Pneumonic Plague

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INSTRUCTIONS

The questions that appear throughout this case are intended as a self-assessment tool. For each question, select or provide the answer that you think is most appropriate and compare your answers to the key at the back of this booklet. The correct answer and a discussion of the answer choices are included in the answer key.

Note: These self-assessment questions are not intended for CME credit. To apply for CME credit, you must complete the CME Test at the back of this booklet and submit it according to the directions provided.

In addition, a sign is provided in the back of this booklet for posting in your office or clinic. Complete the sign by adding your local health department's phone number.

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INTENDED AUDIENCE

Internal medicine, family medicine, and emergency medicine physicians, and other clinicians who will provide evaluation and care in the aftermath of a terrorist attack or other public health disaster

EDUCATIONAL OBJECTIVES

Upon completion of this case, participants will be able to:

- Describe the epidemiologic characteristics of plague that distinguish bioterrorist events from natural endemic outbreaks of disease.
- Describe the clinical features of pneumonic, septicemic, and bubonic plague.
- List the differential diagnoses of pneumonic plague and identify specimens and lab tests needed to confirm the diagnosis.
- Discuss the ramifications of a plague outbreak including healthcare workers' fear and absenteeism and depletion of healthcare teams.
- Describe infection control precautions and recommendations for notifying infection control and the local health department.
- Summarize basic treatment regimens, post-exposure prophylaxis, and management relevant to adult, pediatric, and pregnant patients with plague.

CASE HISTORY

A 29-year-old man from New Mexico was attending a professional conference in Washington, DC when he began experiencing abdominal pain, diarrhea, nausea, vomiting, and cough. He developed fever and chills and presented to a local primary care clinic. On evaluation he was febrile to 104°F and orthostatic. The lung examination was normal. The abdomen was soft and non-tender with slightly hyperactive bowel sounds. There was no lymphadenopathy. He was administered intravenous fluids and an anti-emetic for presumed gastroenteritis.

COMMENT: The presence of cough may be a subtle clue that this was not a typical case of gastroenteritis. However, it is easy to see how this symptom might have been missed or discounted in a busy acute care clinic. The challenge of diagnosing many agents of bioterrorism is that the initial signs and symptoms are often indistinguishable from common illnesses that are seen in day-to-day medical practice. Table 1 describes the 3 primary manifestations of plague and their associated differential diagnoses.

Table 1. Clinical Features of Plague

	Bubonic	Pneumonic	Septicemic
Exposure	Innoculation of bacteria from infected flea; exposure of abraded skin to contaminated tissue	Hematogenous spread to lungs during bacteremia associated with bubonic or septicemic plague; alternatively, primary pneumonic plague occurs after inhalation of bacteria during contact with person or animal with plague pneumonia	Same as bubonic or pneumonic plague
Incubation Pathophysiology	3-6 days After inoculation, *Y. pestis* migrates to regional lymph nodes where aggressive intracellular multiplication occurs, resulting in enlargement, inflammation and associated hemorrhage with necrosis	1-5 days Inhalation of aerosolized organisms into the lungs results in foci of infection	3-6 days Rapid progression results in release of organisms causing overwhelming bacteremia prior to the development of lymphadenopathy; or enlarged lymph nodes may be internal (e.g. abdominal, mediastinal) and difficult to appreciate
Primary manifestations	Fever, malaise, focal lymphadenopathy (1 – 10 cm), often in femoral or inguinal areas that becomes extremely tender	Cough and hemoptysis, chest pain. Chest radiographs may demonstrate infiltrates, cavities or consolidation	Systemic toxicity with *Y. pestis* bacteremia
Other manifestations	May progress to sepsis syndrome with disseminated intravascular coagulation (DIC)	Gastrointestinal symptoms e.g. nausea, vomiting, diarrhea, abdominal pain may occur	DIC and acral necrosis may occur
Differential diagnosis	Staphylococcal, streptococcal or pasturella infections Tularemia (*Francisella tularensis*) Cat scratch disease (*Bartonella henselae*) Chancroid (*Haemophilus ducreyi*) Lymphogranuloma venereum (*Chlamydia trachomatis*) Mononucleosis, CMV, Toxoplasmosis	Typical and atypical agents of community acquired pneumonia	Sepsis due to gram negative or gram positive agents, especially meningococcemia, pneumococcal sepsis

