



Plague September 2003

Plague is the zoonotic disease caused by the bacterium *Yersinia pestis*.

Plague is an ancient disease that is thought to be responsible for over 200 million deaths, many of which occurred during three pandemics, including the infamous Black Death of 14th century Europe. Populations were decimated by up to 50% during these pandemics. *Yersinia pestis* is one of the agents that the Japanese attempted to use as a biological weapon in World War II at the Unit 731 camp in Manchuria, and it is thought to have been produced in large quantities by the former Soviet Union bioweapons program.

Plague remains endemic in many areas of the world, including the southwestern United States, where up to 10 cases per year are reported. Globally, there are approximately 1700 cases each year. Plague is primarily a disease of rodents, but can be transmitted to humans through the bite of infected fleas, the most common route, or through direct contact with infected animals. Additionally, plague can be transmitted via inhalation of infectious droplets from persons with pneumonic plague or from infected animals, particularly cats. Experiments with primates have confirmed that an infectious aerosol of *Y. pestis* can be created, and this would likely be the form encountered in a bioterrorist event.

There are 3 predominant forms of human plague: pneumonic, bubonic and septicemic. Pneumonic plague can be either primary, which is the development of pneumonia from direct inhalation of organisms, or secondary through the hematogenous spread of organisms from any primary site to the lungs. Two percent of United States plague cases are primary pneumonic, while 12% of bubonic and septicemic cases spread to secondary pneumonic. Presentation and clinical course are similar for both with an overall case fatality of 50-70%, which nears 100% when treatment is delayed by 18-24 hours or after onset of symptoms. In the United States, 84% of cases are bubonic, caused by flea bites or handling infected animals, and characterized by buboes, or tender and markedly

swollen regional lymph nodes. Mortality is less than 5% in treated cases, but can reach 40-60% in cases that go untreated or where treatment is significantly delayed. Bubonic plague would not likely be the initial form of disease in a bioterrorism-related outbreak, but could occur after development of an epidemic and subsequent widespread rodent infection. Septicemic plague accounts for 13% of cases in the United States and consists of a severe systemic illness without preceding lymphadenopathy or pneumonia. Any route of exposure can lead to septicemic plague, and this form of disease might be seen after aerosol exposure in rare individuals who did not develop a substantial pneumonia. Mortality is 30-50% despite treatment and greater than 90% when treatment is delayed.

Yersinia pestis is one of the three pathogenic *Yersinia* species within the family Enterobacteriaceae. The other two, less virulent species, are *Y. enterocolitica* and *Y. pseudotuberculosis*. It is a nonmotile, intracellular, aerobic Gram-negative coccobacillus that has a characteristic bipolar appearance on Wright, Giemsa and Wayson's stains. It is among the most virulent human pathogens, with an antiphagocytic capsule, lipopolysaccharide endotoxin and other virulence factors.

This photo demonstrates the characteristic bipolar, or "safety pin", appearance of *Yersinia pestis* on Wright, Giemsa and Wayson stains.

Primary pneumonic plague ensues after live organisms are inhaled into the alveoli where they cause a severe lobular pneumonia that often progresses rapidly to dense lobar consolidation with necrosis and subsequent high-grade bacteremia. The bacteremia can lead to seeding of multiple organs and a typical Gram negative sepsis syndrome mediated by the lipopolysaccharide endotoxin.

The incubation period is typically 1-4 days, but can be as long as 6 days. Disease starts suddenly with non-specific symptoms resembling an acute flu-like illness, including fevers, chills, myalgias, malaise and headache. There are often prominent gastrointestinal symptoms including nausea, vomiting, diarrhea and abdominal pain, before more specific symptoms of pneumonia appear. Patients typically progress from feeling well to having severe pneumonia with severe dyspnea, cough, chest pain, and stridor within 24 hours. Hemoptysis is a common finding reflecting the degree of necrosis occurring in the lung, and may be a helpful clue in the differential diagnosis. Sepsis, manifested by hypotension, multi-organ failure and DIC, ensues in inadequately treated patients. Purpuric lesions and gangrene of the digits are complications of the sepsis and DIC that result from any form of the disease. The differential diagnosis of pneumonic plague includes any severe pneumonia, and should be considered in any case of severe Gram negative pneumonia without nosocomial exposure, especially if there is no response to typical antibiotic therapy.

