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228 *Pasteurella* Species

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SHORT VIEW SUMMARY

Definition
- Frequently, *Pasteurella* infection is a cause of skin and soft tissue infections after an animal bite or scratch.
- *Pasteurella* infection often is part of a mixed bacterial infection.
- Complications include septic arthritis and osteomyelitis.
- Less frequently, *Pasteurella* infection causes pneumonia in patients with underlying lung disease.
- Other deep-seated complications are uncommon but carry high morbidity and mortality.

Epidemiology
- Distribution is worldwide.
- The principal reservoir is animals.
- Infection most often occurs after bites or scratches from dogs and especially cats.
- Infections have been reported after bites or scratches from a large number of other animals.
- Infections also occur in individuals with animal exposure without bites or scratches.

Microbiology
- Nonmotile, facultatively anaerobic, gram-negative coccobacilli
- Grows best on sheep blood and chocolate agar, not usually on MacConkey agar
- Somewhat fastidious
- Can be difficult to isolate from nonsterile specimens, especially sputum
- *P. multocida* with three subspecies: *multocida, septica, gallicida* (least common) (see Table 228.1)
- Several other related species of genus *Pasteurella* cause human disease.

Diagnosis
- Progressive skin and soft tissue inflammation after an animal bite injury, especially after puncture wounds
- Isolation of the organism from wound/tissue culture, often as part of a mixed bacterial infection
- Sputum or pleural fluid isolates from patients with underlying lung conditions presenting with lower respiratory tract infections

Therapy
- See Chapter 315 for management of bite wounds. *P.* multocida is susceptible to most penicillins, second- and third-generation cephalosporins, carbapenems, tetracycline, fluoroquinolones, and trimethoprim-sulfamethoxazole. Susceptibility is less or variable with macrolides, linezolid, aminoglycosides, clindamycin, vancomycin, and antistaphylococcal penicillins.
- Once identified as *Pasteurella* spp., a penicillin is the antimicrobial agent of choice.
- β-Lactam resistance is rare, mostly described in respiratory isolates.
- Aggressive surgical débridement of soft tissue infections is important. Penetrating bite wounds over the hands lead to tenosynovitis and are a surgical emergency, requiring incision and drainage.

Prevention
- Antimicrobial prophylaxis for selected bite wounds is usually with amoxicillin–clavulanic acid 875 mg orally twice daily for 5 days (see Chapter 315).

Pasteurella are gram-negative coccobacilli that inhabit the oral cavity and gastrointestinal tract of many animals and cause various infectious problems, including septicemia and pneumonia. In humans infection is most often caused by dog and cat bites, resulting in cellulitis, subcutaneous abscesses, and a number of other syndromes. Bacteria belonging to the genus *Pasteurella* were first isolated from birds with cholera in 1878; they were characterized 2 years later by Pasteur. In 1886 Hueppe speciated the organism *Bacterium septicemia haemorrhagica* as the cause of hemorrhagic septicemia in animals. The first human case of *Pasteurella* infection, a case of puerperal sepsis, was described by Brugnatelli in 1913. The isolation of *Pasteurella multocida* from an infection occurring after a cat bite was first described in 1930. Subsequently, as additional isolates were recovered and characterized, related species were grouped together, first as *Pasteurella septica* and then by the late 1930s as the *P. multocida* group. The complete genome of *P. multocida* was sequenced in 2001, offering an opportunity to elucidate the mechanisms of pathogenicity more accurately.[1]

DESCRIPTION OF THE PATHOGEN

The family Pasteurellaceae includes the genera *Pasteurella, Haemophilus, Actinobacillus, Aggregatibacter,* and *Mannheimia,* among others.[2,3] On the basis of the genomic sequence, it appears that *Pasteurella* and *Haemophilus* diverged approximately 270 million years ago.[1] DNA hybridization separates the *Pasteurella* spp. into two groups: (1) *Pasteurella* sensu stricto and (2) *Pasteurella*-related spp., with the latter more closely related to *Haemophilus* and *Aggregatibacter* (Table 228.1).[3] Species of the genus *Pasteurella* are nonmotile, facultatively anaerobic, gram-negative coccobacilli measuring 1 to 2 μm in length. Organisms grow in culture on a variety of commercial media, including sheep blood and chocolate agar, but not usually on MacConkey agar media. They are fastidious and can be difficult to isolate and identify from nonsterile specimens such as sputum. In one study matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF) accurately identified 59 of 66 *Pasteurella* isolates and had the advantage of rapidity.[4] Most strains are catalase, oxidase, and indole positive and produce acid from sucrose. The most common human isolates belong to the *P. multocida* group and appear as smooth, iridescent, blue colonies on growth media. Encapsulated isolates typically appear mucoid. Strain differences of *P. multocida* have traditionally been identified on the basis of capsular antigens that define 5 serogroups (A–F) and somatic antigens that define 16 serovars (1–16).[5] Strains in groups B, E, and F have been rarely associated with human infection. Of the remaining strains (A, D), group A strains have been more frequently isolated as respiratory tract colonizers or pathogens, whereas non-A strains have been isolated more frequently from nonrespiratory tract specimens, including blood, cerebrospinal fluid, and abscess fluid.[6] Ribosomal DNA and other sequence-based molecular techniques offer better resolution than serotyping and have now superseded it for identification and typing of *Pasteurella*.[7,8] Because

TABLE 228.1 *Pasteurella* Species

***Pasteurella* Sensu Stricto**
P. multocida
Subsp. *multocida*
Subsp. *septica*
Subsp. *gallicida*
P. canis
P. dagmatis
P. stomatis
***Pasteurella*-Related Species**
P. aerogenes
P. bettyae
P. caballi
P. pneumotropica