By the following morning the patient's condition had deteriorated, and he reported to a local emergency room complaining of weakness, cough, and chest pain in addition to gastrointestinal symptoms. He described a single episode a few hours earlier in which he had expectorated a small quantity of blood. He appeared extremely ill and was intermittently incoherent. His temperature was 104.4°F, and his blood pressure was 78/50 mm Hg. A chest radiograph revealed bilateral pulmonary infiltrates. The patient was admitted to the intensive care unit. Aggressive resuscitation was initiated with intravenous fluids in conjunction with empiric antibiotic therapy with piperacillin-tazobactam, azithromycin and vancomycin. He developed an increasing oxygen requirement that required endotracheal intubation and the implementation of mechanical ventilation. Gram stain of an endotracheal tube aspirate specimen showed numerous small gram-negative coccobacilli.

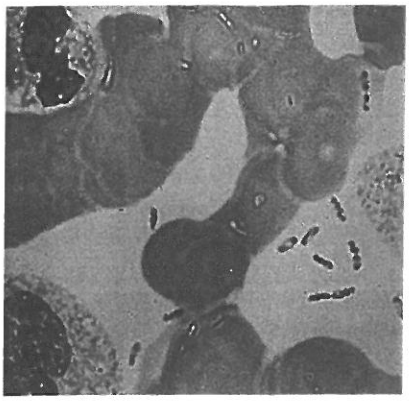

FIGURE 1. Wayson stain of peripheral blood in bacteremic *Y. pestis* infection demonstrating the characteristic bipolar ("safety pin") staining. Figure from Centers for Disease Control and Prevention.

COMMENT: *Yersinia pestis* (*Y. pestis*) can readily be isolated from deep sputum specimens, tracheal aspirates, or bronchial washings of patients with pneumonic plague. In addition, patients may be bacteremic allowing for isolation of the organism from the blood. If the patient has CNS signs and symptoms, a lumbar puncture gram stain and culture may reveal the pathogen. The organism has a characteristic safety pin appearance (Figure 1) and will grow on most microbiology culture media, including MacConkey agar plates that are part of the routine laboratory workup of gram negative rods.

Over the next 36-48 hours, the patient remained febrile. The microbiology lab reported that their automated identification system was unable to identify the gram-negative rods that had been isolated from the tracheal aspirate. Manual biochemical assays were set up in order to make a definitive diagnosis.

The following day, the microbiology lab reported their suspicion that the isolated organism might be Y. pestis. The infectious disease attending physician was immediately notified.

QUESTION 1

What precautions are required while caring for a patient with suspected pneumonic plague?

a. Standard precautions
b. Contact precautions
c. Droplet precautions
d. Airborne precautions

Reminder: You can find the Answer Key & Discussion on page 8.

The proper precautions were implemented. Table 2 reviews the differences between droplet and airborne transmission. The hospital lab notified the local health department of their concern for *Y. pestis*, and the isolated organism was transported to their laboratory for definitive identification.

In the meantime, with a presumptive diagnosis of pneumonic plague, gentamicin, doxycycline, and ciprofloxacin were added to the patient's antibiotic regimen; azithromycin was discontinued.

COMMENT: Streptomycin has traditionally been the treatment of choice for plague, since the drug has a strong, clinically tested record. However, the drug is not in frequent use today, and it is not widely obtainable, particularly on short notice. Gentamicin is much more readily available and considered to be an alternative agent. In situations where gentamicin and streptomycin are either unavailable or contraindicated, doxycycline, or chloramphenicol can be used. The fluoroquinolones have also demonstrated efficacy against the plague bacillus. Most of the available clinical data involve ciprofloxacin, and for this reason most authorities still recommend this drug as the first choice among fluoroquinolones. However, in vitro data suggest that levofloxacin would also be effective. Table 3 lists the doses of drugs that are used in the treatment of plague. Of note, several of these agents are relatively contraindicated in pregnant or lactating women or young children. However, in the event of a proven case of plague, the risks associated with these agents are outweighed by the benefits of therapy. It is generally recommended that patients receive at least 10 days of therapy, even though they may show clinical improvement and become afebrile within 4 – 5 days. In cases where the patient is critically ill, many clinicians will use a combination of agents (as in this case) in the hope of improving efficacy. Failure of therapy due to antimicrobial resistance in *Y. pestis* has not been a problem to date, but naturally occurring strains with multi-drug resistance have been isolated,[2] and the potential for genetic manipulation of the organism for use in a bioterrorist attack is unknown.

