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CHAPTER 41

Plague

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INTRODUCTION

Plague is an uncommon but life-threatening zoonosis caused by the Gram-negative bacillus *Yersinia pestis*. Humans acquire infection through the bite of infected rodent fleas, by handling or ingesting infected animal tissues, or by inhaling contagious airborne particles. Most human infections occur in rural areas of the developing world, where sanitation is poor and humans live in close association with rodent reservoirs. The principal clinical forms of plague are bubonic, septicemic, and pneumonic. Bubonic and septicemic plague account for approximately 80% and 15% of primary cases, respectively. Pneumonic plague can occur as a primary infection but more often develops as a complication of bubonic or septicemic plague. All forms of plague can be cured if diagnosed and treated promptly; however, even short delays can lead to overwhelming endotoxemia, organ failure, and death.

Plague has caused three major pandemics over the past 1500 years. The "Justinian" pandemic began in the mid sixth century AD and killed an estimated 40 million persons while spreading from central Africa to the Mediterranean, Europe, and Asia Minor. The second pandemic began in the fourteenth century in Central Asia and traveled along caravan routes to reach the Near and Middle East. Entering Messina by ship in 1347, the "Black Death" spread swiftly through Europe and the British Isles. Although some historians contend that this rapid advance suggests an alternative etiology,[1] recent evidence from archeological and transmission studies strongly supports the role of *Y. pestis* as the cause of the Black Death.[2–4] Medieval plague persisted in Europe for several centuries and is thought to have killed a quarter or more of some affected populations.

The last global surge of plague, the third or so-called modern pandemic, arose in the latter half of the nineteenth century in Yunnan Province, China. It struck Hong Kong and from there spread by rat-infested steamships to port cities throughout the world, including several in the United States. [5–7] It was in Hong Kong that Alexandre Yersin established the etiology of plague by isolating the plague bacillus from enlarged lymph nodes of plague victims in 1894.[8] Four years later in Bombay, Paul-Louis Simond identified the plague bacillus in the tissues of dead rats; he subsequently proposed that rat fleas transmitted the bacillus from rat to rat, and from rats to humans. Within 30 years of its appearance, the third plague pandemic resulted in 26 million human cases and more than 12 million deaths, most of them in India.[5]

After 1900, the global spread of plague was limited by regulations that controlled rats in ports and imposed inspection and rat-proofing of ships. *Y. pestis* did, however, become newly established among urban and rural rodent populations in many previously unaffected areas of the Americas, Europe, Africa, and Asia, resulting in scattered zoonotic foci that still exist throughout the world.[9,10] In San Francisco, between 1900 and 1908, major outbreaks of rat-borne plague killed more than 200 persons. By 1908, plague was epizootic among ground squirrels in counties surrounding the city,[7] and in subsequent years spread to wild rodent populations throughout California and other states in the western third of the country. The last outbreak of urban plague and of person-to-person pneumonic transmission in the United States occurred in Los Angeles in 1924–1925. By the middle of the twentieth century, cities in the United States and elsewhere had enforced higher sanitary standards and building codes, effective insecticides and rodenticides had become widely available, and several classes of antibiotics had been shown to be efficacious in treating plague. Most human plague since then has been sporadic and rural in distribution. Outbreaks have been relatively slow to develop and readily controlled by a combination of surveillance, early diagnosis and treatment, and flea and rat suppression.[11] The major exceptions to this generalization were the large rat-borne plague epidemics that occurred from 1962 to 1975 in war-torn Vietnam and in the 1990s in Madagascar.[12,13]

Plague can be prevented through steps to reduce risks of exposure, and outbreaks can be readily halted using standard public health measures. Cases should be reported immediately to local health authorities so that appropriate investigative and control measures can be implemented promptly. Routine reporting of plague cases is not required under World Health Organization (WHO) international health regulations; however, individual cases and outbreaks must still be reported if, as in the case of pneumonic plague, they potentially constitute an international concern.[14] Concern has been raised over plague as a potential weapon of terrorism, and *Y. pestis* has been classified as a Category A select agent subject to federal laws governing its management and transport. Medical and public health response plans have been developed to counter the threat of an intentional release.[15]

THE AGENT

Y. pestis is a nonmotile, nonsporulating, Gram-negative coccobacillus in the family Enterobacteriaceae.[6,16] It is microaerophilic, nonfastidious, oxidase- and urease-negative, non-lactose-fermenting, and biochemically unreactive. *Y. pestis* grows slowly but well on a wide variety of common media (e.g., brain-heart infusion broth, sheep blood agar, chocolate agar, and MacConkey agar). Growth occurs across a wide range of temperatures (4–40°C) and pH (5.0–9.6), but is optimal at 28°C and pH 7.4. In the environment, *Y. pestis* is rapidly killed by temperatures above 40°C and by desiccation. Incubation at 37°C for 24 hours on agar yields pinpoint, transparent colonies that are easily overlooked, especially if there is contamination of the culture by other bacteria. At 48 hours, colonies are typically gray, 1–2 mm in diameter, and have an irregular "hammered metal" appearance when viewed under magnification. In broth, *Y. pestis* grows in flocculent clumps, typically attached to the sides of the tube in downwardly projecting stalactite forms that leave a clear broth. With polychromatic stains such as Wayson, Wright, or Giemsa, plague bacilli from clinical specimens demonstrate a characteristic bipolar appearance resembling closed safety pins (***Fig. 41.1***). Although not

truly encapsulated, *Y. pestis* produces an envelope that contains the unique fraction 1 (F1) glycoprotein surface antigen. Diagnostic specimens can be safely handled under Biosafety Level 2 (BSL-2) procedures, but manipulation of isolates requires BSL-3 measures to adequately protect laboratory workers.[16]