Data from Zbinden R, Carroll KC, Jorgensen JH, et al, eds. Manual of Clinical Microbiology. *11th ed. Washington, DC: American Society for Microbiology Press; 2015:652–666.*

of their sometimes fastidious nature, specific guidelines for methodologies to accurately determine minimal inhibitory concentrations (MICs) of *Pasteurella* spp. have been published.[9]

EPIDEMIOLOGY

On the basis of case reports and case series of infected patients, *Pasteurella* spp., particularly *P. multocida,* appear to have a worldwide distribution. For most *Pasteurella* spp. the principal reservoir is in animals. *P. multocida* has been isolated from the upper respiratory tracts of a variety of animals, including dogs, cats and other felines, pigs, and a wide variety of domestic and wild animals. Dogs and cats have particularly high colonization rates. In most cases carriage is asymptomatic, although both upper and lower respiratory tract infections and septicemia are well known to occur in animals.[3,10] Although the reservoirs of most of the non-*multocida* spp. (*P. canis, P. stomatis, P. dagmatis, P. aerogenes,* and *P. pneumotropica*) are likely animals, notable is *Pasteurella bettyae,* a cause of neonatal infection and genitourinary infection in adults, whose reservoir is not well defined.[11] Respiratory tract colonization by *P. multocida* in humans is well known to occur. In most cases colonized patients have underlying upper or lower respiratory tract diseases, including chronic sinusitis, chronic obstructive pulmonary disease (COPD), or bronchiectasis.[12–14] Most colonized patients have a history of household or domesticated animal contact.[15]

Broadly speaking, human infection with *Pasteurella* can be divided into three types: infection occurring after animal bites, usually from dogs or cats; infection occurring after other animal exposures; and infection with no known animal contact. Infection after animal bites is the most commonly reported clinical setting for the organism (see Chapter 315).[15–22]

Among animal bites, dog bites are most common, followed by cat bites. Approximately 15% to 20% of dog bite wounds and greater than 50% of cat bite wounds become infected.[15,21] The higher incidence of infection after cat bites probably results from the fact that cat teeth are thinner and more commonly result in puncture wounds, which are known to carry a higher risk of infection. *Pasteurella* spp. are the most commonly isolated pathogens from dog and cat bites, present in 50% and 75% of cases, respectively; followed by *Staphylococcus* and *Streptococcus* spp.[19–24] Francis and associates,[20] studying bite-related *P. multocida* infections in Oregon between 1962 and 1972, noted that 76% were the result of cat bites, and the remaining 24% were from dog bites. The difference in incidence of *Pasteurella* infections in dog and cat bites also may reflect the higher rate of upper respiratory colonization in cats. *Pasteurella* infections have also been reported after bites from a variety of other animals, including pigs, rats, lions, opossums, and rabbits.[22] In addition to bites, *Pasteurella* infections have also been reported after dog and cat scratches and from the licking of open wounds by these animals.[17,25,26]

Pasteurella infections are well known to develop in patients exposed to animals but without a history of bites or scratches. These include skin and soft tissue infections, bone and joint infections, pneumonia, meningitis, endocarditis, and septicemia.[15,27,28] Persons at risk for infection from animal exposure include veterinarians, farmers, livestock handlers, pet owners, and food handlers. Although the route of infection in many reported cases is not clear, most have been presumed to result from inadvertent direct inoculation of organisms or from upper respiratory tract colonization, with subsequent dissemination to the target organ or organs. In one case report a patient with underlying bronchiectasis and diabetes was hospitalized with pneumonia caused by *P. multocida*. Pulsed-field gel electrophoresis of her sputum isolate, compared with *P. multocida* isolated from her dog's pharynx, yielded identical patterns, strongly implicating her dog as the source of her infection.[27,29]

In a significant proportion of *Pasteurella* cases, no known animal exposure or contact can be identified. In 1970 Hubbert and associates[28] reviewed what was then the world's literature; they identified 72 reported cases of *P. multocida* infection unrelated to bites and described 136 additional cases. In 16% of the reviewed cases and 31% of their additional cases, no animal exposure or contact could be identified. Once again, the spectrum of infectious complications was wide, similar to that described for patients with nonbite animal exposures. In a more recent literature review of 156 *Pasteurella* bacteremia adult cases, 20% did not have animal exposures reported. Vertical transmission of *P. multocida* has been described rarely.[30,31]

PATHOGENESIS

Despite *Pasteurella* spp. having been long established as human pathogens, the precise mechanisms of pathogenicity remain uncertain. In animals virulent *P. multocida* strains adhere to mucosal epithelial cells in the upper respiratory tract, particularly in the tonsils, and in some cases they are mediated by fimbriae.[32] Several virulence factors have been described in *Pasteurella* spp.[10] Much attention has focused on *P. multocida* toxin (PMT). PMT, produced by strains A and D, is a potent mitogen that has been shown to activate a number of intracellular signaling cascades, resulting in a multitude of deleterious effects.[33] Specifically, PMT has been shown to inhibit the migratory response of dendritic cells, thereby impairing immune surveillance.[34] Along with ToxA protein, also produced by *P. multocida,* PMT is associated with progressive atrophic rhinitis in pigs.[35] *P. multocida* lipopolysaccharide (LPS) is another virulence factor, proven by the fact that strains with truncated LPS have been shown to be attenuated in virulence.[36] In addition, most virulent *Pasteurella* strains produce polysaccharide capsules that confer many possible mechanisms of pathogenicity, including resistance to desiccation, promotion of adherence, and resistance to phagocytosis and complement-mediated killing.[37] Finally, binding of transferrin by some pathogenic *Pasteurella* strains has been demonstrated and may be a mechanism used by the bacteria to ensure an iron supply necessary for growth.[38] Indeed, on the basis of the genomic sequence data, 2.5% of the entire genome encodes for proteins involved in iron acquisition.[1]

