Zoonosis Update

Plague: a veterinary perspective

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For most people, mention of plague conjures up images of an antiquated threat. Infection by the bacterium *Yersinia pestis* is most often associated with the infamous Black Death of the Middle Ages, a pandemic that cost Europe a third of its population in the 14th and 15th centuries.[1] Far from being a historic medical curiosity, this zoonotic disease continues to be a threat to the health of humans and animals in the western United States and throughout the world, including Eurasia, Africa, and North and South America.[2] In addition to rodents, a number of mammalian species have been found to be naturally infected with *Y pestis*, including lagomorphs, felids, canids, mustelids, and some ungulates. Between 5 and 15 human plague cases are reported each year in the United States. Although most humans with plague were exposed through a bite from an infected flea, others have become infected as a result of contact with infected wild animals such as rabbits and wild rodents and infected domestic cats.[3] By quickly recognizing and treating plague in domestic animals, veterinarians protect the health of companion animals, the people who care for them, and the surrounding community, playing a vital role in public health.

Organism

Yersinia pestis, the causative agent of plague, is a gram-negative, nonmotile member of the family Enterobacteriacae, which resembles a safety pin when stained with Wright, Giemsa, or Wayson stains.[2] The organism is sensitive to high temperatures and dry environments, but grows slowly even at an optimum temperatures (28°C [82°F]).[4] If cultures are discarded prior to 48 hours, a diagnosis of plague may be missed. Several types of media will support *Y pestis* growth, including nutrient broth, blood agar, and unenriched agar. The small (1 to 2 mm) gray colonies are nonmucoid and have a characteristic hammered copper appearance.[4] The differential expression of transmission and virulence factors, moderated by temperature and environment, allows *Y pestis* to survive in flea vectors, transmit readily to mammalian hosts, and propagate in the new host.[5] This adaptability has resulted in *Y pestis* enzootics in rodents on every populated continent except Australia.[4]

Ecology

Yersinia pestis is maintained in the environment by susceptible rodent species and their associated fleas. Dog and cat fleas (*Ctenocephalides* spp) may become infected with *Y pestis* but are not efficient vectors for the organism. In the southwestern United States, the rodent species important in maintaining enzootic transmission include prairie dogs (*Cynomys* spp), ground squirrels (*Spermophilus* spp), antelope ground squirrels (*Ammospermophilus* spp), chipmunks (*Tamias* spp), woodrats (*Neotoma* spp), and mice (*Peromyscus* spp).[2] In the Pacific coastal states, the important rodent species include ground squirrels, chipmunks, and wood rats. In other regions of the western United States, susceptible rodent species are less well-defined.[2] The principal vectors for plague in the western United States include prairie dog fleas (*Opisocrostis* spp), ground squirrel fleas (*Oropsylla montanus*, *Thrassis* spp, and *Opisocrostis* spp), and various species of woodrat and mouse fleas. Morbidity rates are substantial in rabbits and susceptible rodents, with mortality rates often approaching 100%. Fleas feeding on bacteremic animals ingest *Y pestis*, where the organism multiplies and blocks the gastrointestinal tract, preventing the flea from digesting and obtaining nutrition from blood meals. Blocked fleas regurgitate plague bacteria as they repeatedly attempt to feed, thereby inoculating the host with *Y pestis*. Fleas can survive for several months in abandoned rodent burrows, serving as a source of infection for potential hosts, including domestic animals.

Epidemiology

Plague is a seasonal disease, with most reported human cases occurring between March and October. *Yersinia pestis* is endemic to the western half of the United States and has been isolated as far east as Dallas and the western edges of Kansas, Nebraska, Oklahoma, and South Dakota. From 1970 to 2001, plague was reported in 377 humans in the United States; most cases were in New Mexico (201 cases), followed by Arizona (55), Colorado (42), and California (37).[a] Other states that have reported human cases of plague include Idaho, Nevada, Oklahoma, Oregon, Texas, Utah, Washington, and Wyoming. Approximately 15% of reported humans with plague die.[6]

Domestic animals such as cats and dogs are most

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The authors thank Drs. Katherine Feldman, Kenneth Gage, and David Dennis, Bacterial Zoonoses Branch, Division of Vector-borne Infectious Diseases, National Center for Infectious Diseases, Centers for Disease Control and Prevention, Fort Collins, Colo, for their assistance in preparation of this manuscript.