Genomic studies suggest that the plague bacillus evolved from *Y. pseudotuberculosis* as recently as 1500 to 20 000 years ago.[17–19] This transition from enteric to flea-borne pathogen was made possible by the acquisition of several virulence factors that allow survival in rodents, humans, and fleas.[6,20–22] Most of these virulence factors are encoded on three plasmids, of approximate sizes 9.5, 70, and 110 kb. The 9.5 kb plasmid (pPCP1) encodes a bacteriocin (pesticin) that promotes iron uptake and a temperature-dependent plasminogen activator (Pla). At ambient temperatures, the plasminogen activator protease facilitates the formation of a bolus of blood and aggregated bacteria in the flea midgut, which blocks the flea's proventriculus and leads to regurgitation of infective material when the "blocked" flea attempts to feed. The 70 kb plasmid (pCD1 or pLcr) encodes gene products active in low calcium environments. These products include *Yersinia* outer surface proteins (Yops) and soluble V antigen, thought to be essential to *Y. pestis* survival in macrophages. The Yop virulon includes a type III secretory system that injects Yop effector proteins into the cytosol of eukaryotic cells. These factors downregulate the immune response of macrophages, epithelial and endothelial cells, and induce apoptosis by blocking signaling pathways.[23] The 110 kDa plasmid (pFra or pMT1) contains genes for the F1 envelope glycoprotein antigen and a murine exotoxin. F1 antigen is produced only by organisms growing at 30°C or greater. *Y. pestis* strains expressing F1 antigen are able to resist phagocytosis in the absence of opsonizing antibodies. The murine toxin (Ymt) is highly toxic to mice and rats, but is not known to be toxic in humans. In the flea midgut, Ymt plays a critical role in protecting *Y. pestis* from a cytotoxic digestion product of blood plasma.

Chromosomally encoded virulence factors include a lipopolysaccharide endotoxin and a pigment factor, the hemin storage locus (*hms*) that regulates the absorption of exogenous iron. When *Y. pestis* is grown on media with Congo red, a heme-analog dye, iron absorption is indicated by pigment production. Strains that do not produce pigment have diminished virulence in mammals and are unable to induce blocking in the flea gut. Hemin storage locus products expressed in the low temperature (28°C or less) environment of the flea assist in forming blockage of the flea gut necessary for efficient transmission.[21,22] An additional chromosomally encoded product, the pH 6 antigen (Psa), inhibits phagocytosis of *Y. pestis* in mammals.

Y. pestis isolates have been classified into three biotypes based on their ability to ferment glycerol and reduce nitrate: Antiqua, Medievalis, and Orientalis. Relict populations of the Antiqua biotype are found in Africa, southeastern Russia, and central Asia; the Medievalis biotype is found around the Caspian Sea; and the Orientalis biotype occurs in Asia and the Western hemisphere. Although these phenotypes have been thought to reflect strains associated with the first, second, and third pandemics, respectively,[24] studies using multiple molecular techniques suggest that *Y. pestis* isolates represent up to eight genetically distinct populations that do not correlate entirely with biovar.[17] Limited archeological evidence suggests that all three pandemics were caused by strains of the Orientalis phenotype.[25]

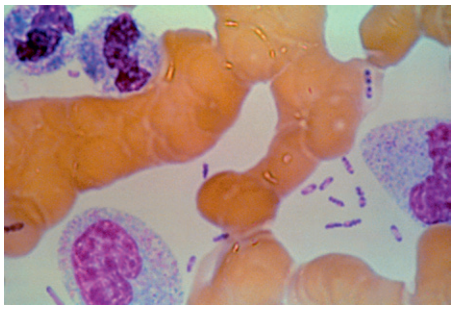

Figure 41.1 Peripheral blood smear from a patient with plague septicemia, showing characteristic bipolar-staining *Y. pestis* (Wright stain, oil immersion).

EPIDEMIOLOGY

Plague foci are distributed throughout the world (***Fig. 41.2***) and involve a diverse array of host and vector species[10,26–29] (***Box 41.1***). Transmission among rodents and fleas is often described in terms of enzootic and epizootic cycles (***Fig. 41.3***).[10,27,28] Enzootic cycles help sustain the organism over time and involve relatively resistant rodent species living in remote,

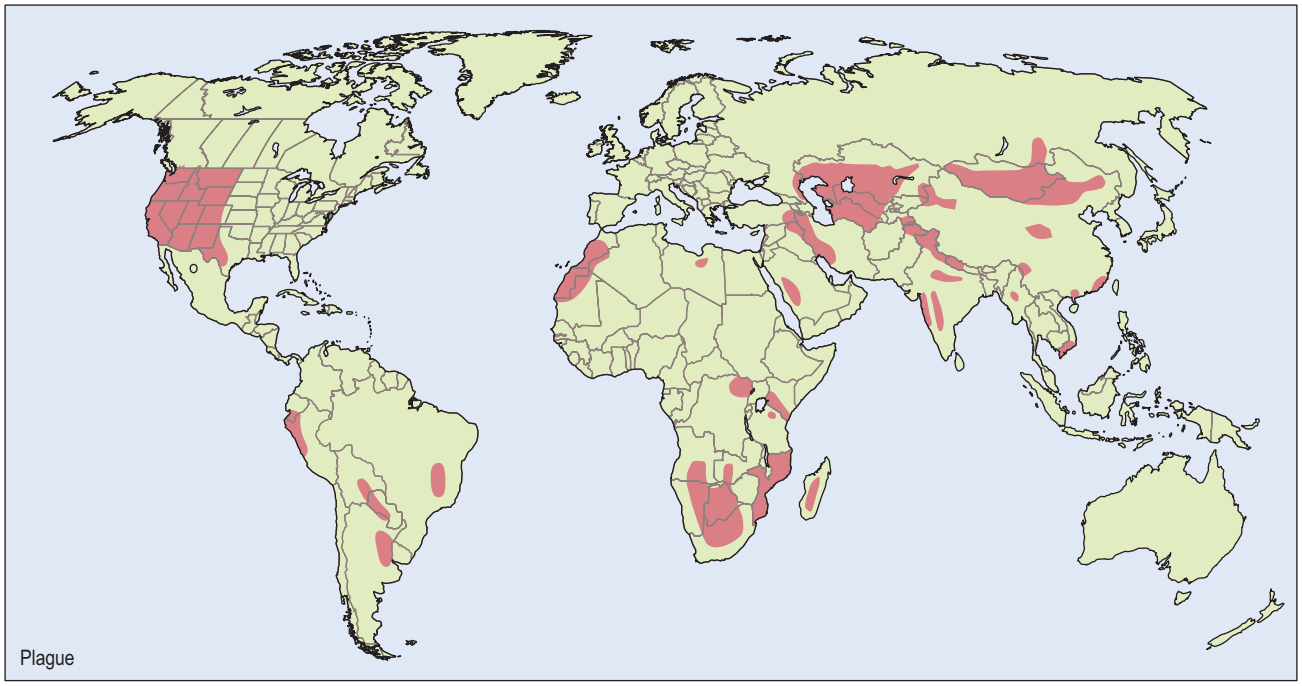

Figure 41.2 Global distribution of known plague foci.