The humoral response to *P. multocida* infection has been characterized. Antibodies to somatic and capsular antigenic determinants develop within 2 weeks after clinical infection. Capsular antibodies are more long-lasting than somatic antibodies.[39] The precise role for such antibodies in host defense in humans is not clear. Studies in healthy breeders whose livestock suffered from pasteurellosis show a high rate of seropositivity to *Pasteurella*, illustrating the limitations of serology for the diagnosis of active *Pasteurella* infection in humans.[40]

CLINICAL MANIFESTATIONS

Most reported *Pasteurella* infections in humans are caused by *P. multocida* and involve skin and soft tissues.[41] Although both subspecies *multocida* and *septica* cause skin and soft tissue infections as a result of animal bites and scratches, subspecies *multocida* has also been found to cause respiratory tract infections and systemic infection.[6,42] Other species have been described much less commonly (Table 228.2).[17] Beyond skin and soft tissues, *Pasteurella* can uncommonly cause chronic respiratory tract infection in patients with underlying pulmonary disease and invasive infection syndromes, such as bacteremia, endocarditis, and meningitis. In a retrospective case-control study seeking to identify risk factors for invasive *Pasteurella* infection, only advanced age was found to be significant in multivariate analysis,[43] but it is thought that immunocompromised hosts are at enhanced risk.

TABLE 228.2 Clinical Characteristics of 159 Strains of *Pasteurella* Species Isolated From 146 Infected Humans Over a 3-Year Period

		SITE OF INFECTION			
SPECIES	***N***	**WOUND INFECTIONS OR ABSCESSES[a]**	**BLOOD**	**CEREBROSPINAL FLUID**	**OTHER**
P. multocida subsp. *multocida*	95	85	5	1	4[b]
P. multocida subsp. *septica*	21	20		1	
P. canis	28	28			
P. stomatis	10	10[c]			
P. dagmatis	5	2[d]			3[e]

[a]Caused by dog or cat bites or wounds licked by dogs or cats.
[b]Includes three cases of infection from cut wounds unassociated with any known animal contact.
[c]In eight cases of wound infection, *P. multocida* subsp. *multocida* was also recovered.
[d]In cases of wound abscesses, *P. multocida* subsp. *multocida* and *P. canis* were also recovered.
[e]One case each of severe cellulitis, groin abscess, and throat abscess.
Modified from Holst E, Rollof J, Larsson L, et al. Characterization and distribution of Pasteurella species recovered from infected humans. J Clin Microbiol. *1992;30:2984–2987.*

Skin and Soft Tissue Infections

Infections of skin and soft tissues most commonly develop after an animal bite or scratch. Less commonly, infections develop after a dog or cat has licked an open wound. Inflammation, swelling, and tenderness develop at the site of injury, usually within 24 hours from the time of exposure.[15,18,20,44] Regional lymphadenopathy occurs in 30% to 40% of cases. Wound discharge, ranging from serosanguinous to frankly purulent, has been noted in 20% to 40% of cases; fever develops in approximately 20%. Anatomically, greater than 50% of cases of infection from both dog and cat bites occur in the upper extremities, followed by the lower extremities, head, face, and neck; multiple sites of infection are sometimes evident.[20,44–46] Abscesses and tenosynovitis are the most frequent complications of *Pasteurella* soft tissue infection, with septic arthritis and osteomyelitis being less common. Bacteremia is uncommon. Weber and colleagues[15] noted an overall complication rate of 39% among 23 patients studied. In a large study analyzing bacterial species isolated from wounds inflicted by dog and cat bites, *P. canis* was the most common isolate from dog bites, whereas *P. multocida* subsp. *multocida* and subsp. *septica* were the most common from cat bites.[23]

Bone and Joint Infections

Bone and joint infections with *Pasteurella* spp. take three different forms—septic arthritis, osteomyelitis, and combined arthritis and osteomyelitis. Ewing and associates[47,48] reported two cases each of septic arthritis and osteomyelitis caused by *P. multocida* and reviewed the literature. Among 14 cases of septic arthritis reported and reviewed, 7 (50%) involved dog or cat bites or scratches and 5 (36%) involved animal exposure without recent or known bites or scratches. In the remaining 2 cases there were no reported animal exposures. The knee was the most common joint involved (11 cases), often in the setting of rheumatoid arthritis, osteoarthritis, or joint prosthesis. Five of the 14 patients were receiving prednisone. Osteomyelitis developed as the result of direct extension of soft tissue inflammation or by direct inoculation of the periosteum at the time of the bite. Among 13 cases of osteomyelitis reported, 9 (69%) involved animal bites or scratches, 1 (8%) involved animal exposure, and 3 had no reported exposure. In contrast with septic arthritis, most cases (69%) of osteomyelitis developed in an upper extremity bone, usually the hand or wrist. Also, unlike septic arthritis, chronic medical conditions and corticosteroid therapy were not common antecedents. Finally, among 7 cases of combined septic arthritis and osteomyelitis, 6 involved bones and joints of the upper extremities, usually a phalanx and interphalangeal joint infected after a cat bite. In a pediatric case series of 14 patients with bone and joint involvement, upper extremities were most commonly affected. Immunocompromising conditions or underlying joint disease were not common. Animal bites, licks, or scratches were reported in 9 of 14 cases (64%), with 4 (29%) cases reporting animal contact without bites or scratches and 1 case with no known exposure.[49]

Several contemporary case series point to a predilection of the organism for prosthetic joints. Knee and hip prostheses are most often involved,[25,50,51] although shoulder prosthesis infection has also been reported.[52] The infection may occur many years after the joint implantation, with the mean being 7.6 years in one series.[50] A single joint is most commonly involved. In virtually all cases there is a history of animal exposure. Risk factors have included older age, rheumatoid arthritis, and corticosteroid use.