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likely to be exposed to *Y pestis* by contact with an infected rodent or rabbit or by the bite of an infected flea. Humans most commonly become infected as a result of being bitten by an infected flea,[2] although humans also acquire plague as a result of contact with secretions or tissues from infected animals. Respiratory droplet transmission can also occur person-to-person or cat-to-person from persons or cats with pneumonic plague. This route of exposure can result in primary pneumonic plague, one of the most dangerous clinical manifestations of plague.

Between 1977 and 1998, 23 humans from 8 western states were reported to have cat-associated plague; 5 (21.7%) died. Prior to 1977, cat-associated plague had not been documented in the United States. Six (26.1%) of the 23 infected humans were veterinary staff; the remainder were pet owners or other persons handling or caring for a sick cat.[3] Seventeen (73.9%) cat-associated human plague patients developed bubonic plague—2 died. One person developed septicemic plague and died. Most important, 5 cat-associated human patients developed primary pneumonic plague, and 2 died. These human patients were exposed to *Y pestis* by inhaling infectious respiratory droplets or infectious oral secretions from a cat with pneumonic plague. Prior to these cat-associated pneumonic plague cases, primary pneumonic plague had not been reported in humans since a 1924 epidemic in California in which human-to-human transmission was the route of infection.

When considering a diagnosis of plague in domestic animals, veterinarians should carefully question pet owners about risk factors for plague. The most important risk factor for cats may be hunting and eating rodents and rabbits.[7] Other risk factors for domestic animals (especially cats and dogs) include living in or visiting a rural area in an endemic region of the United States, having access to areas populated by wild rodents and rabbits, exposure to a rodent or rabbit carcass, and flea infestation. Pet owners will not be able to distinguish between rodent flea species and dog or cat fleas (*Ctenocephalides* spp). Fortunately, dog and cat fleas are quite rare in most plague-endemic areas of the western United States; therefore, finding fleas on pets in these areas is a cause for suspicion. Rodent fleas will only transiently parasitize a nonpreferred host species and will not be present in large numbers on dogs and cats, nor will they establish an infestation in dwellings or in yards. Veterinarians considering a diagnosis of plague in a domestic pet should also ask pet owners about the presence and recent disappearance of wild rodent populations around the home, particularly prairie dogs or ground squirrels. Sudden disappearance of a prairie dog colony, for example, may be evidence of a plague epizootic.

Pathogenesis

There are 3 clinical manifestations of plague: bubonic, septicemic, and pneumonic. Cats experience pathologic changes analogous to those that develop in humans, suggesting that the pathogenesis of plague in humans and cats is similar.[8] *Yersinia pestis* is usually introduced through the skin or mucous membranes by a flea bite or contact with infectious secretions or tissues. After inoculation, the organisms invade cutaneous lymphatic vessels and travel to regional lymph nodes.[6] Infected lymph nodes are called buboes; this localized infection is referred to as bubonic plague. In 7 cats experimentally infected with *Y pestis*, affected lymph nodes had necrosuppurative inflammation with obliteration of normal nodal architecture and numerous *Y pestis*.[8] The lymph nodes were characterized by hemorrhage, edema, fibrin, and acute necrotizing inflammation. Inflammatory debris and bacteria were found outside the lymph node capsule. A tremendous number of *Y pestis* bacteria were found in the lumen of blood and lymphatic vessels within and near affected lymph nodes. Secondary septicemic plague occurs when the infection disseminates beyond the affected regional lymph nodes, potentially involving many organs, including the spleen, liver, heart, and lungs. Disseminated intravascular coagulation can also occur. Septicemic plague in the apparent absence of one or more buboes is referred to as primary septicemic plague. Primary pneumonic plague develops as a result of inhaling infectious droplets of respiratory origin generated by a person or cat with pneumonic plague. Secondary pneumonic plague occurs as a result of hematogenous spread of *Y pestis* to the lungs secondary to bubonic or septicemic plague. In cats that developed pneumonia, pulmonary lesions included diffuse interstitial pneumonia, with lung architecture destroyed by coalescing areas of necrosis that in some cases formed an abscess.[8] Other histopathologic findings included bacteria and large numbers of neutrophils in the spleen and necrosis and multifocal hemorrhage of the adrenal gland cortex.

