Plague in Bioterrorism

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Abstract

Plague is a zoonotic illness caused by the Gram-negative bacillus *Yersinia pestis*. Human are not necessary for persistence of the organism, and we acquire plague from animal fleas, contact with infected animals or rarely from other humans via aerosols or direct contact with infected secretions. To be able to differentiate endemic plague from plague used in biological warfare, medical officers must understand the typical way in which humans contract plague in nature: First, a die-off of animals in the mammalian reservoir that harbors bacteria-infected fleas will occur. Second, troops who have been in close to infected mammals will become infected. By contrast, plague will spread via aerosols in the most likely biological warfare. A rapid person to person spread of fulminant pneumonia would then occur. If an enemy force is to release fleas infected with *Y pestis*, then people would present with classic bubonic plague before a die-off in the local mammalian reservoirs occur. The three clinical forms of human plague are bubonic, septicemic and pneumonic. Bubonic plague, characterized by painful lymphadenopathy and severe constitutional symptoms of fever, chills and headache, is the most common form. Septicemic plague without localized lymphadenopathy occurs less commonly and is difficult to diagnose. Primary pneumonic plague is spread by airborne transmission and has the highest mortality. Diagnosis is established by identifying the organism from blood or other body fluids. Patients should be isolated initially and treated with antibiotics (streptomycin preferably) early. A killed, whole-cell vaccine is available to protect humans against bubonic plague, but not against for primary pneumonic plague. *(Ann Disaster Med 2002;1 Suppl 1:S26-S35)*

Keyword: bioterrorism; biological agents; plague; disaster medicine

Introduction

Plague is a zoonotic illness caused by *Yerinia pestis*, a Gram-negative bacillus, which is an acute, often fatal and potentially epidemic disease.[1-5] The plague life cycle is a complex interaction between rodents and fleas, with human infection occurring occasionally.[6] The most important reservoirs of plague are rodents. The plague bacillus is

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transmitted among rodents and from rodents to humans by fleas. Human acquire plague by being bitten by infected rodent fleas. A bite from an infected flea can release thousands of *Y pestis* organisms into the blood stream to multiply intracellularly within lymph nodes.[1-5]

Plague occurs worldwide, primarily in developing countries of Africa(76.2%) and Asia. Human infection can be acquired by contact with fluids from infected animal.[1-5] Transmission also happens between human, as well as between animal and humans by respiratory droplets from cases with plague pneumonia.[1-5] Therefore, plague fulfills criteria for a high-risk potential weapon of bioterrorism as follow:[7,8]

(1) humans are easily infected via the respiratory tract
(2) aerosolized bacteria are easily propagated person to person
(3) pneumonic plague has a high attack rate and produces severe clinical disease
(4) plague has a high psychological impact

An effective response to a bioterrorist attack requires the earliest cases be detected and reported as soon as possible, so that there is sufficient time to limit morbidity and mortality.[3,7,8] Early detection and reporting will depend on prompt recognition of unusual clinical syndromes. The health providers should be familiar with and be able to recognize the most likely biological agents such as anthrax, brucellosis, plague, Q fever, smallpox, viral hemorrhage fever etc.[1-8] One of the more important biological agents, plague, is discussed further.

History

Epidemics of plague thrust into the collective memory of western civilization three times in past millennia.[2,4] The epidemic plague of the Byzantine Empire during the reign of Justinian I (AD 541-542) is considered to be the first great pandemic which caused as many as 100 million Europeans died. The secondary plague pandemic, known as the Black Death, probably entered Europe via the trans-Asian silk road during the early 14th century. The Black Death killed the lives of 24 million people between the years 1346 and 1352, and perhaps another 20 million by the end of the 14th century. The secondary great pandemic slowly died out finally by 1720 due to several reasons. The third plague pandemic arose in 1894 in China and spread throughout the world via modern transportation. In 1894, Alexandre J.E. Yersin also discovered that *Yersinia pestis*, the etiologic agent of plague. The modern pandemic arrived in Bombay in 1898 and more than 13 million Indians died of plague in the next 50 years.

Plague causes disease both through endemic exposure and as a biological warfare agent.[1-3,8] The first attempt, called as biological warfare, is purported to have occurred at the Crimean port city of Caffa on the Black Sea during the

years 1346-1347. During World War II, the Japanese army established a secret biological warfare research unit (Unit 731) in Manchuria, where epidemics of pneumonic plague had occurred in 1910-1911, 1920-1921, and 1927. The Japanese apparently used plague, via the human flea Pulex irritans, as a biological warfare agent in China several times during World War II. This flea is resistant to air drag, naturally targets human, and could also infect a local rat population to prolong an epidemic. Since World War II, no evidence exists to support plague epidemics as a biological warfare although such claims are not uncommon.