Central Nervous System Infections

Central nervous system infections with *P. multocida* have been reported infrequently, predominantly in infants or elderly patients,[30] although cases in the immunocompetent have been described.[53] Meningitis is most common. There have been rare cases of focal lesions, such as brain abscess and subdural empyema.[15,30,54,55] Of 29 cases of meningitis reported in the English language literature through 1999, most patients had animal contact, usually licking of mucosa or nonintact skin.[55–57] Bacteremia was seen in nearly two-thirds of patients. Mortality was 25% overall, with decreasing mortality among later cases.[57] In a French pediatric meningitis surveillance study, *Pasteurella* accounted for 0.15% of all pediatric meningitis cases. All occurred in infants younger than 4 months. Forty-four out of 48 cases (92%) had a suspected animal source, most commonly household cats or dogs; however, only 8% of cases had a history of traumatic animal contact. A lack of direct contact between the infant and the animal suggests a potential role of horizontal transmission from the caregiver to the patient.[30]

In *Pasteurella* meningitis the CSF characteristics are usually consistent with bacterial meningitis, with pleocytosis and neutrophil predominance, high protein, and low glucose. Gram-negative bacilli or coccobacilli are seen on Gram stain in 70% to 80% of cases,[30] which can be confused with other more common meningitis agents, such as *Neisseria* or *Haemophilus*.

Bacteremia and Endocarditis

Bacteremia can occur as a complication of *Pasteurella* infection. In a comprehensive review of the literature, Vondra and Myers[58] summarized the cases of 156 individuals with *Pasteurella* bacteremia. Fifty-seven (36.5%) had septic shock. Bacteremia was most often associated with skin and soft tissue infections (26.9%), respiratory tract infection (21.8%), endovascular infection (14.7%), intraabdominal-pelvic infection (10.3%), and bone and joint infection (9%). Most cases were associated with animal contact (80%), and most patients had underlying medical conditions, especially cirrhosis, malignancy, alcoholism, COPD, and diabetes.[59] Mortality was high, especially in immunocompromised patients, but overall mortality decreased substantially each decade starting from 1950 to 2010. *P. dagmatis*, although less frequent than *P. multocida*, has more frequently been reported causing bacteremia rather than localized infection.[60]

Infective endocarditis has been reported much less frequently than septicemia. From a group of 32 patients reported in the literature,[61–63]

preexisting heart disease was evident in 12 cases. Animal contact was evident in 50% of patients. Rare cases of prosthetic valve endocarditis with *Pasteurella* spp. (especially *P. dagmatis*) have been reported.[64–66]

Respiratory Tract Infections

Respiratory tract infections with *Pasteurella* spp. involve the upper respiratory tract, causing sinusitis and bronchitis, and the lower respiratory tract, causing both pneumonia and empyema.[67] The respiratory tract is second only to skin and soft tissue in frequency of clinical isolation of *Pasteurella*. *P. multocida* subsp. *multocida* has been reported to be the most common *Pasteurella* spp. to cause respiratory tract infections.[6,42] As noted, asymptomatic *Pasteurella* colonization of the upper respiratory tract has been reported in patients with underlying respiratory tract disease, including COPD and bronchiectasis.[12] Presumably for a subset of this patient group, the organism invades and causes disease. Chronic symptomatic exacerbations of underlying lung disease with isolation of *Pasteurella* have been described uncommonly.[14] There is nothing clinically distinguishing about upper respiratory tract infections. Pneumonia usually occurs in patients with underlying lung disease and is usually lobar, with a short prodrome. Twenty-one *Pasteurella* pleural effusion and empyema cases were reviewed by Jogani and colleagues.[68] The median age was 69 years, and 57% had comorbidities, such as COPD, bronchiectasis, or cirrhosis. In 87% of cases the pleural fluid obtained was grossly purulent. Although respiratory and constitutional complaints are dominant presenting symptoms, fever seems surprisingly uncommon.[69]

Intraabdominal Infections

Of the few reported cases of *Pasteurella* intraabdominal infections, spontaneous bacterial peritonitis and appendicitis, with or without associated peritonitis, have been the most frequent clinical syndromes. Among the reported cases of spontaneous bacterial peritonitis, almost all have had cirrhosis (usually alcoholic) and preexisting ascites.[70,71] Raffi and associates[72] reported three cases of *P. multocida* appendiceal peritonitis and identified eight additional well-documented cases of appendicitis in the literature. Accompanying peritonitis was variably present. It was postulated that the source of the organism was most likely from oropharyngeal colonization. Several cases of peritonitis have been reported in association with peritoneal dialysis.[73,74] Cats were the presumed source in most patients, but dog- and hamster-related cases have been reported, some with *P. aerogenes* and *P. pneumotropica* as the causative organism.[75,76] Poor hygiene, including manipulation or puncture of the peritoneal dialysis access, was thought to be the likely cause of infection.

