonic plague around the world. However, it is associated only with urban outbreaks, which no longer occur in the U.S. The last urban plague epidemic in the U.S. occurred in Los Angeles from 1924 – 1925. Plague spread from urban rats to rural rodent species, and became endemic in many areas of the western U.S.

B. Over 80% of U.S. plague cases have been the bubonic form. In recent decades, an average of seven human plague cases have been reported each year in the U.S. (range: 1 – 17 cases per year). Most cases in the U.S. occur in two regions: 1) Northern New Mexico, northern Arizona, and southern Colorado and 2) California, southern Oregon, and far western Nevada. A variety of wild rodents (ground squirrels, prairie dogs, marmots) and their fleas are associated with an enzootic transmission cycle in these areas. Domestic cats are also quite susceptible to plague and infected cats have been the source of infection with pneumonic plague to animal owners and veterinarians. Dogs and cats may also bring plague-infected fleas into the home.

C. Man is an accidental host in the plague cycle and is not necessary for the persistence of the organism in nature. Humans usually acquire plague from:

1. Flea bites: Plague bacteria are most often transmitted by the bite of an infected flea whose usual host is another mammal. These fleas may be seeking another blood source after their host dies, or they may be brought into the home by domestic cats and dogs. This type of exposure may result in primary bubonic plague or septicemic plague.

2. Contact with contaminated animal fluid or tissue: Humans can become infected when handling tissue or body fluids of a plague-infected animal. This form of exposure most commonly results in bubonic plague or septicemic plague.

3. Infectious droplets: When a person has plague pneumonia, they may cough respiratory droplets containing the bacteria into the air. If these bacteria-containing droplets are breathed in by another person, they can cause pneumonic plague. Typically this requires direct or close contact with the ill person. Transmission of these droplets is the only way that plague can spread person-to-person. Cats infected with plague also pose a risk of transmitting bacteria-containing droplets to their owners and veterinarians.
III. CLINICAL FORMS:

A. Bubonic Plague – Bubonic plague is characterized by abrupt onset of high fever, shaking chills, prostration or severe malaise, headache, nausea, vomiting, and painful swollen regional lymph nodes (i.e. a bubo). Buboes manifest after 2 to 8 eight days incubation period and may suppurate. If the patient is not treated with appropriate antibiotics, the bacteria can spread to other parts of the body.

B. Septicemic Plague—Septicemic plague may occur primarily, or secondarily from hematogenous dissemination. Symptoms of septicemic plague are fever, chills, extreme weakness, abdominal pain, nausea, vomiting, diarrhea; later hypotension, acute respiratory distress, endotoxic shock, purpuric skin lesions, disseminated intravascular coagulation (DIC), acrocyanosis and necrosis, and organ failure.

C. Pneumonic Plague—Pneumonic plague may occur primarily from inhalation of aerosols, or secondarily from hematogenous dissemination. It is the most severe and fatal form of plague. Symptoms of pneumonic plague are sudden onset of chills, fever, headache, weakness, body pains, rapidly developing pneumonia with shortness of breath, chest pain, cough, and hemoptysis. Patients typically have blood tinged sputum within 24 hours after onset of symptoms, which progresses to copious hemoptysis. The most common x-ray findings are bilateral alveolar infiltrates. The pneumonia may cause respiratory failure and shock. The incubation period for pneumonic plague is less than one day to up to four days and is usually short. Untreated pneumonic plague is almost always fatal, and mortality is very high in persons whose treatment is delayed beyond 18 to 24 hours after symptom onset.

D. Plague Meningitis—Plague meningitis may be a primary manifestation, but it usually occurs a week or more after onset of bubonic or septicemic plague. It is often associated with delayed, inappropriate, or bacteriostatic antibiotic therapy. It is also more common in patients with axillary buboes. Symptoms are similar to other forms of bacterial meningitis such as: fever, headache, stiff neck, sensorial changes, and meningismus.

IV. LABORATORY TESTING:

A. Isolation of Y. pestis from a clinical specimen

B. Fourfold or greater change in serum antibody titer to Y. pestis F1 antigen.

V. PLAGUE AS A BIOLOGICAL TERRORISM AGENT:

A. Advances in living conditions, public health, and antibiotic therapy make future naturally occurring pandemics improbable. However, plague outbreaks following use of a biological weapon are a plausible threat. In 1970, the World Health Organization reported that, in the worst case scenario, if 50 kg of Y. pestis were released as an aerosol on a city of 5 million, pneumonic plague could infect up to 150,000 persons, 36,000 of whom would be expected to die.

B. Though naturally occurring plague most commonly presents as bubonic plague, purposeful aerosol dissemination as a result of bio warfare or a terrorist event would manifest primarily as pneumonic plague.