Box 41.1 Plague Foci

North American Plague Foci

Wild rodent plague has been reported west of the 100th meridian in 17 contiguous western states and in some areas of adjacent Canada and Mexico.[9,30] The major plague sites are the southwestern focus, comprising mainly semi-arid grassland plateaus, foothills, and forested uplands of northeastern Arizona, most of New Mexico, southern Utah, and southern Colorado; the Pacific Coast focus, comprising mostly valley grassland, foothills, and the montane habitat of California and southern Oregon; the Great Basin focus, encompassing parts of Utah, Nevada, and southern Idaho; and the Rocky Mountain and northern focus, comprising mostly northern Colorado, Wyoming, and Montana.[9,29] The principal rodent hosts in the southwestern focus are various burrowing ground squirrels (*Spermophilus* spp.), prairie dogs (primarily *Cynomys gunnisoni*), wood rats (*Neotoma* spp.), antelope ground squirrels (*Ammospermophilus* spp.), deer mice (*Peromyscus maniculatus*), and related species. The major rodent hosts in the various niches of the Pacific Coast focus include *Spermophilus* spp., especially the California ground squirrel (*S. beecheyi*), the golden-mantled ground squirrel (*S. lateralis*), chipmunks (various *Tamias* spp.), deer mice and other *Peromyscus* spp., and voles (*Microtus* spp.). Other important hosts in the United States include various small ground squirrels (*S. elegans*, *S. beldingi*, and *S. townsendi*) in the Rocky Mountain and Great Basin regions, and the black-tailed prairie dog (*Cynomys ludovicianus*) in the Great Plains region. Epizootics of plague have recently occurred in urban tree squirrel (*Sciurus niger*) populations in cities along the eastern foothills of the Colorado Rocky Mountains, but pose a small risk to humans because these squirrels are parasitized by nonanthropophagic fleas. Since 1950, a few cities in the United States have rarely been found to have *Y. pestis*-infected rats (e.g., Tacoma, San Francisco, Los Angeles, Dallas). However, no widespread epizootics or human plague cases have resulted, possibly because the rats have been infested with only small numbers of fleas or with flea species that are inefficient vectors of *Y. pestis.* The principal fleas transmitting plague among wild rodent epizootic hosts in the United States include various ground squirrel fleas (*Oropsylla montana* (*Diamanus montanus*), *Hoplopsyllus anomalus, Thrassis* spp., *Opisocrostis* spp., *Oropsylla idahoensis*), prairie dog fleas (*Opisocrostis* spp.), wood rat fleas (*Orchopeas* spp.), and chipmunk fleas (*Eumolpianus eumolpi*).[9,29] *O. montana* is the most important vector of *Y. pestis* to persons in the United States because it is a competent host that readily feeds on a wide range of rodents, and on other mammals, including humans.

South American Plague Foci

In South America, active enzootic plague foci exist in Brazil, Bolivia, Peru, and Ecuador, and have been described previously in Paraguay, Argentina, and Venezuela. *Y. pestis* infection in these foci has been variously found in commensal rats (*Rattus* spp.), cotton rats (*Sigmodon* spp.), rice rats (*Oryzomys* spp.), field mice (*Akodon* spp.), cane mice (*Zygodontomys* spp.), wild cavies, and domesticated guinea pigs (*Cavia* and *Galea* spp.).[5,28] Domestic guinea pigs are reared in homes for food in the Andean region and are considered a potential commensal risk of infection to humans; human plague outbreaks in the Andean region, including a recent extensive bubonic plague epidemic in northern Peru and a mixed bubonic/pneumonic plague outbreak in Ecuador, have been suspected to be associated in the domestic environment with infected guinea pigs as well as *R. rattus.* A previously active plague area in northeastern Brazil has been quiescent over the past 20 years. The various fleas that serve as principal vectors in South American foci are *X. cheopis* on *Rattus* spp. and *Polygenis* and *Pleochaetis* spp. on wild rodents. *Pulex irritans,* the human flea (which also parasitizes domesticated guinea pigs), has been implicated as a potential transmitter of plague to humans in some Andean outbreaks.

African Plague Foci

Widely scattered active plague foci exist in East and southern Africa, including Democratic Republic of the Congo (previously Zaire), Uganda, Kenya, Tanzania, Zambia, Zimbabwe, Mozambique, Botswana, South Africa, Namibia, and Angola, and on the Indian Ocean island of Madagascar.[5,10,28,31] Less active foci exist in some northern African states (e.g., Libya, Algeria). The principal wild rodent hosts in Africa include gerbils (*Tatera* and *Desmodillus* spp.), swamp rats (*Otomys* spp.), various grass mice (*Arvicanthis* spp.), multimammate rats (*Mastomys* spp.), and commensal rats (*Rattus* spp.). One scenario describes plague in grassland gerbil populations spreading to multimammate rats in agricultural fields, and then to commensal rats in villages, resulting in human plague outbreaks. The principal flea vectors of wild rodent hosts are *Xenopsylla* and *Dinopsyllus* spp., while *X. cheopis* and *X. braziliensis* are the principal flea species involved in transmission among commensal rats and to humans.

Asian Plague Foci

The most important Eurasian plague hosts are gerbils (various *Meriones* spp.) in Iran, Kurdistan, Transcaucasia, other areas around the Caspian Sea, and the plains of southeastern Russia and Kazakhstan; marmots (*Marmota* spp.) in Central Asia, including mountainous Khazakstan, northeastern China, Mongolia, Manchuria, and in Transbaikalia; and ground squirrels (*Spermophilus* spp.) in Mongolia, northern-central China, the central Asian plains and steppes, and some areas around the Caspian Sea.[5,10,28] The primary flea vectors on gerbils are *Xenopsylla* and *Nosopsyllus* spp.; on marmots, various *Oropsylla*, *Rhadinopsylla*, and *Citellophilus* spp.; and on ground squirrels, *Citellophilus* and *Neopsylla* spp.