Other *Pasteurella* Infections

Infections of other sites with *Pasteurella* spp. have been reported rarely and include genitourinary tract, infection,[77,78] epiglottitis,[79] keratitis,[80] and endophthalmitis.[15,81] *Pasteurella* infections have also been reported in a variety of immune deficiencies, including bronchitis in a patient with Sweet syndrome,[82] fatal sepsis in a patient with hairy cell leukemia,[83] cellulitis with bacteremia in a neutropenic host,[84] and malacoplakia in a patient with acquired immunodeficiency syndrome.[85]

THERAPY, PREVENTION, AND PROGNOSIS

See Chapter 315 for management of bite wounds. Several decades of clinical experience with *Pasteurella* and numerous in vitro studies have indicated that penicillin is the best antimicrobial agent for treating virtually all forms of infection.[15,16,20] Penicillins with good in vitro activity include penicillin G, penicillin V, ampicillin, amoxicillin, and amoxicillin-clavulanic acid. Antistaphylococcal penicillins, including oxacillin, nafcillin, dicloxacillin, and cloxacillin are not as active and are not recommended for treatment of documented *Pasteurella* infections.[86,87] Many cephalosporins demonstrate in vitro activity against *P. multocida*. In general, activity increases with later-generation cephalosporins. Goldstein and associates[88] have reported high MICs for cephalexin, cefaclor, and cefadroxil and recommended that they not be used for treatment of documented infections. The oral cephalosporins, cefuroxime and cefixime, along with parenteral agents, including ceftriaxone, cefoperazone, and ceftaroline, demonstrate excellent in vitro activity and are probably good substitutes for penicillin.[87]

Plasmid-mediated β-lactamase production has been described in *P. multocida* strains isolated from animals. Human cases of *Pasteurella* infection caused by penicillin-resistant strains have been reported. Virtually all penicillin-resistant isolates have come from respiratory tract specimens.[14,89] Among non–β-lactam antibiotics, agents with in vitro activity include tetracyclines, fluoroquinolones, macrolides, trimethoprim-sulfamethoxazole (TMP-SMX), and chloramphenicol.[90,91] A fluoroquinolone, doxycycline, or TMP-SMX should be considered as an alternative for patients with intolerance to β-lactams. Aminoglycosides have moderate-to-poor activity in vitro and probably should not be used, particularly given the paucity of clinical experience. Clindamycin and erythromycin consistently demonstrate high MICs in vitro and are not recommended. The long-acting macrolides, such as azithromycin, appear to have better activity but should be used with caution because clinical experience with these agents is limited.[91]

Because animal bite wound infections are frequently polymicrobial and may include *Staphylococcus aureus,* streptococcal species, and anaerobes in addition to *Pasteurella,* empirical antibiotic therapy should be directed at these organisms until or unless wound cultures define the specific bacteriology of the infection.[22] Outpatient treatment of documented, uncomplicated *Pasteurella* cellulitis can be undertaken with penicillin VK, amoxicillin, or ampicillin, with close follow-up.[15] Duration of therapy is not well defined, but 10 to 14 days is probably a reasonable time course. Patients with evidence of involvement of deeper structures (e.g., tenosynovitis, arthritis) should be hospitalized and treated parenterally, with β-lactam–β-lactamase combinations being the treatment of choice until the microbiology is defined. Drainage and débridement may be necessary for patients who have progressive infection with extensive suppuration. Infection of the hand tendons should be regarded as a surgical emergency for incision and drainage.[92]

Treatment of septic arthritis should consist of antimicrobial therapy along with frequent drainage of the involved joint(s).[47] Most patients recover fully. Similarly, the outcome for osteomyelitis appears to be good, although débridement in addition to antimicrobial therapy is often necessary. The outcome of septic arthritis with osteomyelitis is not as good, with residual deformity and loss of function being common. For patients with *Pasteurella* osteomyelitis, antimicrobial therapy should be continued for 4 to 6 weeks.

Patients with other end-organ forms of *Pasteurella* infection do poorly overall. High mortality has been reported for most of these cases. A third-generation cephalosporin is recommended for *Pasteurella* meningitis. For patients with bacteremia without endovascular infection, the mortality rate is high, probably as a result of the infection itself combined with the underlying medical problem, usually alcoholic cirrhosis. For endocarditis, among 32 reported patients, 8 died and 10 required valve replacement.[61–63] For patients with pneumonia, morbidity and mortality are high, almost certainly as a result of severe underlying pulmonary disease. Finally, patients with spontaneous bacterial peritonitis have an extremely high mortality rate, whereas those with appendicitis, with or without peritonitis, generally do well.[70,72]

The use of antimicrobial prophylaxis for patients presenting with animal bites shortly after the injury that are not obviously infected is controversial. The Infectious Diseases Society of America guidelines on skin and soft tissue infections recommends prophylaxis after dog or cat bites in the following groups of patients: (1) are immunocompromised; (2) are asplenic; (3) have advanced liver disease; (4) have preexisting or resultant edema of the affected area; (5) have moderate-to-severe injuries, especially to the hand or face; or (6) have injuries that may have penetrated the periosteum or joint capsule[93] adjacent to bones or joints, or wounds in certain immunocompromised hosts (e.g., splenectomy). Although a few small trials have been completed, none has been large enough or seen enough patients to reach significant end points to determine the efficacy of such therapy unequivocally.[94,95] Amoxicillin–clavulanic acid is a commonly used agent that has activity against *S. aureus,* streptococci, anaerobes, and *Pasteurella*. The combination of either cefuroxime, doxycycline, a fluoroquinolone or TMP-SMX, plus either metronidazole or clindamycin should be alternatives for patients with serious penicillin allergies. Courses of 3 to 5 days are usually recommended.[93]

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The complete reference list is available online at Expert Consult.