C. Epidemiology:

1. Human plague most commonly occurs following a bite from a plague–infected flea. Humans then develop bubonic plague. Die-offs of wild rodents, in which rodent fleas lose their hosts and seek new ones, may precede human cases, but rodent die-offs are not a necessary precursor to human infections.
2. Neither bubonic nor septicemic plague spreads directly person to person.

3. The epidemiology of plague caused by a bioterrorist event would differ from the naturally occurring disease. Intentional dissemination of plague would most likely occur via an aerosol of *Y. pestis*, a mechanism that has been shown to produce disease in non-human primates. A pneumonic plague outbreak would result with symptoms initially resembling those of other severe respiratory illnesses.

4. Symptoms would begin to occur within 1 – 6 days (most often 2 – 4 days) following exposure, and people would die quickly following onset of symptoms. Possible clues that plague has been artificially disseminated include:
   a. The sudden occurrence of a large number of previously healthy persons with fever, cough, shortness of breath, and chest pain. The presence of hemoptysis in this situation would also strongly suggest plague.
   b. Disease in persons without known risk factors for acute pneumonia.
   c. Many patients with an unusually severe respiratory course and high mortality.

5. Clinical Features
   a. Signs and Symptoms
      1) Subjective:
         a) Incubation period 1 – 6 days (most often 2 – 4 days)
         b) Fever
         c) Cough
         d) Dyspnea
         e) Bloody, watery, or purulent sputum
         f) Chest pain
         g) Nausea
         h) Vomiting
         i) Abdominal pain
         j) Diarrhea
      2) Objective:
         a) Chest x-ray, bilateral infiltrates and consolidation
         b) Leukocytosis with toxic granulations
         c) Coagulation abnormalities
         d) Aminotransferase elevations
         e) Azotemia
         f) Other evidence of multi-organ failure
         g) Absence of buboes (except rarely, cervical buboes)
   b. Complications:
      1) Adverse drug reactions
      2) Disseminated Intra-vascular Coagulation (DIC)
      3) Acute respiratory distress syndrome (ARDS)
      4) Shock
      5) Multi-organ failure
      6) Death
VI. MANAGEMENT PLAN:

A. Laboratory Studies
   1. Whole blood for culture or gram stain.
   2. Sputum for culture or gram stain.
   3. Serum for acute and/or convalescent titer.

B. Treatment of Pneumonic Plague
   1. Plague pneumonia is often fatal if treatment is not initiated within 18 – 24 hours of symptom onset.
   2. Physicians may be asked to obtain informed consent for administration of certain medications supplied by the Strategic National Stockpile (SNS).

C. Post-Exposure Prophylaxis (PEP)
   1. Post-exposure prophylaxis is indicated in persons with known exposure to aerosolized Y. pestis or those in close contact with a confirmed pneumonic plague patient.
      a) Close contact with a case patient is defined as less than 2 meters (6 ft.) away from the case during a period when a case was symptomatic (coughing) and before the case had completed at least 48 hours of prescribed antibiotic therapy.
      b) Household contacts, healthcare worker contacts, and anyone who had direct contact with infected body fluids or tissues of the case should be considered exposed and should receive PEP.
   2. All antibiotic therapy should continue for 7 days after the last exposure to the case.

<table>
<thead>
<tr>
<th>Category</th>
<th>Primary Druga</th>
<th>Alternate Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults</td>
<td>Doxycycline 100 mg orally twice daily for 7 days</td>
<td>Ciprofloxacin 500 mg orally twice daily for 7 days</td>
</tr>
<tr>
<td>Children</td>
<td>Doxycycline &gt;8yrs. and weighs ≥ 45kg (99lb.): 100mg orally twice daily for 7 days. (same as adult dose) &lt;8 yrs, and weighs &lt;45 kg (99lb.): 2.2mg/kg orally twice daily for 7 days.</td>
<td>Ciprofloxacin* &gt;25kg (55lb.): 500mg orally twice daily for 7 days (Not to exceed 1gm daily) &lt;25kg (55lb.): Give 20mg/kg orally twice daily</td>
</tr>
<tr>
<td>Pregnant women</td>
<td>Ciprofloxacin 500 mg orally twice daily for 7 days</td>
<td>Refer to Physician or APRN</td>
</tr>
</tbody>
</table>

*a) The State Health Officer or designee will determine which medication will be primary based on supply issues
3. Follow the attached algorithm to determine which antibiotic to issue.

4. During mass antibiotic prophylaxis clinics, when possible, all family members should receive the same medications. For example, if one family member is allergic to Doxycycline, but all family members can take Ciprofloxacin, then all family members would receive Ciprofloxacin, the secondary drug of choice. It is important to note that this might not be possible with a family with multiple drug allergies and issues.

5. Persons receiving PEP should be monitored for fever and cough. Also persons refusing PEP should be closely monitored for fever or cough for the first 7 days after exposure and should receive treatment immediately if either occurs.