Epidemiology

Yersinia pestis, the organism responsible for plague, is a Gram-negative, nonacid-fast, nonmotile, nonsporulating, nonlactose-fermenting, bipolar coccobacillus measuring 0.5-0.8 × 1.5-2.0 μm.[1-3,6] *Y pestis* grows optimally at 28℃. The known virulence factors are encoded on the chromosome and its three plasmids. It primarily infects rodents such as rats and mice but can also infect squirrels, prairie dogs, cats, and camels. Throughout history, the oriental rat flea (*Xenopsylla cheopis*) has been largely responsible for spreading bubonic plague. After the flea ingests a blood meal on a bacteremic animal, bacilli can multiply and eventually block the flea's forgot, or proventriculus. When an infected flea with a blocked foregut attempts to feed again, it regurgitates clotted blood and bacteria into the victim's blood stream, and pass the infection to the next mammal. Man is an accidental host in the plague cycle in nature.

The flea, primary vector of plague spreading, desiccates rapidly in very hot and dry weather when away from its hosts, but flourishes at humidity just above 65% and temperatures between 20℃ and 26℃, can survive 6 months without a feeding. The greatest risk to humans occurs when large concentrations of people live under unsanitary conditions in close proximity to large commensal or wild rodent populations that are infected with fleas that bite both humans and rodents. Human to human transmission of plague can occur from patients with pulmonary infection. Most epidemics have occurred in cool climates with moderate humidity and close contact between susceptible individuals. Outbreaks of pneumonic plague have been rare in tropical climates even during epidemics of bubonic disease.

In fact, the medical officers should differentiate endemic plague from plague used as a biological warfare agent. The following concepts will help to make a diagnosis of biological warfare:[8]

(1) the whole surrounding area of reported cases has never been afflicted by plague
(2) plague usually spreads with rice along shipping routes, but epidemic center is far away by land or river
(3) No evidence of excessive rat mortality occurs after the people

begin dying due to plague

(4) A rapid, person-to-person spread of fulminant pneumonia, characterized by blood-tinged sputum

Clinical manifestations

As few as 1 to 10 *Y pestis* organisms are sufficient to infect rodents and privates via the oral, intradermal, subcutaneous, and intravenous route. Estimates of infectivity by respiratory transmission vary from 100-20,000 organisms. After being introduced into the mammalian host by flea, the bacilli most commonly spread to regional lymph nodes, where suppurative lymphadenitis develops, producing the characteristic bubo. Infection will progress to septicemia and spread to other organs if untreated. The most commonly infected tissues include the spleen, liver, lungs, skin, and mucous membranes. Meninges also could be infected late, especially if suboptimal antibiotic therapy has been given. The secondary clinical form of human plague is primary pneumonic plague, the most severe and more rapidly fatal form of disease, which arises from inhalation of an infectious aerosol. This clinical form is the least common but has the highest mortality if antibiotics are not begun within 24 hours of onset of symptoms. Primary septicemic plague can occur from direct inoculation of bacilli into the bloodstream, bypassing initial multiplication in the lymph nodes. Bubonic plague, characterized by developing an acute regional lymphadenopathy, is most frequent clinical form, accounting for 80-90% of US cases. The pneumonic form would be the most likely presentation during a biological attack. Septicemic plague without obvious lymphadenopathy may be more difficult to diagnose than bubonic plague because of nonspecific manifestations.[1-6]

Bubonic Plague

Buboes manifest after a 1 to 8 days incubation period, with regular onset of symptoms of sudden fever, chills, and headache often followed several hours later by nausea and vomiting. Presentation of symptoms includes severe malaise (75%), headache (20-85%), vomiting (25-49%), chills (40%), altered mentation (26-38%), cough (25%), abdominal pain (18%), and chest pain (13%). Six to eight hours after onset of symptoms, buboes, heralded by severe pain, occur in the groin (90%), axillary, or cervical lymph nodes. Buboes become visible within 24 hours and are intensely painful that the patients will attempt to abduct their extremities to decrease pressure. Other manifestations include bladder distension, apathy, confusion, fright, anxiety, oliguria/ anuria, tachycardia, hypotension, and leukocytosis. Untreated, septicemia will develop in 2-6 days. Approximately 5-15% of bubonic plague patients will develop secondary pneumonic plague and the potential for airborne transmission.