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229A Plague (*Yersinia pestis*)

Paul S. Mead[a]

SHORT VIEW SUMMARY

Definition
- Life-threatening zoonosis caused by *Yersinia pestis*
- Naturally cycles among rodents and their fleas
- Potential bioterrorism agent

Epidemiology
- Globally distributed but found within distinct ecologic foci
- Vector borne, highly invasive, all ages, frequently fatal

Microbiology
- Aerobic, gram-negative member of Enterobacteriaceae, closely related to *Y. pseudotuberculosis*
- Growth at 37°C on MacConkey agar, sheep blood, and brain-heart infusion
- Automated identification systems may misidentify

Clinical Manifestations and Diagnosis
- Regional suppurative lymphadenitis, sepsis, or fulminant pneumonia with plague
- Bioterrorism mass exposure: fulminant pneumonia
- Culture of blood, bubo, or sputum
- Acute and convalescent serology

Therapy
- Immediate use of antimicrobial agents: lifesaving for plague
- Plague: streptomycin, 1 g twice daily; gentamicin, 5 mg/kg once daily; or levofloxacin, 500 to 750 mg once daily, preferred (see Table 229A.2 for options)

Prevention
- Reduce rodent harborage; control fleas on pets
- Avoid contact with rodents and sick animals
- Bioterrorism exposure: doxycycline 100 mg twice daily or levofloxacin 500 mg, once daily

The genus *Yersinia* includes at least 19 described species, of which 3 are important human pathogens.[1] *Yersinia enterocolitica* and *Yersinia pseudotuberculosis* are enteric pathogens usually acquired through ingestion of contaminated food or water. The third species, *Yersinia pestis,* causes plague. Although closely related to *Y. pseudotuberculosis, Y. pestis* has undergone a marked evolutionary shift to become a vector-borne pathogen capable of achieving the high levels of bacteremia in mammalian hosts.

HISTORY

Plague has been credited with causing at least three major pandemics over the past 1500 years.[2] The first struck the Byzantine Empire during the sixth century, killing an estimated 40 million persons in the Mediterranean basin. The second pandemic began in Central Asia and spread west along caravan routes to reach the Crimean Sea port of Kaffa (now Feodosiya in Ukraine) in 1346.[3] In what is believed to be the first use of plague as a weapon, the Mongols, who were battling the Genoese for control of the city, reportedly catapulted bodies of plague victims over the city walls. Genoese ships returning to Italy introduced the disease into several port cities, and from 1347–54, the "Black Death" spread swiftly through Europe and the British Isles, killing an estimated one-third of the population.[4] Although some historians have questioned whether the Black Death was actually caused by plague,[5] evidence from archeologic and transmission studies strongly supports the role of *Y. pestis* as the causative agent.[6–8] Plague persisted in Europe for the next 300 years, causing periodic outbreaks before dying out.

The third, or "modern," pandemic began in China's Yunnan Province in the 1850s. Infection spread along trade routes to Hong Kong, where Alexandre Yersin isolated the causative agent in 1894. Four years later Paul-Louis Simond identified the plague bacillus in the tissues of dead rats and subsequently proposed a role for fleas in transmission. Over the ensuing 20 years steamships helped disseminate *Y. pestis*–infected rats and fleas to port cities worldwide, including several in North America. Rat-associated plague was soon brought under control in most urban areas; however, infection spread to other species of rodents and became entrenched in rural areas of the Americas, Africa, and Asia. The region most affected has shifted over time from India, where more than 20 million cases occurred during the first half of the 20th century, to war-torn Vietnam during the 1960s and 1970s, and finally to sub-Saharan Africa. Collectively, Madagascar, Uganda, Tanzania, and the Democratic Republic of Congo currently account for the majority of cases reported worldwide.[9–12]

Along with its historical importance, *Y. pestis* has considerable potential as a biological weapon. During World War II the Japanese military dropped ceramic bombs with plague-infected fleas over areas of China, apparently causing outbreaks. Both the United States and the Soviet Union evaluated *Y. pestis* as a potential weapon during the Cold War era, and in the 1980s a Soviet defector to Great Britain revealed that the Russians had succeeded in preparing a powdered aerosolized form, genetically engineered to be resistant to several antibiotics. The potential for misuse by terrorists is considered an important national security threat, requiring special measures for medical and public health preparedness.[13] The plague bacillus is designated as a Tier I (formerly Category A) select agent whose handling is regulated by federal law.[14,15]

MICROBIOLOGY

Y. pestis is an aerobic, gram-negative coccobacillus that exhibits bipolar staining with Giemsa, Wright, and Wayson stains. A member of the Enterobacteriaceae, it grows well on blood or MacConkey agar and in nutrient broths, such as brain-heart infusion. When incubated at 37°C, small colonies 1 to 2 mm in diameter are visible on blood or MacConkey agar after 24 to 48 hours. At 72 hours, colonies grown on blood agar can take on a raised, irregular, "fried-egg" morphology. *Y. pestis* does not form spores and, unlike *Y. enterocolitica* and *Y. pseudotuberculosis,* is nonmotile when incubated at lower temperatures. It does not ferment lactose and is citrate, urease, and indole negative.[16]

Genomic studies indicate that *Y. pestis* evolved recently from the enteric pathogen *Y. pseudotuberculosis*.[17,18] The transition from enteric to flea-borne pathogen required the ability to survive in the flea gut and to achieve high concentrations in the blood of mammalian hosts. These traits were endowed in part through the acquisition of two plasmids encoding factors that are differentially expressed at temperatures encountered in fleas and mammals.[19–21] The 110-kilobase (kb) pMT1/pFra plasmid encodes both *Yersinia* murine toxin (Ymt), which is

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necessary for colonization of the flea midgut, and the fraction 1 (F1) envelope antigen, which inhibits phagocytosis in mammals (Table 229A.1). The smaller 9.5-kb pPCP1 plasmid encodes a plasminogen activator protein (Pla protease) that is responsible for temperature-dependent coagulase and fibrinolysin activities. The origins of these plasmids remain uncertain; however, approximately half of the DNA sequences of the pMT1/pFra plasmid are shared with a plasmid of *Salmonella enterica* serotype Typhi.[22]