In India, the gerbil, *Tatera indica*, has been described as the principal wild rodent maintenance host.[5,10,28] Although it lives principally in open grassland sites in its natural state, it does invade agricultural fields and village peripheries. Other maintenance hosts include *Mellardia meltada*, various field mice, and palm squirrels (*Funambulus* spp.). The important commensal rat species are *Bandicota bengalensis*, *B. indica*, *R. rattus*, and *R. norvegicus.* Investigations in Maharashtra in western-central India suggest that *Y. pestis* may spread from reservoir gerbil populations in open grasslands to peridomestic *R. rattus* populations through intermediary populations of bandicoot rats (*B. bengalensis*). The primary vectors of plague in India are *X. cheopis* and *X. astia.*

The principal rodent hosts in Myanmar, Vietnam, and Indonesia are *R. rattus* subsp. *diardii* and the Polynesian rat (*R. exulans*).[5,10,28] *R. rattus* subsp. *flavipectus* is an important host in southern China. *R. norvegicus* and the bandicoot *B. indicus* have been described as important hosts in Vietnam. The shrew, *Suncus murinus*, has been described as a possibly important host of plague in Vietnam and Indonesia. *X. cheopis* is the principal vector of plague in southern China, Myanmar, Vietnam, and Indonesia; *X. astia* (a less efficient vector) is also found on rats in Myanmar and Vietnam. *Stivalius cognatus*, a rat flea, is considered to be an important secondary vector of plague in Indonesia.

sparsely populated areas. In enzootic cycles, infection spreads slowly, mortality among rodent populations is unremakable, and the risk of human infection is generally low. In contrast, epizootic cycles are characterized by rapid transmission among highly susceptible rodent hosts, resulting in mass die-offs of rodent populations and accelerated dispersal of infected fleas. Epizootics among rodent populations living in close proximity to humans pose an increased risk of human infection. Of particular concern are epizootics involving the commensal black and Norwegian rats (*Rattus rattus* and *R. norvegicus)* and their highly efficient rat flea vectors (*Xenopsylla cheopis* and *X. braziliensis*).[5,10,11] These species are adapted to live intimately with humans and historically are thought to have played an important role in pandemic spread of plague.

Humans are incidental hosts who become infected through the bite of infected rodent fleas, by handling or ingesting infected animal tissues, or

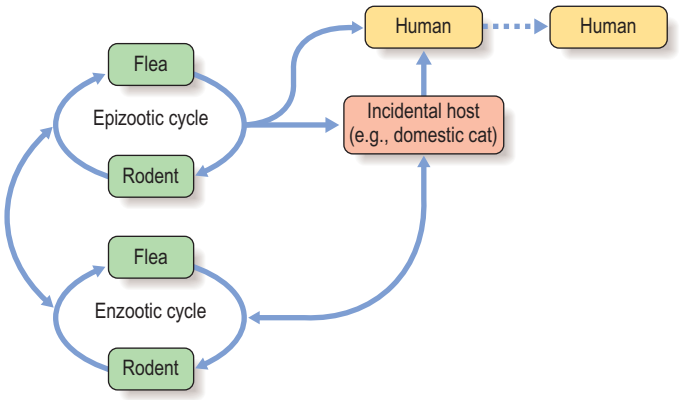

Figure 41.3 Plague transmission cycles demonstrating hosts and principal routes. *Y. pestis* usually cycles between rodents and fleas in enzootic (maintenance) or epizootic (amplifying) cycles. Infection may be transmitted to humans or other incidental mammalian hosts through flea bites or through direct contact with or consumption of infected animal tissues. Pet dogs and cats may further promote transmission by bringing infective rodent fleas into the home environment. Plague pneumonia can be transmitted from one person to another or from cats to humans through infective respiratory droplets.

Figure 41.4 Right inguinal bubo with surrounding edema.

by inhaling contagious airborne particles. The risk of human infection varies with environmental circumstances and human behaviors. Low socioeconomic status is an important risk factor because infestation by rats and their fleas is associated with poor housing and unsanitary conditions. In addition, humans may be exposed through contact with other, incidentally infected domestic and wild mammals. Cats are highly susceptible to plague and can transmit infection to humans through respiratory secretions, resulting in primary pneumonic plague.[32,33] Dogs are relatively resistant to illness but may still play a role in human infection by transporting rodent fleas into the domestic environment.[34] For example, a recent study in New Mexico found that plague patients were significantly more likely than controls to have allowed dogs to sleep on their bed at night.[35] Hunters may become infected through direct inoculation while skinning or otherwise handling carcasses of infected rodents, rabbits and hares, domestic and wild felids, and coyotes.[10,32,36] This is a particular risk among marmot hunters in Mongolia and northeastern China.[37] Direct inoculation is associated with an increased risk of septicemia and a high fatality rate. Ungulates, including antelope, deer, camels, dromedaries, and goats, are also susceptible to plague; handling and ingesting undercooked meat of these animals has been responsible for limited human plague outbreaks in northern Africa, the Middle East, and Central Asia.[38] Once infected, humans with pneumonic plague pose a risk for person-to-person transmission, a risk that is enhanced in the cramped living quarters of nomadic hunters and impoverished populations.

Routine reporting of plague cases to the WHO was discontinued after 2003. During the 15-year period from 1989 to 2003, a total of 38 359 human cases (approximately 2500 cases a year) and 2845 deaths (7%) were reported to the WHO by 25 countries.[39] Nearly 80% of cases were reported from Africa, 15% from Asia, and the remainder from the Americas. Countries reporting more than 1000 cases include Madagascar, Tanzania, Democratic Republic of the Congo, Vietnam, Mozambique, Namibia, and Peru. A recent report of human plague in Algeria, 50 years after the last occurrence, underscores the potential for reemergence.[39] In Madagascar, outbreaks have occurred in coastal urban as well as rural highland areas.[13,40] In the tropics, plague incidence usually peaks in the cooler, moist months of the year. Following the extraordinary epidemics of pneumonic plague involving tens of thousands of cases in Manchuria in the period 1910–1926, pneumonic plague outbreaks around the world have occurred only sporadically, usually involving three or fewer generations of cases, and typically affecting family members, close friends, and care providers of pneumonic plague patients. The 1994 outbreak of reported pneumonic plague in Surat, India, probably involved fewer than 100 cases.[41] Small clusters of cases of pneumonic plague have more recently been reported from China, Ecuador, Madagascar, and northern India.