Table 2. Droplet Vs. Airborne Transmission

Droplet Characteristics	Droplet Transmission	Airborne Transmission
Size	Large	Very small (5 microns or smaller)
Suspension in air	Do not remain suspended in air	Can remain suspended in the air, ie, airborne, for long periods of time
Dispersal	Travel short distances, 3 feet or less	Travel widely via air currents, ie, greater than 3 feet
Ability to infect others	Requires close contact (within 3 feet or less) between a patient and the susceptible individual	Does not require contact (within 3 feet or less); can be inhaled easily by a susceptible person

Table 3. Recommended Regimens for the Treatment of Plague*

	Recommended Regimens
Adults	Streptomycin 30 mg/kg IM in 2 divided doses for a maximum of 2 gm/day Gentamicin 5 mg/kg/day IV or IM Gentamicin 2 mg/kg loading dose followed by 1.7 mg/kg IV or IM three times/day Doxycycline 100 mg IV two times/day Doxycycline 200 mg IV once/day Ciprofloxacin 400 mg IV two times/day Chloramphenicol 25 mg/kg IV four times/day
Children	Gentamicin 2.5 mg/kg IV or IM three times/day If ≥ 45 kg, Doxycycline 100 mg IV two times/day If < 45 kg, Doxycycline 2.2 mg/kg IV two times/day Ciprofloxacin 15 mg/kg IV two times/day Chloramphenicol 25 mg/kg IV four times/day

* Adapted from Inglesby et al.[1]

A respiratory therapist caring for the patient commented that she had developed a cough and asked if she might have acquired pneumonic plague. Two nurses who had cared for the patient at the time of initial presentation reported flu-like symptoms and were worried that they too might have acquired plague. Another nurse, who was 4 months pregnant, refused to care for the patient because of fear that the droplet precautions that had been instituted would not provide adequate protection for her and her unborn baby.

COMMENT: It is critical to notify your infection control department and your local health department as soon as a case of plague is suspected or confirmed. Infection control practitioners and the hospital epidemiologist will determine the continued risk to people in the facility, as well as follow-up on any healthcare workers exposed to the source patient since admission.Table 4 reviews the recommended prophylactic regimens for people exposed to a patient with pneumonic plague.

Health department officials can often facilitate the transportation of specimens or isolates to a reference laboratory where a definitive identification can be made, and they will initiate the detailed and systematic investigation that is required in order to identify exposed individuals, and ascertain whether a bioterrorist event has occurred. Health department personnel are also trained in risk communication, a skill that can prove invaluable in the face of widespread panic and fear.

ABSENTEEISM[4]

In the United States, healthcare professionals have little experience in diagnosing and managing causalities caused by chemical, radiological, or biological agents. As a result, in the immediate aftermath of a bioterrorism event involving one of these agents, healthcare professionals may experience fear, shock, anger, helplessness, and may have concerns about the health and safety of their families and friends. Potentially, these feelings can contribute to absenteeism among the healthcare staff. For example, in 1994, during an outbreak of pneumonic plague in Surat, India, 80% of the private physicians fled the city.

Familiarity with chemical and biological agents, as well as training and drilling on your emergency plan may enhance performance by healthcare staff and help to minimize or prevent absenteeism.

Table 4. Prophylactic Regimens for People Exposed to a Patient With Pneumonic Plague*

		Post-exposure Prophylaxis
Adults	Recommended	Doxycycline 100 mg orally twice per day
	Recommended	Ciprofloxacin 500 mg orally twice per day
	Alternative	Chloramphenicol 25 mg/kg IV or orally four times per day
Children	Recommended	If ≥ 45 kg, Doxycycline 100 mg orally twice per day
	Recommended	If < 45 kg, Doxycycline 2.2 mg/kg orally twice per day to a maximum of 200 mg/day
	Recommended	Ciprofloxacin 20 mg/kg orally twice per day
	Alternative	Chloramphenicol 25 mg/kg IV or orally four times per day

* Adapted from Inglesby et al.[1]

QUESTION 2

An appropriate post-exposure intervention for people who have been in contact with a patient with pneumonic plague includes which of the following?

a. Administration of the plague vaccine within 72 hours of exposure
b. Administration of anti-plague immunoglobulin within 72 hours of exposure
c. Administration of prophylactic antibiotics for 7 days

Two health department officials came to the hospital to assist with identification of contacts and to conduct an investigation into the source of the case. They reported that no other cases were confirmed or suspected in the local area.