As with the other yersiniae, the plague bacillus also has an approximately 70-kb plasmid that mediates expression of virulence factors that prevent production of proinflammatory cytokines, increases resistance to phagocytosis, and enhances intracellular survival.[23] Chromosome-mediated factors include a potent lipopolysaccharide endotoxin and a pigmentation factor, the hemin storage locus *(hms),* which regulates iron uptake and enables the bacteria to form blockages of the flea gut that enhance transmission.[19,20]

Y. pestis isolates can be classified into three principal biovars based on their ability to ferment glycerol and reduce nitrate. It has been postulated that these biovars—Antigua, Medievialis, and Orientalis—reflect strains associated with the first, second, and third pandemics, respectively. Various molecular methods suggest, however, that these biovars do not correlate fully with phylogenetic relationships, and although Orientalis is associated with the third pandemic, the association of earlier pandemics with specific biovars remains uncertain.[18,24,25]

EPIDEMIOLOGY

Although not the scourge it once was, plague remains a threat in areas of Africa, Asia, and the Americas, including the western United States (Fig. 229A.1).[11,26] Before 2007, when required notification was discontinued, between 1000 and 6000 cases were reported annually to the World Health Organization (WHO) from 25 countries.[27] Nearly 80% of cases were reported from Africa, 15% from Asia, and the remainder from the Americas. During 2010–15, only about 500 plague cases were reported annually to WHO.[12] Nevertheless, the potential for cases and outbreaks persists, especially in rural areas of Madagascar, Uganda, and the Democratic Republic of Congo. In 2017 an outbreak of pneumonic plague was reported in the capital city of Madagascar, with more than 2700 suspect cases identified. Although the true number of infections

TABLE 229A.1 Key Virulence and Transmission Factors of *Yersinia pestis*

LOCATION	FACTOR(S)	PUTATIVE FUNCTION
pPCP1 plasmid (9.5 kb)	Plasminogen activator (Pla protease)	Protease: targeted activity at mammalian tissue barriers; adhesion: enhances invasion of mammalian cells; coagulase: promotes blockage of flea midgut
pCD1 plasmid (70–75 kb)	*Yersinia* outer protein (Yop) virulon	Type III secretion system inhibits phagocytosis and lymphocyte proliferation; transport of effector proteins to host cells
	V antigen	Facilitates intracellular survival; required for type III secretion system translocation pore
pMT1/pFra plasmid (≈110 kb)	Fraction 1 antigen	Expressed at higher temperatures; creates capsule that interferes with phagocytosis
	Yersinia murine toxin (Ymt)	Phospholipase D activity upregulated at lower temperatures, necessary for colonization of flea midgut and blockage formation; toxic for mice and rats
Chromosome (4.6 Mb)	Hemin storage system (Hms)	Proteins produced at lower temperatures; iron acquisition; colonization of flea proventriculus, biofilm production
	Yersiniabactin (Ybt) system	Siderophore; iron acquisition
	Yersinia Fe uptake system	Adenosine triphosphate–binding cassette transport system; iron acquisition
	Lipopolysaccharide	Temperature-dependent remodeling of lipid A structure; prevents containment by mammalian immune response
	pH 6 fimbriae antigen (Psa)	Blocks phagocytosis; pH dependent

kb, Kilobase; *Mb,* megabase.
Data from references 1, 12, and 14.