In the United States, 447 plague cases (~9 cases per year) and 65 deaths (15%) were reported during 1960–2008[42] (Centers for Disease Control and Prevention (CDC), unpublished data). Although plague in animals occurs in 17 of the contiguous western states, more than 80% of human cases are reported from the southwestern states of New Mexico, Arizona, and Colorado, and approximately 10% from California.[32,43] In the United States, flea-borne plague is highly seasonal, occurring most often between May and October; winter plague cases are uncommon and usually associated with hunting. More than half of plague exposures in the United States are thought to occur in the general area of patients' homes.[36] This is particularly true in the southwest, where homes in rural and semi-rural areas are often situated near habitats of highly plague-susceptible animals, such as prairie dogs, rock squirrels, and woodrats.[10] In the Sierra Nevada mountains of California and Nevada, epizootic plague in chipmunks and ground squirrels is a risk to visitors to public parks. Hikers, campers, and hunters throughout the western United States have a small but definite risk of exposure, especially in the warmer months of the year.

THE DISEASE

Plague takes several clinical forms depending in part on the route of exposure.[5,15,44,45] The most common primary form is bubonic plague, which accounts for 80–85% of cases in the United States. An additional 15% of patients present with septicemic plague, and 1–3% with pneumonic or other forms of plague.[15] The usual incubation period for all forms is 2–7 days, but can be as short as 1 day for patients with primary pneumonic plague.

Bubonic Plague

Bubonic plague typically begins with fever (38–40°C), headache, chills, myalgias, arthralgias, and a feeling of weakness.[44] Simultaneously or shortly thereafter, the patient notices tenderness and pain in regional lymph nodes proximal to the site of inoculation of the plague bacillus. The femoral and inguinal groups of nodes are most commonly involved, followed by the axillary and cervical nodes. Upper body sites may be relatively more involved in children than adults. The enlarging bubo(es) becomes progressively swollen, painful, and tender, and the patient typically guards against palpation and limits movement. The surrounding tissue often becomes edematous, and the overlying skin may be erythematous, warm, and tense, and may desquamate (***Fig. 41.4***). Inspection of the skin surrounding or distal to the bubo sometimes reveals the site of a flea bite marked by a small papule, pustule, scab, or ulcer. Larger pustular lesions (furuncles or carbuncles), ulcers, and eschars may rarely occur and can be confused with those caused by tularemia

or anthrax. Treated in the uncomplicated state with an appropriate antibiotic, bubonic plague usually responds quickly, with disappearance of fever and resolution of other systemic manifestations over 2–5 days. Buboes often remain enlarged and tender for a week or more after treatment has begun and can occasionally become fluctuant. Without effective antimicrobial treatment, bubonic plague may progress to an increasingly toxic state of fever, tachycardia, lethargy, agitation and, occasionally, convulsions and delirium. Plague patients typically have white blood cell counts of 12 000–25 000/μL, with a predominance of immature polymorphonuclear leukocytes. Leukemoid reactions showing white blood cell counts as high as 50 000/μL or more can occur.[45] Mild forms of bubonic plague, called pestis minor, have been described in South America and elsewhere; in these cases, the patients are ambulatory, only mildly febrile, and have subacute buboes. Differential diagnostic possibilities for bubonic plague include streptococcal or staphylococcal adenitis, tularemia, cat-scratch disease, mycobacterial infection, acute filarial lymphadenitis, chancroid and other sexually transmitted diseases that cause regional lymphadenitis, and strangulated inguinal hernia. The bubo of plague is usually distinguishable from lymphadenitis of most other causes by its rapid onset, extreme tenderness, accompanying signs of toxemia, and usual absence of cellulitis or obvious ascending lymphangitis.

Septicemic Plague

Septicemic plague is a sudden, nonspecific febrile illness that occurs in the absence of apparent regional lymphadenitis.[46–48] It is characterized by rapidly progressive, overwhelming endotoxemia and dissemination of infection, and the diagnosis of plague is often not suspected until preliminary blood culture results are reported by the laboratory. Patients may have gastrointestinal symptoms such as nausea, vomiting, diarrhea, and abdominal pain, making a correct clinical diagnosis even more challenging.[49] If not treated early with appropriate antibiotics and aggressive supportive care, septicemic plague is usually fulminating and fatal. In the United States from 1960 to 2008, 20 of 72 primary septicemic plague cases were fatal, yielding a case-fatality rate of 28%. Differential diagnostic possibilities include any other overwhelming systemic infection, including Gram-negative sepsis with other agents, meningococcemia, and bacterial endocarditis. Some patients develop adult respiratory distress syndrome (ARDS), which can lead to confusion with other conditions such as hantavirus pulmonary syndrome and severe acute respiratory syndrome (SARS).

Pneumonic Plague

Pneumonic plague occurs in two forms, primary and secondary, both of which are potentially contagious and frequently fatal.[5,50] Primary plague results from direct inhalation of plague bacteria into the lungs. Onset is sudden with chills, high fever, headache, body pains, weakness, dizziness, and chest discomfort. Cough, sputum production, increasing chest pain, tachypnea, and dyspnea typically predominate on the second day of illness and may be accompanied by hemoptysis, increasing respiratory distress, cardiopulmonary insufficiency, cyanosis, and circulatory collapse. Principally an alveolar process, primary pneumonic plague is characterized by sputum that is initially watery or mucoid, and quickly becomes blood-tinged or frankly bloody. Chest signs in primary plague pneumonia may indicate localized pulmonary involvement in the early stage, with rapidly developing segmental consolidation before bronchopneumonia spreads to other segments and lobes of the same and opposite lung. Liquefaction necrosis and cavitation may develop at sites of consolidation and may leave significant residual scarring.