Clinical Manifestations

Plague causes a rapidly progressing febrile illness. Untreated, or treated inappropriately, bubonic plague will often advance to septicemic or pneumonic plague within days. The most common clinical form of plague in cats is bubonic plague.[9] Some cats will not develop signs consistent with classic bubonic plague; therefore, veterinarians must consider plague as a diagnosis in cats with signs of a systemic infectious process in conjunction with an appropriate history and risk factors for plague. Cats with bubonic plague will have fever, lethargy, anorexia, and a large lymph node that may or not may be abscessed and draining. Palpation of the large lymph node may elicit signs of extreme pain. The incubation period is 1 to 4 days.[9-11]

Three studies[8,10,11] have reported on the outcome and clinical illness in 25 cats experimentally exposed to *Y pestis*. Nineteen cats were exposed orally through ingestion of a laboratory mouse that had died of plague,[10,11] and 6 cats were exposed by SC inoculation.[8,10] The latter is believed to mimic exposure by fleabite. Of the 25 cats, 20 (80%) developed clinical illness, 3 (12%) did not develop clinical illness but developed measurable antibodies to *Y pestis*, and the clinical outcome was not specified for 2 (8%). None of the cats in these studies were treated with antimicrobials or supportive care. In cats that developed illness, rectal temperature peaked at 40.5 to 41.1°C (105 to 106°F) approximately 3 days after exposure.

Of the 16 clinically ill, orally exposed cats, 8 died. Ten developed enlarged, palpable lymph nodes in the head and neck region, 4 did not, and the outcome for 2 cats was not specified. Swollen lymph nodes were located in medial

retropharyngeal, submandibular, sublingual, and tonsillar regions and were evident by days 4 to 6 after exposure. *Yersinia pestis* was isolated from the throats of 15 of 16 and from the oral cavity of 5 of 13 orally exposed cats (culture of oral cavity specimens was not attempted for 3 cats).[11] Of the 6 SC exposed cats, 4 developed clinical illness, and illness status was not described in detail for 2 cats. Three of 6 cats died. None of the 6 SC exposed cats had palpably enlarged lymph nodes in the head or neck region, but 4 developed a subcutaneous abscess at the site of inoculation. *Yersinia pestis* was not isolated from the throats or oral cavities of 2 cats exposed SC; however, this information was not specified for the remaining 4 cats.

Findings from these studies indicate that cats with oral exposure are more likely to develop enlarged lymph nodes in the head and neck region, whereas cats exposed by fleabite do not. In a retrospective review of cats with plague in New Mexico, Eidson et al[9] found that 63 of 119 (53%) cats had bubonic plague. Most of the cats with enlarged lymph nodes, 50 of 67 (75%), had submandibular lymphadenopathy. These observations support the long-held theory that cats are more frequently exposed to *Y pestis* by an oral route than by fleabite.[8,9] This observation has important implications for prevention of plague in cats.

Similar to bubonic plague in humans, most cats with bubonic plague will develop lymphadenitis in a single lymph node or single cluster of nodes; symmetrically affected lymph nodes are uncommon. Abscesses caused by *Y pestis* cannot be grossly distinguished from abscesses induced by other causes such as bite wounds, although the presence of puncture wounds over the abscessed area may provide evidence of trauma.[9] Other lesions that have occurred in cats with plague include oral and lingual ulcers or abscesses, abscesses in locations other than lymph nodes, ocular discharge, vomiting, diarrhea, dehydration, cellulitis, and weight loss.[9]

Cats with primary septicemic plague will develop fever, lethargy, and anorexia but no obviously enlarged or abscessed lymph nodes. In addition, these cats will have signs of sepsis including vomiting, diarrhea, tachycardia, pale or brick-red mucous membranes, cold extremities, weak pulse, prolonged capillary refill time, disseminated intravascular coagulopathy, and respiratory distress syndrome. Primary pneumonic plague has not been documented in cats. Cats with secondary pneumonic plague pose a serious public health risk of direct respiratory transmission of infectious droplets to the people caring for them. In humans, meningitis is a rare form of the disease that has not been documented to occur in domestic animals.