6. Special measures should be taken for PEP of those unaware of the outbreak or those requiring special assistance, such as persons who are homeless or who have cognitive disorders.

D. Infection Control:

1. The use of disposable surgical masks is recommended to prevent transmission via respiratory droplets.

2. Other respiratory droplet precautions (gown, gloves, and eye protection) should also be used by persons caring for pneumonic plague cases.

3. Patients with pneumonic plague should be isolated and unnecessary close contact should be avoided until the patient has had at least 48 hours of antibiotic therapy and shown clinical improvement.

4. If large numbers of patients make isolation impractical, pneumonic plague patients may be cohorted. Patients should wear surgical masks while they are being transported.

5. Bodies of patients who have died should be handled with routine strict precautions. Aerosol-generating procedures (bone-sawing associated with surgery or post-mortem examinations) should be avoided.

E. Contamination of personnel

1. Remove outer clothing where exposure occurred and place in a labeled, plastic bag for later incineration or steam sterilization.

2. Remove rest of clothing in the locker room and place in a labeled, plastic bag for later incineration or steam sterilization.

3. Shower thoroughly with soap and water.

F. If exposure to contaminated sharps occurs:

1. Follow standard reporting procedures for sharps exposures.

2. Notify the Oklahoma State Department of Health Acute Disease Service at (405) 271-4060.

3. Bubonic or septicemic plague would be the risk associated with a sharps exposure.
G. Decontamination of environment:

1. There is no evidence to suggest that environmental decontamination following an aerosol release is warranted. *Y. pestis* is very sensitive to sunlight and heating and does not survive long outside its host. According to a WHO analysis, a plague aerosol would be viable for 1 hour after release, long before the first cases would alert medical personnel and public health officials. If concerned about environmental contamination, a solution of 0.5% hypochlorite (a 1:10 dilution of household bleach) could be used for surfaces.

2. Cremation should be considered because of potential risk associated with embalming.

H. Plague Vaccine: A plague vaccine is no longer manufactured or available in the United States.

REFERENCES:


Sidell FR, Takafuji ET, Franz DR. 1997, Medical Aspects of Chemical and Biological Warfare: Chapter 23 Plague, Office of The Surgeon General, Washington, DC.


# MEDICATION INTERACTION TABLE FOR CLIENT USE

<table>
<thead>
<tr>
<th>HEALTH HISTORY OR CURRENT MEDICATION</th>
<th>INTERACTION</th>
<th>RECOMMENDATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>SEIZURE DISORDER</td>
<td>Ciprofloxacin (CIPRO) may increase number of seizures or duration of seizures</td>
<td>Use Doxycycline if available or check with your private provider</td>
</tr>
<tr>
<td>KIDNEY DISEASE</td>
<td>Ciprofloxacin (CIPRO) or Doxycycline (DOXY) - You may experience increased levels of this antibiotic in your system</td>
<td>It is recommended that you see your private provider for further evaluation to adjust the dosage by creatinine clearance levels</td>
</tr>
<tr>
<td>MYASTHENIA GRAVIS</td>
<td>Ciprofloxacin (CIPRO) may increase muscle weakness and cause serious adverse events in people with this condition.</td>
<td>It is recommended that you take Doxycycline if available but may talk with your private provider about taking the other.</td>
</tr>
<tr>
<td>COUMADIN – If you take this or other blood thinner</td>
<td>Ciprofloxacin (CIPRO) or Doxycycline (DOXY) may increase the effects of the medication by increasing bleeding time</td>
<td>See private provider in 3-5 days for further evaluation and PT/INR lab levels for recommendation of adjustment of dose</td>
</tr>
<tr>
<td>PROBENECID – If you take this medication</td>
<td>Ciprofloxacin (CIPRO) or Doxycycline (DOXY) may increase the effects of the medication</td>
<td>You may need to stop taking this medication while taking the antibiotic. It is recommended you see your private provider for further evaluation</td>
</tr>
<tr>
<td>THEOPHYLLINE – If you take this medication</td>
<td>Ciprofloxacin (CIPRO) – Increases the level of Theophylline in your system</td>
<td>It is recommended that you reduce the Theophylline dose by ½ and contact your private provider within 3-5 days for further evaluation</td>
</tr>
<tr>
<td>DILANTIN – If you take this medication</td>
<td>Ciprofloxacin (CIPRO) – May alter your Dilantin levels</td>
<td>It is recommended that you take Doxycycline if available. It is also recommended that you contact your private provider.</td>
</tr>
<tr>
<td>CYCLOSPORINE – If you take this medication</td>
<td>Ciprofloxacin (CIPRO) May increase blood creatinine levels</td>
<td>It is recommended that you contact your private provider to see if a blood creatinine and drug level is necessary.</td>
</tr>
<tr>
<td>ROPINIROLE – If you take this medication</td>
<td>Ciprofloxacin (CIPRO) may cause a Ropinirole toxicity (a toxic build up of the medication)</td>
<td>It is recommended you contact your private provider for further follow up of any dosage adjustments</td>
</tr>
<tr>
<td>ORAL CONTRACEPTIVES – If you take this medication</td>
<td>Ciprofloxacin (CIPRO) and Doxycycline (DOXY) may lessen the effectiveness of your birth control pills</td>
<td>It is recommended that you use additional methods of birth control while taking these antibiotics</td>
</tr>
<tr>
<td>ISOTRETINOIN – If you take this medication</td>
<td>Doxycycline (DOXY) – There is a slight increased risk of developing a condition that causes neurological symptoms</td>
<td>It is recommended that you report increased and persistent headaches, vomiting, or blurred vision to your private physician</td>
</tr>
<tr>
<td>GLYBURIDE – If you take this medication or if you are a diabetic</td>
<td>Ciprofloxacin (CIPRO) may decrease your blood sugar levels</td>
<td>It is recommended that you increase the monitoring of blood sugar levels and report this to your local provider if necessary</td>
</tr>
</tbody>
</table>
This Page Intentionally Left Blank
Plague Post-Exposure Mass Antibiotic Prophylaxis Issuing Algorithm
Ciprofloxacin as primary drug

