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 - 8 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) Fever
         b) Cough
         c) Dyspnea
         d) Bloody, watery, or purulent sputum
         e) Chest pain
         f) Nausea
         g) Vomiting
         h) Abdominal pain
         i) 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 to 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 Drug*</th>
<th>Alternate Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults</td>
<td>Doxycycline</td>
<td>Ciprofloxacin 500 mg orally twice daily for 7 days</td>
</tr>
<tr>
<td></td>
<td>100 mg orally twice daily for 7 days</td>
<td></td>
</tr>
<tr>
<td>Children</td>
<td>Doxycycline</td>
<td>Ciprofloxacin*</td>
</tr>
<tr>
<td></td>
<td>&gt;8yrs, and weighs ≥ 45kg (99lb.): 100mg orally twice daily for 7 days. (same as adult dose)</td>
<td>&gt;25kg (55lb.): 500mg orally twice daily for 7 days (Not to exceed 1gm daily)</td>
</tr>
<tr>
<td></td>
<td>&gt;8 yrs, and weighs &lt;45 kg (99lb): 2.2mg/kg orally twice daily for 7 days</td>
<td>&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>

*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.


Plague Prophylaxis, CDC website: https://www.cdc.gov/plague/healthcare/clinicians.html
<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 buildup 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>
Plague Post Exposure Prophylaxis Screening Questionnaire and Algorithm

Doxycycline Dominant Dispensing Algorithm

Evaluate for Doxycycline

- Is this person allergic to Doxycycline, Tetracycline, or any other “cycline” drugs?
- Is this person Pregnant?

All “no”

- Does this person have difficulty swallowing pills?
- Is this person both <76 lbs. & < 18 years of age?

All “no”

Dispense Doxycycline & FDA approved Doxycycline fact sheet

Evaluate for Ciprofloxacin*

- Is this person allergic Ciprofloxacin, Levoquin or any other “floxacin” drug?
- Does this person have seizure disorder or epilepsy?
- Is this person currently taking Tizanidine (Zanaflex)?
- Is this person both <76 lbs. & < 18 years of age?
- Does this person have difficulty swallowing pills?

“Yes” to any

“Yes” to any

Dispense Ciprofloxacin & FDA approved Ciprofloxacin fact sheet

Refer to clinician

Dispense Doxycycline & FDA approved Doxycycline fact sheet and include the following:
- Oral syringe
- FDA Pamphlet on preparing doxycycline for children and adults who cannot swallow pills.

*Ciprofloxacin is not FDA approved for treatment or post-exposure prophylaxis of plague. Dispense Assist algorithm is based from the consensus recommendations of the Working Group on Civilian Biodefense. Local public health agencies should not dispense medications that have not been issued a EUA from the FDA.
Plague Doxycycline Fact Sheet

What is doxycycline?
Doxycycline belongs to a class of drugs called tetracycline antibiotics. It is approved by the Food and Drug Administration (FDA) to treat and protect people who have been exposed to plague bacteria. Doxycycline is usually prescribe as a 100 mg oral tablet or as an oral suspension for children.

How to take doxycycline?
**Adults:** Take 1 tablet every 12 hours as directed. Each person should take all the pills in their bottle.
**Children:** A child’s dose depends on body weight. Give the medication to your child as directed on additional dosing documentation.

Take doxycycline with food and at least one full glass of water. Avoid taking antacids (like Tums or Maalox), cholestyramine (Questran), colestipol (Colestid), dairy products (like milk or yogurt) or vitamins 3 hours before or after taking doxycycline.

**Doxycycline dosing in a Plague Attack:**
A 7 day course will be provided to all individuals who may have been exposed to plague.

**What to do if you miss a dose?**
If you miss a dose, start taking one tablet every 12 hours. Do not take 2 pills to make up for the missed dose. Finish all your pills, even if you feel okay, unless your doctor tells you to stop. If you stop taking the medicine too soon, you may become ill.

**Side effects of doxycycline?**
Common side effects of doxycycline include an upset stomach, vomiting, or diarrhea. If you have problems with any of these symptoms, tell your doctor. Less common side effects include dark urine, yellowing of the eyes or skin, sore throat, fever, unusual bleeding or bruising, fatigue, white patches in the mouth. If any of these symptoms occur, call your doctor right away. **Severe allergic reactions are very rare.** Signs of an allergic reaction include rash, itching, swelling of the tongue, hands or feet, fever, or trouble breathing. If any of these symptoms occur, call your doctor right away.