Although less likely to develop clinical illness than cats, dogs with plague can also have clinical illness. Of 10 dogs experimentally infected with *Y pestis* by oral exposure, all developed transient mild to moderate fever; 2 of the most severely affected dogs had a rectal temperature of 40.5°C for 72 hours.[10] Signs of infection have been documented in 3 naturally infected dogs in New Mexico.[12] In these 3 dogs, clinical signs included fever, lethargy, submandibular lymphadenitis, a purulent intermandibular lesion, oral cavity lesions, and cough. In dogs, antibodies to the F1 antigen of *Y pestis* appear by day 8, peak by day 21, and decline by day 100 after exposure. This characteristic, combined with their relative resistance to clinical illness, makes dogs useful sentinels for plague activity.[10]

Of the domestic livestock species common in the United States, cattle, horses, sheep, and pigs are not known to develop plague.[2] Goats and camels with plague develop clinical illness, and there have been human outbreaks of plague attributable to ingestion of *Y pestis*-infected camel meat in several Middle Eastern countries. In 1999, a llama died of plague in New Mexico.[b] Evidence of infection in wild species other than rodents has been reported[2] in mule deer, prong-horned antelope, and nonhuman primates. Other wild species that appear to be resistant to plague-induced illness include foxes, bears, raccoons, and skunks. Wild cats such as mountain lions and bobcats are thought to have morbidity and mortality rates similar to those in domestic cats.

Diagnosis

The primary differential diagnoses for plague are tularemia, injuries resulting in abscess formation (eg, catfight bite wounds in cats), and other causes of infection (eg, *Staphylococcus aureus*, group A β-hemolytic streptococcal infections).[6] To definitively diagnose plague, appropriate clinical specimens should be submitted to a public health laboratory. There are no laboratory tests specific for plague that can be done in a veterinary clinic laboratory. Performing a Gram stain of the exudate from an abscess can assist with distinguishing whether an abscess is associated with plague, cat bite, or other trauma. Draining material from an abscess resulting from *Y pestis* infection should reveal a nearly homogenous population of gram-negative organisms, whereas material from a cat bite-induced abscess will be a mixture of organisms found in the oral cavity of cats.[13] Giemsa or Wayson stains are used in diagnostic laboratories to look for gram-negative, bipolar coccobacilli as a screening evaluation for *Y pestis*; however, the results of this test can be unreliable when performed by untrained or inexperienced laboratory personnel. Expertise for conducting tests for plague is primarily limited to state public health laboratories in plague-endemic states and the national **Centers for Disease Control and Prevention (CDC)** plague laboratory.

During the acute phase of the disease, the most valuable diagnostic information will come from detecting *Y pestis* antigen in secretions or tissues. If possible, diagnostic samples for antigen detection should be taken before antimicrobials are administered; however, samples should still be taken and submitted for testing if antimicrobial treatment has already been initiated. Samples should be placed on ice or frozen and shipped overnight, but they should not be placed in a preservative. Preferred antemortem samples are lymph node aspirates, swabs of any draining lesions, or a swab of the oral cavity of cats with oral lesions or of the pharyngeal region of cats with pneumonia. If no fluid can be aspirated from a bubo, 1 mL of nonbacteriostatic saline solution can be injected into the bubo and aspirated back into the syringe. Bacteriologic cultures of blood have been useful in diagnosing plague in human patients, and their use is encouraged in animals. If an animal is suspected to have died from plague, the entire carcass can be submitted for testing. Alternatively, samples of liver, spleen, lung (for animals with pneumonia), and affected lymph nodes can be submitted for test-

ing. Antigen detection will initially consist of a screening fluorescent antibody test that detects the F1 antigen on *Y pestis* cells. The fluorescent antibody test is the most sensitive and specific test that can be done rapidly (within hours). *Yersinia pestis* grows slowly, requiring up to 48 hours for visible growth. Presumptive cultures of *Y pestis* are confirmed by use of biochemical profiling and susceptibility to bacteriophage lysis.