This is an example of a chest x-ray showing an extensive left lower lobe consolidation from pneumonic plague.

Bubonic plague also begins with flu-like symptoms 2-8 days after exposure, but is accompanied by painful, enlarged, and sometimes draining lymph nodes called "buboes"

proximal to the inoculation site, generally in the groin or axilla. Lymph node destruction and hi-grade bacteremia with systemic disease and sepsis occur in severe cases. Septicemic plague presents only as the severe systemic disease after nonspecific flu-like symptoms and without preceding lymphadenopathy or pneumonia, making initial diagnosis extremely difficult.

Timely diagnosis is difficult as there are no tests available that are rapid, specific and confirmatory, making a high index of suspicion necessary. A preliminary diagnosis can be made when bipolar staining bacilli are visualized in samples prepared with Wayson, Giemsa or Wright stain. Culture of blood, sputum, bubo fluid and CSF onto blood and MacConkey agar can confirm the presence of *Y. pestis* if the appropriate biochemical tests are available. Serologic tests identifying the presence of the F1 capsular antigen are helpful retrospectively. Rapid confirmatory tests such as PCR and fluorescent antibody assays are generally only available at reference laboratories.

Treatment of *Yersinia pestis* consists primarily of antibiotic therapy that must be initiated rapidly upon first suspicion and prior to confirmation. Historically, monotherapy with an appropriate antibiotic results in rapid improvement. Aminoglycosides are first line therapy, particularly streptomycin, which is approved by the Food and Drug Administration (FDA) for this purpose at 1g IM bid for adults. Gentamicin is also recommended and is easier to administer, because it can be given intravenously and can be dosed once daily at 5mg/kg. Tetracyclines can be used, such as doxycycline 100mg IV bid for adults, which is also the first choice if oral therapy is required, for example in the setting of mass casualties. Other alternatives include ciprofloxacin 400mg IV q12 hours for adults, which is effective versus *Y. pestis* in vitro, although there are no human data. Other fluoroquinolones may be effective as well, but have not been studied. Chloramphenicol is the first choice for plague meningitis as it penetrates the blood-brain barrier. The dose for chloramphenicol is 25mg/kg given intravenously q 6h maintaining levels between 5mcg/ml and 20mcg/ml. Children under 2 years old should not be treated with chloramphenicol if at all possible to avoid the "grey baby" syndrome.

Antibiotics that are generally ineffective and should not be used for *Yersinia pestis* include beta-lactams such as penicillins and cephalosporins, rifampin, aztreonam and macrolides. Natural antibiotic resistance to the drugs of choice is rare, but it should be anticipated that genetically-engineered antibiotic resistance may be encountered in a bioterrorism scenario. Intravenous antibiotics can be switched to oral therapy if available for the drug being used after clinical improvement occurs. Duration of therapy should be for 10-14 days, or at least 3 days after becoming afebrile with clinical improvement.

Post-exposure prophylaxis with oral doxycycline or ciprofloxacin should be administered for 7 days to anyone who may have had inhalational exposure to *Yersinia pestis* within the prior 6 days, either as an aerosol or as droplets from a patient with pneumonic plague. Significant exposure is defined as a household or hospital contact, or being within 2 meters of the infected patient. Contacts who refuse prophylaxis should be observed closely for 7 days and started on full treatment regimens for the development of any cough or fever.

A vaccine produced from a killed virulent strain was used in the United States in the past, but has not been commercially available since 1999. It was effective against bubonic plague only and did have some adverse effects.

It is thought that pneumonic plague is transferred person-to-person via respiratory droplets. Thus, any suspected pneumonic plague patients should be placed in respiratory droplet isolation*, where a surgical mask is required. These precautions should be maintained until the patient has received at least 48 hours of appropriate antibiotics and is clinically improving. Patients with draining buboes should be in contact isolation. Routine processing of clinical specimens can be performed in a Biosafety Level 2 (BSL-2) setting, but BSL-3 is necessary for high-risk procedures such as grinding and shaking.

* *Editor's Note*

Transcript reflects updated/corrected information.