Secondary pneumonic plague arises through hematogenous spread from a bubo or other untreated source. It manifests first as an interstitial pneumonitis in which sputum production is scant, and the sputum is more likely to be inspissated and tenacious in character than the sputum found in primary pneumonic plague. In the United States from 1960 to 2008, 55 cases of secondary plague pneumonia and 11 cases of primary plague pneumonia were reported to the CDC, with no known secondary transmission to contacts and an overall case-fatality rate of 42% (CDC, unpublished data, 2009). Observers of pneumonic plague in the early twentieth century remarked on minimal auscultatory findings, the appearance of toxemia, and the frequency of sudden death, as compared to patients with other bacterial pneumonias.[50] Differential diagnostic possibilities include other bacterial pneumonias such as mycoplasma pneumonia, legionnaires' disease, staphylococcal or streptococcal pneumonia, tularemia pneumonia, and Q fever. Severe viral pneumonia, including hantavirus pulmonary syndrome and SARS, could be confused with plague.

Because respiratory spread of *Y. pestis* occurs by infective droplets, only persons with close respiratory exposure have a high risk of infection. Primary plague pneumonia is considered more contagious than secondary pneumonia because it is more likely to produce copious watery sputum, and the patient may be mobile and expose a wider circle of individuals in the early stage of contagiousness.

Meningeal Plague

Meningitis is an unusual manifestation of plague, occurring in 18 (4%) of 447 cases reported to CDC during 1960–2008 (CDC, unpublished data, 2009). Most cases were late complications of bubonic plague, and 14 patients (78%) survived. Although meningitis may be a part of the initial presentation of plague, its onset is often delayed and may be the result of insufficient antibiotic treatment of the primary illness.[51] Chronic, relapsing meningeal plague over periods of weeks and even months was described in the preantibiotic era. Plague meningitis presents as typical bacterial meningitis, with fever, headache, altered mental status, meningismus, and a polymorphonuclear leukocytic pleocytosis.

Pharyngeal Plague

Plague pharyngitis is an unusual condition and presents with fever, sore throat, and cervical lymphadenitis. In its early stages, it may be clinically indistinguishable from more common causes of pharyngitis. Cervical or submandibular buboes usually develop secondary to the pharyngeal involvement. Cases arise following respiratory droplet exposure, or from the ingestion of undercooked meat.[5,38] Pharyngeal plague may give rise to secondary plague pneumonia. Care providers working in plague-endemic areas should be alert to the possibility of plague in the differential diagnosis of acute bacterial pharyngitis. Pharyngeal colonization with *Y. pestis* sometimes occurs without symptoms among contacts of persons with pneumonic plague. Epidemiological observations do not suggest that persons with pharyngeal carriage present a contagious threat to others.

PATHOGENESIS AND IMMUNITY

Y. pestis inoculated through the skin or mucous membranes is carried via lymphatics to regional lymph nodes. This early stage of infection may be facilitated by macrophages which engulf but do not kill the pathogen, providing it with both transportation to the lymph node and a protected, intracellular niche in which to acclimatize to the mammalian host.[23] Growing intracellularly at 37°C, the bacteria begin expressing F1 envelope antigen, a key factor in their ability to resist subsequent phagocytosis by polymorphonuclear lymphocytes.[6,23] Within the lymph node, *Y. pestis* initiates an intense inflammatory reaction, creating a bubo. Initially the affected lymph nodes are edematous, congested, and have minimal inflammatory infiltrates and vascular injury. However, microscopic examination of fully developed buboes reveals infiltration by polymorphonuclear leukocytes, hemorrhagic necrosis with destruction of normal architecture, and dense concentrations of extracellular bacilli.[52] Affected nodes may be surrounded by a serosanguineous effusion, and when several adjacent lymph nodes are involved, a boggy, edematous mass

can result. Spontaneous bubo rupture and suppurative drainage may occur.

Bacteremia is common in plague and can result in seeding of other organs. In addition, untreated bacteremia can reach high levels, leading to excessive release of proinflammatory mediators, such as tumor necrosis factor-α and other cytokines. The resulting systemic inflammatory response may lead to hypotension, disseminated intravascular coagulation, acute renal failure, ARDS, and irreversible shock.[44] Affected tissues contain inflamed microvasculature occluded by fibrin thrombi, resulting in necrosis and hemorrhage. Blockage of vessels in acral sites can lead to gangrene of fingertips, toes, ears, and nose.[52] These cutaneous signs may be the origin of the term "Black Death." Patients who recover from plague typically have elevated antibodies to various antigens, including the diagnostically useful F1 antigen.

Pneumonic plague can result from inhalation of infective respiratory droplets from a person or animal with respiratory plague or secondary to hematogenous spread in a patient with bubonic or septicemic plague. It can result also from inhalation of *Y. pestis* in a laboratory accident.[53] Primary plague pneumonia generally begins as a lobular process and then extends by confluence, becoming lobar and then multilobar. Typically, plague organisms are most numerous in the alveoli. Secondary plague pneumonia begins more diffusely as an interstitial process, with organisms initially most numerous in the interstitial spaces. In untreated cases of both primary and secondary plague pneumonia, the usual findings are diffuse pulmonary hemorrhage, necrosis, and scant neutrophilic leukocyte infiltration.[50]

DIAGNOSIS

A high index of clinical suspicion, a careful clinical and epidemiologic history, and a thorough physical examination are required to make a timely diagnosis of plague. A delayed or missed diagnosis of plague is associated with a high case-fatality rate, and infected travelers who seek medical care after they have left endemic areas (peripatetic plague cases) are especially at risk.[43,54] When plague is suspected, close communication is essential between clinicians and the diagnostic laboratory, and between the diagnostic laboratory and a qualified reference laboratory. Laboratory tests for plague are highly reliable when conducted by persons experienced in working with *Y. pestis*, but such expertise is usually limited to specialized reference laboratories. Because of recent concerns with possible bioterrorism, a network of participating laboratories across the United States has been developed with the ability to make rapid and confirmatory diagnoses. All state public health laboratories now have this capability and can, if necessary, forward materials to the CDC for rapid advanced procedures.[55]