QUESTION 3

Which of the following scenarios is most suspicious for a bioterrorist event?

a. A 22-year-old college student and his girlfriend acquire bubonic plague while camping in Colorado.
b. A 60-year-old businessman acquires pneumonic plague while attending a conference in New York City.
c. A 49-year-old professor acquires septicemic plague while hunting prairie dogs in New Mexico.
d. A 37-year-old housewife acquires pneumonic plague after her sick cat dies in Arizona.

COMMENT: The existence of even a single case of pneumonic plague in a non-endemic area should raise suspicion of an act of bioterrorism and requires further investigation. Table 5 compares characteristics of naturally occurring plague infections with the possible features of a bioterrorism event.

Table 5. Clinical and Epidemiologic Characteristics of Plague

	Naturally Occurring Infection	Bioterrorism Event
Clinical manifestations	• Typically bubonic plague with occasional septicemic cases • Pneumonic plague is a relatively rare event that has been associated with infected cats	• Aerosolization of the plague bacillus would be expected to result in cases of pneumonic plague
Numbers of cases	• Isolated cases with common risk factors	• Large clusters of cases with a common mechanism of exposure
Geography	• Plague is enzootic in the southwestern United States. However, in an era of rapid and global travel, cases may potentially present anywhere, and a careful travel history is required to identify travel through or from an endemic area.	• Non-enzootic areas • Large metropolitan cities or locations of social, cultural, or political importance
Seasonality	• Most cases occur between April and October • Cases involving direct animal contact have occurred in the colder months (hunting season)	• None
Risk factors	• Working, camping, hunting outdoors, and in contact with fleas and/or host animals • Veterinarians and their staff who may be in contact with small animals in an enzootic area • Contact with domestic cats in an enzootic area • Communities with very poor hygiene/sanitation where rodents and fleas come in contact with humans • During rodent "die-offs" when infected fleas seek alternative hosts	• Non-specific

One of the ICU nurses obtained the name and telephone number of the patient's housemate in New Mexico, and the health department officials called her as part of their investigation. She reported that the day before he left for his trip the patient had removed a stray cat from the crawlspace of their house. The cat had oral abscesses and lesions that, in retrospect, were consistent with feline plague. The animal died in the local animal shelter and was cremated without any diagnostic studies. While this information transpired, the local health department laboratory confirmed that the tracheal isolate was indeed *Y. pestis*. Once the isolate was identified and confirmed and susceptibility results were available, the infectious disease specialist narrowed the patient's antibiotic coverage.

COMMENT: As more information becomes available, it is evident that this case was unlikely to represent a bioterrorist event. Although the patient presented in Washington, DC, a likely target for a terrorist event, he lived in and traveled from New Mexico, where plague is enzootic. Additionally, he had a clear risk factor for pneumonic plague since he had made close contact with a sick cat that probably had feline plague. It was also reassuring that no other cases of plague were identified in the Washington, DC area; a terrorism event would likely result in a number of cases, rather than a single index case.

QUESTION 4

Other than isolating *Y. pestis* from a clinical specimen, what test is available to make the diagnosis of plague?

a. **When plague antigen is administered intra-dermally, people who have been infected with plague have a positive skin test that is analogous to the positive skin test in patients who have been exposed to tuberculosis.**
b. **People who have been infected with plague produce an antibody to the plague bacteria that can be detected in the serum.**
c. **People who have been infected with plague excrete a plague antigen that can be detected in the urine.**

The patient made steady improvement and was successfully extubated on the 7th hospital day. He ultimately made a complete recovery and returned to work approximately 6 weeks after his initial presentation. Although over 30 people gave a history of close contact with him and received prophylactic antibiotics, no additional cases of plague were identified.