START

Quinolone Allergy

YES

Pregnant or Breastfeeding

NO

Tetracycline Allergy

YES

Refer to APRN or Physician

NO

Kidney Problems

YES

Refer to APRN or Physician

NO

<25kg (55lb.)

NO

YES

Ciprofloxacin 500 mg PO q 12 hours for 7 days.

NO

NO

≥8 years of age and ≥45kg (99lb)

YES

NO

≥25kg (55lb.)

YES

Give 20mg/kg Ciprofloxacin PO q 12 hours for 7 days.

Do NOT Exceed 500mg dose or Maximum Daily Dose 1g

Refer to child dosing sheets if available

Review Medication Table to identify possible contraindications

Ciprofloxacin 500 mg PO q 12 hours for 7 days.

Doxycycline 100mg PO q 12 hours for 7 days

Give 2.2 mg/kg Doxycycline PO q 12 hours for 7 days

Do NOT exceed 100mg dose or 200mg daily

Refer to child dosing sheets if available

Tetracyclines
Declomycin; Adoxa; Bio-Tab; Doryx; Doxy; Monodox; Periostat; Vibra-Tab; Vibramycin; Araretin; Dynacin; Minocin; Vectrin; Terak; Terra-Cotril; Terramycin; Urobactro-250; Achromycin V; Sumycin; Topicycline; Helidac

Allergic reactions may include: Hives, redness of the skin, rash, difficulty breathing or worsening of lupus.

Quinolones
Eradacil; Cimobac; Cipro; Ciloxan; Tequin; Zaxar; Levaxin; Quibin; Maxaquin; Avelox; ABC Pal; Acuqistm; Chibrocin; Noroxin; NegGram; Floxin; Ocuflox; oxolinic acid; Perflacine; rufloxacin; Zagan; Respipac; tamoxacin; Trovan

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 or eosinophilia.
Plague Post-Exposure Mass Antibiotic Prophylaxis Issuing Algorithm
Doxycycline as primary drug

START

Pregnant or Breastfeeding

YES

Quinolone Allergy

NO

Tetracycline Allergy

YES

Refer to APRN or Physician

NO

Review Medication Table to identify possible contraindications

YES

Tetracyclines
Declomycin; Adox; Bio-Tab; Doryx; Doxy; Monodox; PerioStat; Vibra-Tabs; Vibramycin; Arespin; Dynacin; Minocin; Vectrin; Terak; Terra-Cotril; Terramycin; Urobloc-t-250; Achromycin V; Sumycin; Topicycline; Helidac

Allergic reactions may include: Hives, redness of the skin, rash, difficulty breathing or worsening of lupus.

NO

≥8 years of age and ≥45kg

YES

Give 2.2 mg/kg Doxycycline 100mg PO q 12 hours for 7 days

NO

Give 20mg/kg Ciprofloxacin PO q 12 hours for 7 days.

Do NOT exceed Maximum Dose of 500mg or 1g Daily

Refer to child dosing sheets if available

Kidney Problems

NO

<25kg (55lb.)

YES

Ciprofloxacin 500 mg PO q 12 hours for 7 days.

Quinolones
Eradacil; Clnobac; Cipro; Ciloxan; Tequin; Rasar; Levaquin; Quin; Maxaquin; Avelox; ABC Pak; Acutab; Chibrocin; Noroxin; NegGram; Floxin; Ocuflox; oxaline acid; Perflacin; rufloxacin; Zagan; Respipac; tamafloxacil; Trovan

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 or eosinophilia.