When plague is suspected, specimens should be obtained promptly for microbiologic studies, chest radiographs taken, and effective antimicrobial therapy initiated empirically. Appropriate diagnostic specimens for smears and culture include blood in all patients, lymph node aspirates in those with suspected buboes, sputum samples or tracheobronchial aspirates in those with suspected pneumonic plague, and cerebrospinal fluid in those with meningeal signs. A portion of each specimen should be inoculated onto suitable media (e.g., brain-heart infusion broth, sheep blood agar, chocolate agar, or MacConkey agar). Smears of each specimen should be stained with Wayson or Giemsa stain, and with Gram stain, and examined using light microscopy. If possible, the specimens should also be examined using direct fluorescent antibody (FA) testing.[16] An acute phase serum specimen should be collected for *Y. pestis* antibody testing, followed by a convalescent phase specimen collected 3–4 weeks later. For diagnosis in fatal cases, autopsy tissues should be collected for culture, FA testing, and histological processing, including buboes, samples of solid organs (especially liver, spleen, and lung), and bone marrow. For culture, specimens should be sent to the laboratory either fresh or frozen on dry ice and not in preservatives or fixatives. Cary–Blair or a similar holding medium can be used to transport *Y. pestis*-infected tissues.

Laboratory confirmation of plague is best achieved through the isolation of *Y. pestis* from body fluids or tissues. When the patient's condition allows, several blood cultures taken over a 45-minute period before treatment may increase the chances of successful isolation. *Y. pestis* strains are readily distinguished from other Gram-negative bacteria by polychromatic and immunofluorescence staining properties, characteristics of growth on microbiologic media, biochemical profiles, and confirmatory lysis by the *Y. pestis*-specific bacteriophage.[16] Automated systems may misidentify *Y. pestis* as other species. Laboratory mice and hamsters are susceptible to *Y. pestis* and are used in specialized laboratories to make isolations from contaminated materials and for virulence testing.

In the absence of a positive culture, plague can be confirmed by demonstrating a fourfold or greater change in serum antibodies to *Y. pestis* F1 antigen by passive hemagglutination (PHA) testing or by detecting a serum antibody titer of 128 or greater in a single serum sample from a patient with a compatible illness who has not received plague vaccine. The specificity of a positive PHA test is confirmed by F1 antigen hemagglutination inhibition (HI) testing. A small percentage of plague patients will develop diagnostic antibody levels within 5 days after illness onset, most seroconvert within 1–2 weeks, a few seroconvert more than 3 weeks after onset, and <5% fail to seroconvert.[56] Early specific antibiotic treatment may delay seroconversion by several weeks. Following conversion, serologic titers diminish gradually over months to years. Enzyme-linked immunosorbent assays (ELISAs) for detecting IgM and IgG antibodies to *Y. pestis* are useful in identifying antibodies in early infection and in differentiating them from antibodies developed in response to previous vaccination. Recently, antigen capture ELISA procedures, polymerase chain reaction assays, and handheld immunodiagnostic antigen detection tests for rapid, early diagnosis have been developed and are being evaluated. The handheld devices allow diagnostic testing of clinical materials at the bedside, even under primitive conditions.[57]

TREATMENT AND PROGNOSIS

Untreated, plague is fatal in over 50% of bubonic cases and in nearly all cases of septicemic or pneumonic plague. The overall plague case-fatality rate in the United States in the past 50 years has been approximately 15%.[15] Fatalities are almost always due to delays in seeking treatment, misdiagnosis, and delayed or incorrect treatment. Rapid diagnosis and appropriate antimicrobial therapy are essential. The case-fatality rate is very high for pneumonic plague patients who begin treatment more than 18–24 hours after the onset of pulmonary symptoms.

Effective antibiotic therapy should be given immediately after obtaining diagnostic specimens. Streptomycin has been considered the drug of choice since its introduction in the 1940s, and prompt administration can reduce mortality in bubonic plague to 5% or less. Streptomycin should be administered intramuscularly in two divided doses daily, in a dosage for adults of 30 mg/kg of body weight per day for 7 days, or for at least 3 days after remission of fever and other symptoms. Most patients improve rapidly and become afebrile after about 3 days of therapy.[44] Streptomycin is ototoxic and nephrotoxic, although the risk of severe vestibular damage and hearing loss is considered to be small in the short courses required for treating plague. Streptomycin should be used cautiously in pregnant women, in older patients, and in patients with hearing difficulty.

Streptomycin is not always readily available, and gentamicin has been proposed as an acceptable alternative based on *in vitro* susceptibility studies, animal models, and case series.[15,48,58–61] Retrospective analysis of 50 patients in New Mexico suggests that gentamicin, or a combination of gentamicin and doxycycline, is at least as efficacious as streptomycin.[62] A randomized trial of 65 patients in Tanzania found that 94% of those treated with gentamicin recovered.[63] Studies of patients with other diseases indicate that gentamicin is less ototoxic but more nephrotoxic than streptomycin. Renal toxicity associated with gentamicin is usually mild and reversible, and the drug is generally considered safer than

streptomycin for use in pregnant women and children. For these and other considerations, gentamicin has been recommended as an alternative in first-line treatment of plague in the event of a bioterrorist attack and is included in the US strategic national stockpile.[15]

For patients with contraindications to the use of aminoglycosides, tetracycline and chloramphenicol are effective alternatives. Doxycycline has become the tetracycline of choice because of its ease of administration, rapid and efficient absorption after ingestion, and its superior ability to achieve and maintain peak serum concentrations following oral administration. Doxycycline treatment should be initiated with a loading dose, either intravenously or orally depending on the severity of illness. In adults, a loading dose of 200 mg every 12 hours on the first day rapidly achieves a peak serum concentration of approximately 8 μg/mL, and is followed by a daily dosage of 100 mg every 12 hours.[61,64] Tetracycline is administered to adults in an initial loading dose of 2 g, followed by a usual dose of 2 g/day in four divided doses. Doxycycline or tetracycline can also be used to complete a course of treatment begun with an aminoglycoside. When used as principal treatment, a tetracycline should be given for 7–10 days, or for at least 3 days after fever and other symptoms have subsided.[15]

For conditions in which high tissue penetration is important, such as plague meningitis, pleuritis, or myocarditis, chloramphenicol is considered the drug of choice.[15,58] It may be used separately or in combination with an aminoglycoside. A loading dose of 25–30 mg/kg of body weight is given, followed by 50–60 mg/kg of body weight per day in four divided doses. As indicated by clinical response, chloramphenicol dosage may be reduced to a daily dose of 25–30 mg/kg to lessen the magnitude of reversible bone marrow suppression. The irreversible marrow aplasia associated with chloramphenicol is so rare (estimated to occur in 1 in 40 000 patients) that its consideration should not deter its use in patients who are seriously ill with plague infection.