Early in the course of disease, results of serologic tests are often negative because animals have not yet seroconverted; therefore, an acute serum specimen should be collected but held for testing until a convalescent serum sample can be obtained 2 to 3 weeks after illness onset. Serologic confirmation of plague requires demonstrating a 4-fold increase in antibody titer between acute and convalescent samples. Eidson[9] recommended that a single titer of 1:32 or greater, accompanied by signs consistent with plague, is also supportive of a diagnosis of plague. Serologic testing for antibodies against the F1 antigen of *Y pestis* is performed by use of either an ELISA or passive hemagglutination.

The state health department should be contacted prior to sending samples to the state public health laboratory. In the event that a state public health laboratory is unable to perform necessary tests, samples can be tested at the CDC.[c] The state health department and CDC should be contacted by telephone before sending samples for diagnostic testing to CDC.

Treatment

Treatment should be initiated quickly and prior to obtaining a definitive diagnosis in an animal in which plague is suspected. Prompt initiation of appropriate antimicrobial treatment is essential. Human deaths from plague usually occur because of delays in treatment with appropriate antimicrobials either because of a delay in seeking medical care or misdiagnosis by health care providers. The treatment of choice for humans with plague is streptomycin[6]; however, this drug is not available for veterinary use. Gentamicin has been used successfully to treat humans with plague[6] and is the drug of choice in veterinary medicine, particularly for seriously ill animals. Doxycycline is an appropriate choice for less complicated cases. Other treatment options include tetracycline and chloramphenicol. Sulfonamides can be used but only if other antimicrobials are not available. The recommended duration of treatment is 10 to 21 days; rapid improvement including defervescence should be expected within 3 days.[6,13] Penicillins are not effective in treating plague, despite having in vitro activity against *Y pestis*. The fluoroquinolones ofloxacin and ciprofloxacin were comparable to streptomycin in treatment studies of mice exposed to *Y pestis*.[14-16] However, there are no data regarding the performance of these fluoroquinolones in a clinical setting in either human or veterinary medicine; therefore, fluoroquinolones are not recommended at this time.

Because of the risk of disease transmission to their owners, cats should not be sent home immediately but should be hospitalized, especially if there is evidence of pneumonia. Sending a cat with suspected plague home with oral medications poses a substantial risk to the person caring for the ill cat. Human plague cases have occurred in pet owners, and in some cases were attributable to contact with the oral cavity and associated secretions while administering oral medications to cats with plague.

The duration of infectivity in treated cats has not been studied, but similar to humans with plague, cats are believed to be noninfectious after 72 hours of appropriate antimicrobial treatment with evidence of clinical improvement. When signs of clinical improvement are evident, route of administration of antimicrobials may be changed from parenteral to oral.

Prevention and Public Health Considerations

When an animal is suspected to have plague, 2 critical issues need to be addressed quickly in addition to caring for the sick animal: protection of persons who will have contact with the infected animal and the initiation of public health interventions. While caring for an animal hospitalized because of suspected plague, veterinary hospital staff should implement isolation precautions for their own protection. The risk of nosocomial transmission may be highest before a definitive diagnosis can be made[17]; therefore, droplet precautions plus eye protection should be implemented in staff caring for animals with known or suspected plague until pneumonia has been excluded or until the animal has been treated for 72 hours and there is evidence of clinical improvement.[18] Humans have developed primary pneumonic plague through droplet transmission from cats with pneumonic plague. After pneumonia has been ruled out or there is evidence of clinical improvement after 72 hours of treatment, standard precautions are sufficient for hospitalized animals with plague.

Droplet transmission may occur with microorganisms that can be transmitted in large-sized droplets (larger than 5 μm in size) and requires close contact (less than 2 meters for *Y pestis*) between the source and recipient persons.[17] Droplets may be generated during coughing, sneezing, or procedures such as suctioning. Droplets do not remain suspended and do not require special air handling or ventilation to prevent transmission.[17] Droplet precautions are used in addition to standard precautions and include physically separating the infected animal from other animals or animal cohorting, wearing a surgical mask when working within 2 meters of the patient, and limiting movement of the infected animal within the hospital.