**Special note for children:** This medicine may cause staining of the teeth in children younger than 8 years old. This means that their teeth can become grayish in color and this color does not go away. This medicine can also cause bone growth delay in premature in facts but this side effect goes away after the medicine is finished.

**Special note for pregnant women:** There is little data about side effects from the use of this drug during pregnancy. If a mother of an unborn baby takes doxycycline, staining of baby teeth or poor bone development can result. There is a remote chance of severe liver damage in some pregnant women.

**Precautions:**
- Be sure to tell the doctor if you are allergic to any medicine
- It is very important to tell your doctor about ALL of the medicine you are currently taking even pills that were bought at the store such as vitamins and antacids.
- Doxycycline can make skin very sensitive to the sun which increases the chance of getting severe sunburn. Avoid sun as much as possible. When outside, wear long sleeve shirt and hat and always apply sunscreen (30 SPF).
- Birth control pills may not work as well when taking this medication. Be sure to use condoms or another form of birth control until you are finished with the entire course of treatment. If you are pregnant or breastfeeding, tell your doctor.
- In women, doxycycline can cause vaginal itching and discharge known as a yeast infection. Tell your doctor if this occurs.
- Tell the doctor if you have ever had problems with you liver or kidneys, or if you have frequent heartburn.

**Resources:**
Plague Ciprofloxacin Fact Sheet

What is ciprofloxacin?
Ciprofloxacin, commonly known as cipro, belongs to a class of drugs called quinolone antibiotics. It has been approved by the Food and Drug Administration (FDA) to treat and protect people who have been exposed to plague bacteria. Ciprofloxacin is usually provided in a 500-mg oral tablet or as an oral suspension for children.

How to take cipro?
Adults: Take 1 tablet every 12 hours as directed. Each person should take all the pills in their bottle.
Children: A child’s dose depends on body weight. Give the medication to your child as directed on additional dosing documentation. It is best to take cipro 2 hours before or after a meal with at least one large glass of water. However, if an upset stomach occurs, cipro maybe taken with food. Avoid dairy products such as milk and yogurt for at least 3 hours before and after taking the medicine. If you take vitamins or antacids such as Tums or Maalox, take them 6 hours before or 2 hours after taking cipro.

Cipro dosing in a Plague Attack:
A 7 day course will be provided to all individuals who may have been exposed to plague.
What to do if you miss a dose?
If you miss a dose, start taking one tablet every 12 hours. Do not take 2 pills to make up for the missed dose. Finish all your pills, even if you feel okay, unless your doctor tells you to stop. If you stop taking the medicine too soon, you may become ill. Side effects of cipro? Common side effects of cipro include an upset stomach, vomiting, diarrhea, fatigue, dizziness or headache. If you have problems with any of these symptoms, tell your doctor. Less common side effects include pain or tingling in arms and/or legs, change in vision, restlessness, ringing in ears, tendonitis, tendon rupture, or mental changes. If any of these symptoms occur, call your doctor right away. Severe allergic reactions are very rare. Signs of an allergic reaction include, rash, itching, swelling of the tongue, hands or feet, fever, or trouble breathing. If any of these symptoms occur, call your doctor right away.
Special note for children: This medicine may cause joint problems in infants and children under 18 years of age. If your child has any joint pain while he/she is taking cipro, tell your doctor.

Precautions:
- Be sure to tell the doctor if you are allergic to any medicine. It is very important to tell your doctor about ALL of the medicine you are currently taking even pills that were bought at the store such as vitamins and antacids.
- Tell the doctor if you have ever had a seizure, stroke, or problems with your kidneys, joints or tendons, liver, or vision. Report any history of unusual bleeding or bruising.
- If this drug makes you dizzy, use caution driving or doing tasks that require you to be alert. Avoid alcohol in this case as it will make the dizziness worse.
- Cipro can make skin very sensitive to the sun which increases the chance of getting severe sunburn. Avoid sun as much as possible. When outside, wear long sleeve shirt and hat and always apply sunscreen (30 SPF).
- In women, Cipro can cause vaginal itching and discharge known as a yeast infection. Tell your doctor if this occurs.
- If you are pregnant or breast feeding tell your doctor. As safety of cipro during pregnancy is unknown. If you are pregnant or become pregnant, tell your doctor.
- Cipro can increase the effects of caffeine and theophylline (a medicine).

Reference