ANSWER KEY & DISCUSSION

QUESTION 1

What precautions are required while caring for a patient with suspected pneumonic plague?

a. **Standard precautions**
b. **Contact precautions**
c. **Droplet precautions**
d. **Airborne precautions**

ANSWER: The correct answer is c. Pneumonic plague may be transmitted from person-to-person via respiratory droplets if an infected individual is coughing. For this reason, it is recommended that droplet precautions and isolation be implemented for all patients with known or suspected plague until pneumonic plague has been ruled out, or until the patient has received at least 72 hours of effective therapy and made clinical improvement. Droplet precautions require the use of a surgical mask within 3 feet of an infected patient. Eye protection, in the form of goggles or face shields, is also recommended to protect the conjunctival mucosa. Standard precautions (formerly called universal precautions) are the precautions that are implemented in the care of all patients, and alone would not provide sufficient protection against transmission via the droplet route. Contact precautions involve the use of gowns and gloves and are used in infections such as methicillin-resistant *Staphylococcus aureus*, which is transmitted via fomites to the hands of health care providers. Airborne precautions require the use of an N95 respirator and a negative pressure environment. This is the form of protection that is required for infections such as pulmonary tuberculosis that result in the production of very small (1 – 10 μm) infectious nuclei that remain suspended in the air and can be inhaled into the pulmonary alveoli. There is no evidence of the formation of infectious particles of this size in pneumonic plague.[1]

QUESTION 2

An appropriate post-exposure intervention for people who have been in contact with a patient with pneumonic plague includes which of the following?

a. **Administration of the plague vaccine within 72 hours of exposure**
b. **Administration of anti-plague immunoglobulin within 72 hours of exposure**
c. **Administration of prophylactic antibiotics for 7 days**

ANSWER: The correct answer is c. Once a case of pneumonic plague has been diagnosed, it is necessary to identify individuals that have had close contact with the patient (defined as coming within 2 meters of the index case) prior to the completion of 72 hours of effective therapy. These individuals should receive post-exposure antibiotic prophylaxis for 7 days.[1] Table 4 gives the recommended prophylactic regimens for adults and children. Here again, it is necessary to balance the possible toxicities of these agents against the benefits of prophylaxis for special populations such as very young children and pregnant or lactating women. Close contacts that are receiving post-exposure prophylaxis antibiotics should be monitored for fever, development of cough, or other signs of illness. Should such signs develop, the patient should receive immediate medical attention with treatment for pneumonic plague on a presumptive basis until or unless this diagnosis can be definitively excluded. There is no plague vaccine currently available. Anti-plague immunoglobulin is not a commercially available product, and there are no data to support its role in post-exposure prophylaxis.

QUESTION 3

Which of the following scenarios is most suspicious for a bioterrorist event?

a. **A 22-year-old college student and his girlfriend acquire bubonic plague while camping in Colorado.**
b. **A 60-year-old businessman acquires pneumonic plague while attending a conference in New York City.**
c. **A 49-year-old professor acquires septicemic plague while hunting prairie dogs in New Mexico.**
d. **A 37-year-old housewife acquires pneumonic plague after her sick cat dies in Arizona.**

ANSWER: The correct answer is b. The existence of even a single case of pneumonic plague in a non-endemic area should raise suspicion of an act of bioterrorism and requires further investigation. Table 5 reviews some of the characteristics of naturally occurring plague infections for comparison with the possible features of a bioterrorism event.

QUESTION 4

Other than isolating *Y. pestis* from a clinical specimen, what test is available to make the diagnosis of plague?

a. **When plague antigen is administered intra-dermally, people who have been infected with plague have a positive skin test that is analogous to the positive skin test in patients who have been exposed to tuberculosis.**
b. **People who have been infected with plague produce an antibody to the plague bacteria that can be detected in the serum.**
c. **People who have been infected with plague excrete a plague antigen that can be detected in the urine.**

ANSWER: The correct answer is b. Serologic testing can be used to confirm the diagnosis of plague retrospectively. The test available through the Centers for Disease Control and Prevention (CDC) detects the presence of anti-F1 antibody (antibody to the antigen of the bacterial envelope). The test is performed using paired serum with acute and convalescent or convalescent and post-convalescent specimens. A 4-fold or greater change in titer, or a single titer of 1:16 or greater is presumptive evidence of plague infection.[3] There is no skin test for plague. There is also no diagnostic plague antigen that can be detected in the urine of infected patients.

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SUGGESTED READING

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