Pneumonic Plague

Pneumonic plague may occur primarily from inhalation of aerosols, or secondary from hamatogenous dissemination. Symptoms of secondary pneumonic plague include shortness of breath, cough, chest pain, and bloody sputum in addition to those attributed to buboes. Primary pneumonic plague manifests as the abrupt onset of fever and flu-like symptoms 2-4 days after exposure and rapidly progresses to fulminating pneumonia and respiratory failure. The findings on chest roentgenography may be variable, bilateral alveolar infiltrates appear to be the most common finding. Both forms of pneumonic plague are readily transmissible via airborne droplets. The patients with this clinical form are almost always fatal if antibiotics are not given within 24 hours of onset of symptoms.

Septicemic Plague

Septicemic plague may occur primarily or secondarily as a complication of bubonic plague. Presentation of primary septicemic plague is essentially the same as those of any Gram-negative septicemia: fever, chills, nausea, vomiting, and diarrhea. Purpura, disseminated intravascular coagulation, and acral cyanosis and necrosis may be seen later. The risk of dying from septicemic plague is higher for those younger than 30 years, although the risk of developing septicemic plague is higher for individuals older than 40 years. This difference is most likely due to older undiagnosed patients being treated empirically with antibiotics that kill *Y pestis*, and younger undiagnosed patients being treated with antibiotics that do not affect it.

Other Manifestations

Plague meningitis is seen in 6-7% of cases, most often in children after 9-14 days of ineffective treatment.[5] Symptoms are similar to those of other forms of acute bacterial meningitis. Asymptomatic pharyngeal carriage has been reported to occur in contacts of plague patients. Pharyngitis with cervical lymphadenopathy occurs rarely. Femoral and inguinal buboes are the most common of cutaneous manifestations because the flea typically bites the lower extremities. Approximately 4-10% of plague patients have an ulcer or pustule at the inoculation site. Petechiae and ecchymoses may occur during hematogenous spread. Patients in the terminal stages of pneumonic and septicemic plague often develop large ecchymoses on the back.

Diagnosis

A patient with a typical presentation of bubonic plague should readily suggest the diagnosis of plague. The differential diagnosis includes tularemia, cat scratch disease, lymphogranuloma venereum, chancroid, tuberculosis, streptococcal adenitis, and scrub typhus.[1-7] In both tularemia and cat scratch disease, the inoculation site will usually be more evident and not be septic. In chancroid

and scrofula, the patient has less local pain; the course is more indolent without sepsis. Patients with chancroid and lymphogranuloma venereum will have a recent history of sexual contact and genital lesions. Streptococcal adenitis may be difficult to differentiate initially, but the nodes are tenderer when plague is present. The differential diagnosis of septicemic plague includes meningococcemia, Gram-negative sepsis, and the rickettsioses. The patient with pneumonic plague suggests a large differential diagnosis. Demonstration of Gram-negative rods in sputum should suggest the correct diagnosis.[6]

Plague is diagnosed by demonstrating *Y pestis* in blood or body fluids such as a lymph node aspirate, sputum, or cerebrospinal fluid.[6] In patient with lymphadenopathy, a bubo aspirate should be done by inserting a 20-gauge needle attached to a 10-ml syringe containing 1 ml of sterile saline. Saline is injected and withdrawn several times until it is tinged with blood. A rapid diagnosis can be made tentatively by Gram stain of aspirate showing compatible Gram-negative coccobacilli or by fluorescent antibody testing. Cultures of blood, bubo aspirate, sputum, and cerebrospinal fluid should be performed. Complete blood counts often reveal leukocytosis with a left shift. Leukemoid reactions may be seen, especially in children. Platelet counts may be normal or low, and partial thromboplastin times are often increased. Because of liver involvement, alanine aminotransferase, aspartate aminotransferase, and bilirubin level are often increased. Serologic studies are useful for retrospective diagnosis or epidemiological studies.

Treatment

All patients with plague should be isolated for the first 48 hours after the initiation of treatment. If pneumonic plague is present, patients must be isolated until they have completed at least 4 days of antibiotic therapy. Since 1948, streptomycin (15 mg/kg, up to 1 g injected intramuscularly every 12 hours) has remained the treatment of choice for bubonic, septicemic, and pneumonic plague.[1,3,5] Alternative drugs can be administered parenterally including chloramphenicol (50-75 mg/kg/d in 4 divided doses) or gentamicin (5 mg/kg/d as a single dose or in divided doses). Treatment should be continued for a minimum of 10 days or 3-4 days after clinical recovery. If clinically indicated, oral tetracycline can be used to complete a 10-days course after at least 5 days of systemic therapy. In patient with very mild bubonic plague without septicemia, tetracycline (2 g/d in 4 divided doses) can be used orally for 10 days. In pregnant woman, streptomycin or gentamicin should be used. Streptomycin is also the treatment of choice in newborns.

