NAPA COUNTY
PUBLIC HEALTH DIVISION

Medical Treatment and Response to Suspected Plague: Information for Health Care Providers During Biologic Emergencies

August 2005

ALL SUSPECTED, LAB CONFIRMED AND CLINICAL DIAGNOSIS OF PLAGUE MUST BE REPORTED IMMEDIATELY BY TELEPHONE TO THE NAPA COUNTY PUBLIC HEALTH DIVISION, COMMUNICABLE DISEASE UNIT

Contact Information:

During Business Hours: (707) 299 -1499

After Hours (Napa County Answering Service: ask to page the on-call Communicable Disease Duty Officer): (707) 265 -3131

I. Key Summary Points

Epidemiology:

- Highly infectious after aerosolization
- Person-to-person and animal-to-human transmission can occur with pneumonic plague via respiratory droplet

Clinical:

- Incubation period is 1-3 days (ranges up to 7 days)
- Aerosolization would most likely result in pneumonic plague
- Pneumonic plague presents with acute onset of high fevers, chills, headache, malaise and a productive cough, that is initially watery before becoming bloody

Laboratory Diagnosis:

- Bacterial cultures (blood, sputum, or lymph node aspirate specimens) should be handled in a Biosafety Level 2 facility
- Wright, Giemsa, or Wayson stain shows gram negative coccobacilli with bipolar “safety-pin” appearance
- Organism grows slowly (48 hrs for observable growth) on standard blood and MacConkey agar
- Immunoflourescent staining for capsule (F1 antigen) is diagnostic

Patient Isolation:

- Strict respiratory isolation with droplet precautions (gown, gloves, and eye protection) until the patient has received at least 48 hours of antibiotic therapy and shows clinical improvement

Treatment:

- Streptomycin (1 g IM bid) or gentamicin (5 mg/kg IM or IV qd) are the preferred antibiotics
- Tetracyclines or flouroquinolones are alternative choices
- Co-trimoxazole is recommended for pregnant women and children between the ages of 2 months and 8 years
- Chloramphenicol should be used for plague meningitis

Prophylaxis:

- Antibiotic prophylaxis is recommended for all persons exposed to the aerosol or persons in close physical contact with a confirmed case
- Tetracyclines or flouroquinolones are recommended for 7 days from last exposure to a case

II. Introduction/Epidemiology

Plague is transmitted by a gram-negative bacillus, *Yersinia pestis*, of the family Enterobacteriaceae. Plague is a zoonosis and can be transmitted by flea vectors from rodents to humans, and by respiratory droplets from animals to humans and humans to humans. Plague has three clinical forms: bubonic, primary septicemic and pneumonic disease. **Primary pneumonic plague would be the most likely presentation in the event of a biological attack.**

Naturally-occurring plague is a disease primarily affecting rodents. Transmission between rodents is via infected fleas. Transmission to humans can occur by respiratory droplets from rodents, from other infected animals/materials to humans or from human to human. In the United States, transmission to humans has been primarily from the bites of fleas from infected rodents. Less frequently, infection is caused by direct contact with body fluids or tissues while handling an infected animal. Currently in the United

States, infected cats are the only source of primary pneumonic plague for humans, since persons who develop secondary plague pneumonia usually receive appropriate isolation and treatment before secondary transmission can occur.

Human plague has been reported most often from the four western states of New Mexico, Arizona, Colorado and California. In the United States, 341 cases of human plague were reported during 1970-1995; the overwhelming majority of cases were bubonic plague.

Since primary pneumonic plague can be transmitted from person to person, patients with compatible clinical symptoms should be placed in respiratory isolation.

III. Significance as a Potential Bioterrorist Agent

- Could be released as an aerosol during a bioterrorist attack
- Has been weaponized by both the United States, former Soviet Union and Japan. Japan purportedly released plague over China during World War II
- Potential for secondary transmission is highest with pneumonic plague
- Aerosolized plague would cause pneumonic disease, with high mortality rates if untreated

IV. Clinical Manifestations

During an act of bioterrorism, release of an aerosol will be the most likely method of dispersal, so that most patients will present with primary pneumonic plague.

A. Primary Pneumonic Plague

Incubation period - Typically 1-3 days (ranges up to 7 days)

Symptoms - Patients exhibit acute and often fulminant onset of high fever, malaise, headache, myalgias and cough with production of sputum that is initially watery, before becoming bloody. Pneumonia rapidly progresses to dyspnea, stridor and cyanosis. Patients may develop respiratory failure, shock and ecchymoses.

B. Primary Septicemic Plague

Incubation period – Typically 1-7 days

Symptoms - Clinically resembles septicemia caused by other gram negative bacteria. Patients are febrile and often have chills, headache, malaise and gastrointestinal disturbances. May progress rapidly to septic shock, consumptive coagulopathy, meningitis and coma. Patients may develop secondary plague pneumonia.

C. Bubonic Plague

Incubation period – Typically 2-7 days

Symptoms - Patients develop fever, headache, chills and swollen, extremely painful lymph nodes (buboes). Nausea, vomiting and diarrhea are common. Swollen nodes typically involve the nodes that drain the site of initial infection. Patients generally do not have overlying skin lesions. Patients may develop secondary septicemic plague or secondary plague pneumonia.