Standard precautions are the first tier of isolation precautions and are designed for the care of all hospitalized animals, regardless of their diagnosis.[17] These precautions include washing hands before and after contact with each animal; using gloves when touching blood, body fluids, secretions, excretions, and contaminated items; washing hands immediately after gloves are removed; using gowns, surgical masks, and eye protection or a face shield during procedures that are likely to generate splashes or sprays of blood, body fluids, secretions, and excretions; handling used patient-care equipment and linen soiled with blood, body fluids, secretions, and excretions in a manner that prevents skin and mucous membrane exposures, contamination of clothing, and transfer of microorganisms to other patients and environments; and ensuring that the hos-

pital has adequate procedures for the routine care, cleaning, and disinfection of environmental surfaces.[17,18] Readers interested in further information regarding isolation precautions in hospitals are referred to the CDC Web site www.cdc.gov/ncidod/hip/ISOLAT/Isolat.htm.

The second critical issue to address quickly is the initiation of public health interventions. The diagnosis of suspected plague in a domestic animal could be the sentinel event indicating there is an epizootic of plague in rodent populations in or near a community. Therefore, it is critical that county or state public health officials be notified promptly when plague is suspected in a domestic animal. Public health officials will follow-up with potentially exposed persons to assess the need for fever watch versus prophylactic treatment with antimicrobials. A fever watch consists of possibly exposed individuals taking their temperature orally 1 or 2 times daily for the duration of the incubation period. Public health officials may choose to conduct an investigation to determine the location and extent of the rodent epizootic and notify the community through public health advisories and press releases. Community awareness of plague activity is essential in preventing human plague cases and deaths. In some states, plague in animals is reportable to the state veterinarian's office.

To minimize the exposure of pets to *Y pestis*, pet owners in plague-endemic areas should be advised to limit unsupervised roaming of pets, limit their pet's hunting activities (especially cats), limit pet contact with rabbit and wild rodent carcasses, and apply a flea control product according to label directions to outdoor pets. Although dog and cat fleas are not efficient vectors of plague, pets that roam may bring *Y pestis*-infected rodent fleas into the household. Following these protective measures is especially important during the most common period of plague transmission (March through October). All ill animals, especially cats, should be seen by a veterinarian.

Bioterrorism and Plague

The same qualities that make plague a serious natural threat also make it a potential biological weapon. With its ability to spread via aerosol transmission and high mortality rates in pneumonic cases, plague has been classified as a Category A Critical Biological Agent by the CDC.[19] Both the United States and the former Soviet Union investigated the use of plague as a biological weapon during the Cold War.[20] The events of the fall of 2001 heightened the need to understand potential bioweapons such as *Y pestis*.

As an intentional release of *Y pestis* would most likely be through aerosol dissemination, the outbreak would not resemble the naturally acquired cases seen in the United States.[21] Large numbers of people would develop severe respiratory illness that would be seen 1 to 6 days after exposure. These humans would appear to have community-acquired pneumonia, with symptoms including chest pain, cough, hemoptysis, and fever. Outbreaks might occur in parts of the United States that typically do not experience plague and with no preceding rodent deaths. In addition, cats could become infected, posing an additional risk to humans. A delay may occur in recognizing plague as more common respiratory illnesses such as Legionnaires' disease may be suspected. Working groups, with members from academic and government institutions, have developed guidelines for prophylactic antimicrobial treatments in contained as well as mass-casualty settings.[21] For these treatment and control measures to be effective, health professionals must maintain high levels of suspicion for diseases not typically encountered and act rapidly to arrive at correct diagnoses.

[a]Enscore R, Centers for Disease Control and Prevention, Fort. Collins, Colo: Personal communication, 2002.
[b]Ettestad P, New Mexico Department of Health, Santa Fe, NM: Personal communication, 2002.
[c]Centers for Disease Control and Prevention, Fort Collins, Colo.

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