If treated with antibiotics, buboes typically recede in 10-14 days, and do not require drainage.[1,3] Untreated bubonic plague has a case fatality rate of 40-60%,

whereas the pneumonic and septicemic plague is typically fatal.[1,3] Treatment of plague has reduced the mortality rate of bubonic form to less than 10%, but 60% for the pneumonic and septicemic form are still common.

Prevention

Not only contacts of patients with pneumonic plague but also individuals who have been exposed to aerosols should be treated with tetracycline (15-30 mg/kg/d in 4 divided doses) for 7 days.[1,3,5,7] Doxycycline (100 mg twice daily) is probably an effective alternative if tetracycline is not available. Pregnant women and children under 8 years should receive trimethoprim/ sulfamethoxazole (40 mg sulfa/kg/d in 2 divided doses) for 7 days. Hospital personnel who are observing recommended isolation patients do not require prophylactic chemotherapy, nor do contacts of patients with bubonic plague. In addition, previously vaccinated individuals should receive prophylactic antibiotics if they are suspected to have been exposed to plague aerosols.

Only individuals at high risk for plague should be immunized such as military troops and other personnel working in plague endemic areas.[3,7] Laboratory personnel working with *Y pestis*, people who reside in enzootic or epidemic plague areas, and those whose vocations bring them into regular contact with wild animals should be vaccinated. Although effective for preventing or attenuating bubonic plague, the vaccine is not effective for pneumonic plague. Approximately 90% of vaccine will produce antibody titers after the serial 3 injections. The dose schedule for adults is 1.0 ml initially, with 0.2 ml at 1-3 months, followed by 0.2 ml 5-6 months. Booster doses are given every 6 months for 1.5 years, and then once every 1-2 years thereafter if risk for exposure continues. Local side effects of vaccination include erythema, soreness, or swelling in 11% of vaccinees. Systemic side effects include headache, malaise, and myalgias in 4% of vaccines. Plague vaccine should not be administered to persons who have a history of hypersensitivity to the vaccine or its components.

Summary

Plague is a zoonotic illness caused by the Gram-negative bacillus *Yersinia pestis*. Human are not necessary for persistence of the organism, and we acquire plague from animal fleas, contact with infected animals or rarely from other humans via aerosols or direct contact with infected secretions. To be able to differentiate endemic plague from plague used in biological warfare, medical officers must understand the typical way in which humans contract plague in nature: First, a die-off of animals in the mammalian reservoir that harbors bacteria-infected fleas will occur. Second, troops who have been in close to infected mammals will become infected. By contrast, plague will spread via aerosols

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鼠疫

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摘要

鼠疫是一種由革蘭氏陰性感菌 *Yersinia pestis* 所引起的動物性疾病，人類不是該微生物生存必經的一環，我們通常是經由動物身上的蚤類，經由與被感染動物的接觸，或在極少情形下經由口沫或感染性分泌物的人與人間途徑感染。為了區分鼠疫流行及生物戰使用鼠疫，醫療人員必須瞭解人類接觸鼠疫的自然方式：第一、曾經接觸可以滋養帶有鼠疫菌的蚤類之哺乳動物宿主身體；第二、可能曾經極為接近受感染哺乳動物的軍隊。相對的，在大多數生物戰中，鼠疫是經由口沫傳染，而產生人與人間快速蔓延的猛爆性肺炎。如果敵人釋放感染有鼠疫菌的蚤類，人們將通常先以傳統淋巴腺腫性鼠疫表現。人類患有鼠疫的三種臨床型態為淋巴腺腫性、敗血性及肺炎性。淋巴腺腫性鼠疫最為常見，臨床上會有疼痛性淋腺腫，以及嚴重的發燒、畏寒及頭痛。敗血性鼠疫較少發生，而且診斷困難。原發性肺炎性鼠疫是經由空氣傳染，且死亡率最高。診斷確立須藉由從血液或其他體液分離出鼠疫菌。病患應該先加以隔離，並早期使用抗生素（如 streptomycin）治療。目前有一種滅菌全細胞疫苗，可以預防淋巴腫性鼠疫，但不能對抗原發性肺炎性鼠疫。*(Ann Disaster Med 2002;1 Suppl 1:S26-S35)*

關鍵詞：生物恐怖主義；生物戰劑；鼠疫；災難醫學

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