V. Laboratory Diagnosis

Laboratory work with clinical specimens must be done in Biosafety Level 2 facilities. If plague is suspected, please call the Napa County Public Health Division, Communicable Disease Unit IMMEDIATELY (Business hours: (707) 299 - 1499; After hours: (707) 265 -3131) to arrange for submission of specimens to an appropriate reference laboratory for confirmatory testing.

The diagnosis of plague may be suspected based on characteristic findings on microscopic staining of appropriate body fluids and confirmed by immunofluorescent staining for the capsule or bacterial culture. Serology is generally used retrospectively to confirm suspect cases.

- **Staining of Specimens**

  - Appropriate clinical specimens include: blood, bubo aspirates, sputum, CSF (if signs/symptoms of meningitis) and skin scrapings (if a lesion is present)

  - **Gram stain**: Polymorphonuclear leukocytes and bipolar staining, "safety-pin" ovoid, gram-negative cocco-bacilli identified in bubo aspirate, sputum or CSF are highly suggestive of plague

  - **Wayson stain**: *Yersinia pestis* appears as light blue bacilli with dark blue polar bodies on a contrasting pink ground

  - **Immunofluorescent staining of capsule (F1)**: A positive finding is diagnostic. Must use fresh specimens to avoid false negatives. This test is available only at reference laboratories.

- **Bacterial cultures**

  - Blood, bubo aspirates, sputum, CSF and skin scrapings can be cultured.

  - Materials should be inoculated into blood and MacConkey agar plates and infusion broth. It generally takes 2 days to identify visible colonies. Rapid biochemical identification systems may not be reliable for identification due to slower growth rate of *Y. pestis.*

- **Serologic Testing**

  - Several serologic tests are available including a passive hemagglutination test (CDC). A fourfold or greater rise is diagnostic, a single titre of > 1:16 in someone without prior immunization against plague is suggestive. Serology is not useful for rapid diagnosis.

VI. Handling Laboratory Specimens

Laboratory staff handling specimens from persons who are suspected of having plague should follow Biosafety Level 2 precautions. Staff must wear surgical gloves, protective gowns and shoe covers. Laboratory tests should be performed in Biological Safety Level 2 cabinets, and blood cultures should be maintained in a closed system. Every effort should be made to avoid splashing or creating an aerosol and protective eye wear and masks should be worn if work cannot be done in a Biological Safety Level 2 cabinet.

Laboratories working with a large amount of organism or doing studies on antibiotic resistant strains should use Biological Safety Level 3 cabinets. A full-face mask respirator with a HEPA (high efficiency particulate air) filter is an acceptable but cumbersome alternative to masks and protective eye wear.

Accidental spills of potentially contaminated material should be decontaminated immediately by covering liberally with a disinfectant solution (0.1% sodium hypochlorite or sodium hydroxide (0.1N)). All biohazardous waste should be decontaminated by autoclaving. Contaminated equipment or instruments may be decontaminated with a hypochlorite solution, hydrogen peroxide, peracetic acid, 1% glutaraldehyde solution, formaldehyde, ethylene oxide, copper irradiation, or other O.S.H.A. approved solutions, or by autoclaving or boiling for 10 minutes.

VII. Treatment

Supportive care combined with the rapid administration of parenteral antibiotics are the keys to successful management of plague. Plague pneumonia is almost always fatal if antibiotics are not begun within 24 hours of onset of symptoms.

- **Recommended Antibiotics**

  The drug of choice for primary pneumonic plague is **streptomycin** [30 mg /kg/day administered by intramuscular injection every 12 hours (15 mg/kg) for 10 days]. However, since streptomycin may be in short supply, **Gentamicin** [1.7 mg/kg every 8 hours intravenously or intramuscularly for 10 days] and **doxycycline** [200mg intravenous loading dose, followed by 100mg IV every 12 hours for 10-14 days] are alternative agents.

  Chloramphenicol should be used for plague meningitis due to its better CNS penetration [loading dose of 25 mg/kg intravenously followed by 50-75 mg/kg/day divided into four equal doses; continue for 10 days after clinical improvement].

  Antibiotic choice may need to be altered as susceptibility information becomes available.

- **Alternative Antibiotics**

  Ciprofloxacin [400 mg intravenously every 12 hours], **Levofloxacin** [500 mg intravenously every 24 hours], and **Ofloxacin** [400 mg orally every 12 hours] are acceptable alternative agents. The efficacy of quinolones in humans has not been formally evaluated.

  Bactrim [1 double-strength tablet orally every 12 hours or its intravenous equivalent] may also be efficacious based on animal and in vitro studies.

  Much less effective drugs (**do not use** unless all other alternatives are unavailable) include: rifampin, aztreonam, ampicillin, ceftazadime, cefotetan and cefazolin.

- **Supportive therapy** - Supportive care is essential, including intravenous fluids and hemodynamic monitoring.