Ciprofloxacin, a fluoroquinolone, has shown promise *in vitro* and in laboratory animal studies,[65–67] but case series demonstrating its utility in human plague have not been reported. Penicillins, cephalosporins, and macrolides have poor efficacy and should not be used. Trimethoprim-sulfamethoxazole has been used successfully to treat bubonic plague, but is not considered a first-line choice and is not recommended for treating severe forms of the disease. In general, antimicrobial treatment should be continued for 7–10 days or for at least 3 days after the patient has become afebrile. Patients begun on intravenous antibiotics may be switched to oral regimens as indicated by clinical response. Improvement is usually evident 2–3 days from the start of treatment, even though lessening fever may continue for several more days.

Consequences of delayed treatment of plague include disseminated intravascular coagulation, ARDS, and other complications of bacterial sepsis and endotoxemia. Patients with these disorders require intensive monitoring and close physiologic support. Buboes may require surgical drainage if they threaten to rupture. Abscessed lymph nodes rarely can be a cause of recurrent fever in patients who have otherwise had satisfactory recovery; the cause may be occult when intrathoracic or intra-abdominal nodes are involved. Viable *Y. pestis* organisms have occasionally been isolated from buboes 1–2 weeks into convalescence.

Natural resistance to recommended antimicrobials is exceedingly rare. Most resistant strains have shown only partial resistance to a single agent and have not been associated with treatment failures. In 1995, two clinical isolates with plasmid-mediated drug resistance were recovered in Madagascar, one with high-level resistance to streptomycin, the second resistant to multiple drugs including streptomycin, chloramphenicol, ampicillin, tetracycline, and sulfonamides.[58] Both patients recovered despite being treated per protocol with streptomycin and trimethoprim-sulfamethoxazole. The plasmids conferring resistance in these two strains are believed to have arisen independently, possibly through horizontal gene transfer in the flea midgut.[58] In the absence of antimicrobial pressure on wild rodent populations, it is questionable whether such resistance would be expected to propagate in nature. To date these remain the only such natural isolates identified among thousands tested worldwide. Antimicrobial resistance is not known to have emerged during treatment of plague in humans, and relapses following recommended courses of treatment are virtually unknown.

PREVENTION AND CONTROL

Surveillance, environmental management, and personal protective measures are the cornerstones of prevention and control.[11,68,69] Surveillance includes environmental monitoring to determine sites of plague activity, inspection of rodent habitats for signs of epizootics, collecting and testing of fleas from abandoned burrows, trapping and testing of live rodents and their fleas for *Y. pestis* infection, and testing of animals found sick or dead from suspected plague. In some circumstances, carnivore seropositivity is used as an indicator of rodent plague activity in an area. Dogs and wild canines readily seroconvert following exposure but retain elevated antibody levels for less than a year, making them useful sentinels of recent plague activity in an area.

Personal protective measures include avoidance of areas with known epizootic plague (these may be posted by government authorities); avoidance of sick or dead animals; use of repellents, insecticides, and protective clothing when there is a potential for exposure to rodent fleas; and use of gloves when handling animal carcasses. The practice of letting domestic dogs and cats sleep on the same bed as humans should be discouraged in endemic areas.

Postexposure prophylaxis for 7 days with doxycycline or other tetracycline, chloramphenicol, or ciprofloxacin is recommended for persons who have had a known close exposure to a pneumonic plague patient in the prior 7 days. Oral doxycycline or ciprofloxacin has been recommended for postexposure prophylaxis in the event of a terrorist attack with *Y. pestis*.[15] Pre-exposure prophylaxis may occasionally be recommended for persons who are unable to avoid visiting or residing in an area where a plague outbreak is in progress or who are screening or caring for plague patients in unusual circumstances, such as an outbreak. To reduce the risk of airborne droplet spread, plague patients should have a chest radiograph to rule out pulmonary involvement. Patients with suspected pneumonic plague should be managed in isolation under respiratory droplet precautions until the patient has responded clinically and sputum cultures are negative (sputum typically is sterile within 24–48 hours of beginning treatment). Persons caring for sick animals (especially cats) in plague-endemic areas should take precautions to avoid contamination with infectious exudates or expelled respiratory secretions.[33]

Sources of rodent food (garbage, feed for livestock and pets) and shelter (brushpiles, junk heaps, woodpiles) should be eliminated in domestic, peridomestic, and working environments, and buildings and food stores should be rodent-proofed. Controlling fleas with insecticides is a principal public health measure in situations where epizootic plague activity places humans at high risk. This includes insecticidal dusting and spraying of rodent burrows, rodent runs, and other sites where rodents and their fleas are found. In known plague foci, pet owners should consider using flea control products to protect their pets and potentially reduce their risk of exposure. The decision to control plague by killing rodents should be left to public health authorities and should only be carried out in conjunction with effective flea control. Killing rodents has no lasting benefit without environmental sanitation.

In the event of a plague epidemic, measures should rapidly be taken to control spread, as described in international regulations and guidelines for plague control.[11,68] These measures include delineation of infected areas, rapid detection and treatment of cases and exposed contacts, isolation and monitoring of suspected human plague cases and case contacts, and control of fleas and rodents in plague-infected areas, in port facilities, and on ships and other conveyances as indicated.

A formalin-killed vaccine was available for many years for use by persons who worked with *Y. pestis* in the laboratory or were otherwise at high risk of exposure. However, it is no longer available for use in the United States. Concern for bioterrorism has stimulated renewed efforts to develop safe, rapidly acting, and efficacious vaccines using advanced molecular approaches.[68] At present, the most promising candidates are

recombinant subunit vaccines that express F1 and V antigens of *Y. pestis* and appear to protect animals against infective aerosol exposures.[70–72] Other approaches under investigation include passive immunization with aerosolized monoclonal antibodies[73] and vaccines based on attenuated *Y. pseudotuberculosis*.[74,75]

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