- **Therapy in pediatric patients**

  First-line agents: **streptomycin** [15 mg/kg intramuscularly every 12 hours] or **gentamicin** [1.7 mg/kg intramuscularly or intravenously every 8 hours].

Alternatively:

If > or = 8 years of age: Doxycycline [100 mg intravenously or orally every 12 hours if > 45 kg; 2.2mg/kg intravenously or orally every 12 hours if < 45 kg],

If < 8 years of age: Co-trimoxazole [4 mg/kg orally or intravenously every 12 hours].

- Newborns up to age 2 months, **ciprofloxacin** 10-20 mg/kg intravenously or orally twice daily, do not exceed 1 gram/day.

- **Therapy in pregnant women** - Avoid streptomycin in pregnancy due to its association with irreversible deafness in children exposed in utero. Gentamicin can be used (1.7 mg/kg every 8 hours). **Bactrim DS (1 tablet twice daily or its I.V. equivalent) is the preferred therapy for pregnant women, except at term, when a fluoroquinolone** (Ciprofloxacin 500 orally or intravenously every 12 hours) **is preferred**. If worsening illness, add a tetracycline agent as the benefits outweigh the risks. (NOTE: Liver function tests should be monitored due to potential hepatotoxicity with tetracycline use during pregnancy.)

VIII. Isolation of Patients

Pneumonic plague can be spread from person-to-person by droplet transmission (coughing, sneezing). All staff should observe **Standard Precautions** when caring for patients with suspected or confirmed plague. Patients with **pneumonic plague** should be placed on **strict respiratory isolation with Droplet Precautions until 48 hours of appropriate antibiotics** have been administered AND the patient is showing clinical improvement. Droplet precautions require that the patient be placed in a private room and that persons entering the patient room wear a surgical mask, especially when within three feet of the patient. *Negative pressure rooms are not indicated*. Transmission can occur from plague skin lesions (such as draining buboes or abscesses) to contacts; wound and skin precautions should be followed if skin lesions are present.

Multiple patients with pneumonic plague may be cohorted as long as all patients are receiving appropriate therapy.

IX. Disposal of Infectious Waste

Use of tracking forms, containment, storage, packaging, treatment and disposal methods should be based upon the same rules as all other regulated medical wastes.

X. Autopsy and Handling of Corpses

All postmortem procedures are to be performed using Universal Precautions. Efforts should be made to avoid aerosolization.

- All persons performing or assisting in postmortem procedures must wear mandated P.P.E. (personal protective equipment) as delineated by O.S.H.A. guidelines.

- Instruments should be autoclaved or sterilized with a 10% bleach solution or other solutions approved by O.S.H.A. Surfaces contaminated during postmortem procedures should be decontaminated with an appropriate chemical germicide such as 10% hypochlorite or 5% phenol (carbolic acid).

XI. Management of Exposed Persons

An exposed person is defined as a person who has been exposed to aerosolized *Yersinia pestis* or has been in close physical contact with a confirmed case-patient (contact at less than 2 meters during a period when the case was symptomatic and before the case had received 48 hours of antibiotic therapy). Household contacts and healthcare worker contacts should be considered exposed and should receive prophylaxis.

Antibiotics: **All antibiotic therapy should continue for 7 days from *last exposure* to the case. Decisions on antibiotic therapy should be based on susceptibility results.**

Non-pregnant Adult Post-Exposure Prophylaxis

Tetracycline 500 mg every 6 hours, orally
Doxycycline 100 mg every 12 hours, orally
Ciprofloxacin 500 mg every 12 hours, orally
Ofloxacin 400 mg every 12 hours, orally
Levofloxacin 500 mg every 24 hours, orally

Alternative Therapy
Trimethoprim/sulfamethoxazole 40 mg/kg/day in 2 equal doses at 12 hour intervals, orally.

Pediatric Post-Exposure Prophylaxis - Co-trimoxazole is the preferred antibiotic, or when benefits outweigh the risks, consider use of doxycycline or fluoroquinolones.

If > or = 8 years of age:

Doxycycline: If > or = 45 kg - 100 mg orally every 12 hours
If < 45 kg - 2.2 mg/kg orally every 12 hours

If < 8 years of age:

Co-trimoxazole: 4 mg/kg orally every 12 hours

Chloramphenicol: 25 mg/kg orally every 12 hours

Newborns up to age 2 months:

Ciprofloxacin: 10-20 mg/kg orally twice daily,
do not exceed 1 gram/day.

Pregnant Women Post-Exposure Prophylaxis - Co-trimoxazole [1 DS tablet orally twice daily], is the preferred antibiotic, except at term, when the risk of kernicteris is greatest -- use fluoroquinolones [ciprofloxacin 500 mg orally twice daily]

XII. Reporting to the Napa County Public Health Division

Plague is a reportable disease in California. *All suspected, lab confirmed and clinical diagnosis (human or animal)* must be **IMMEDIATELY** reported by telephone to the Napa County Public Health Division, Communicable Disease Unit:

- **During business hours:** (707) 299 -1499
- **After business hours:** ask to page the on-call Communicable Disease Duty Officer (707) 265 -3131

XIII. References

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