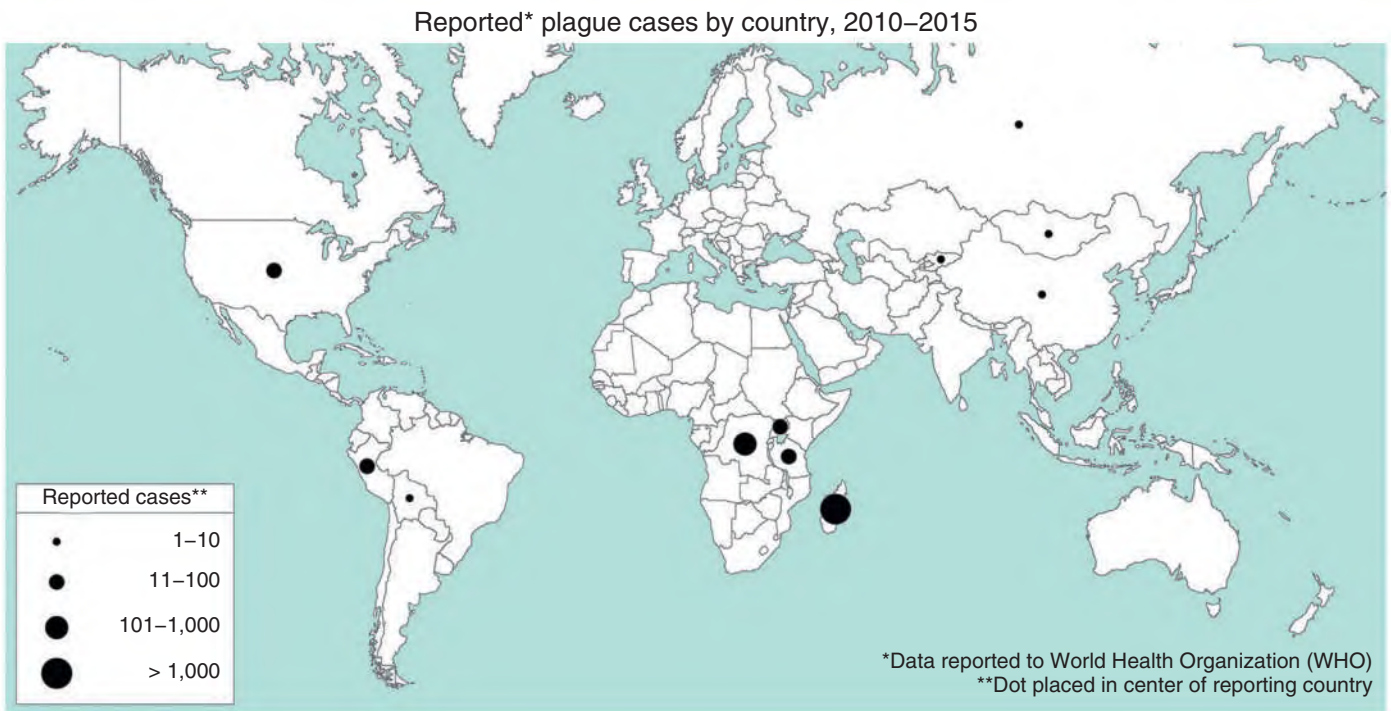

FIG. 229A.1 Worldwide distribution of plague in humans (as reported to the World Health Organization), 2010–15. Dots are placed in center of reporting country and are proportional to the number of reported cases. *(Data compiled from the World Health Organization, Centers for Disease Control and Prevention, and other sources.)*

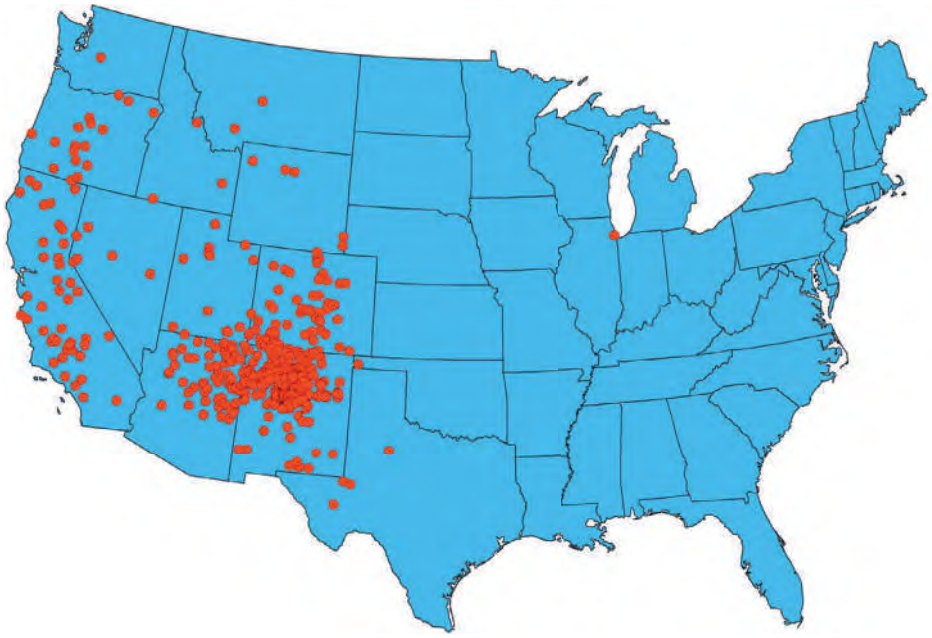

FIG. 229A.2 Cases of plague in the western United States, 1970–2016. Each dot represents one case, with the dot placed randomly in the county of exposure. *(Courtesy Centers for Disease Control and Prevention.)*

was likely far lower, the social and economic impact was substantial.[28] As demonstrated by reports of human plague cases in Algeria and Libya, the disease can reemerge in an area even after decades of quiesence.[29]

In the United States plague has been reported since 1900.[30] Initially restricted to port cities, plague is currently endemic in the 17 contiguous western states extending from the Pacific Coast to the Great Plains. A total of 437 cases in humans were reported during 1970– 2010 (≈10 cases per year), with 60 deaths (14% mortality). During 2010–16 there were 2 to 16 cases per year in the United States.[12,31] Approximately 80% of human cases occur in New Mexico, Arizona, and Colorado and 10% in California (Fig. 229A.2).[32] Human plague is most common during May through October, when fleas are active; wintertime cases are rare and often associated with hunting. Males are slightly more likely to be infected, and more than half of cases occur in persons younger than 20 years. Incidence is highest among Native Americans and Hispanics, although non-Hispanic whites account for the majority of cases.[33] Within endemic areas, elevated plague risk is associated with close contact with rodents and their feline and canine predators, the presence of harborage and food sources for wild rodents in the vicinity of homes, and possibly a failure to control fleas on pet dogs and cats.[34,35] Expanding suburban development in prime plague habitat has led to increasing cases in some areas and a shift toward higher socioeconomic groups in recent years.[36] Travelers with plague can present a diagnostic challenge when encountered outside endemic areas (peripatetic plague) and may trigger concern about possible terrorist exposures.[37]

NATURAL CYCLES

The epizootiology of plague is complex and not completely understood (Fig. 229A.3).[38] Fundamentally a flea-transmitted disease of rodents, plague is found in endemic foci scattered throughout the world. Different foci involve different rodent and flea species, each with their own ecology and predilection for disease. Perhaps triggered by climatic conditions, epizootics characterized by explosive spread and sudden mass mortality among susceptible rodents occur periodically. Epizootics promote dispersal of infected fleas and increase the risk for transmission to humans, especially when rodent species living in close proximity to humans are involved. Worldwide, the most concerning are the peridomestic rats, *Rattus rattus* and *Rattus norvegicus,* and their highly efficient flea vectors, *Xenopsylla cheopis* and *Xenopsylla braziliensis.* In the western United States epizootics occur among ground squirrels (*Spermophilus*

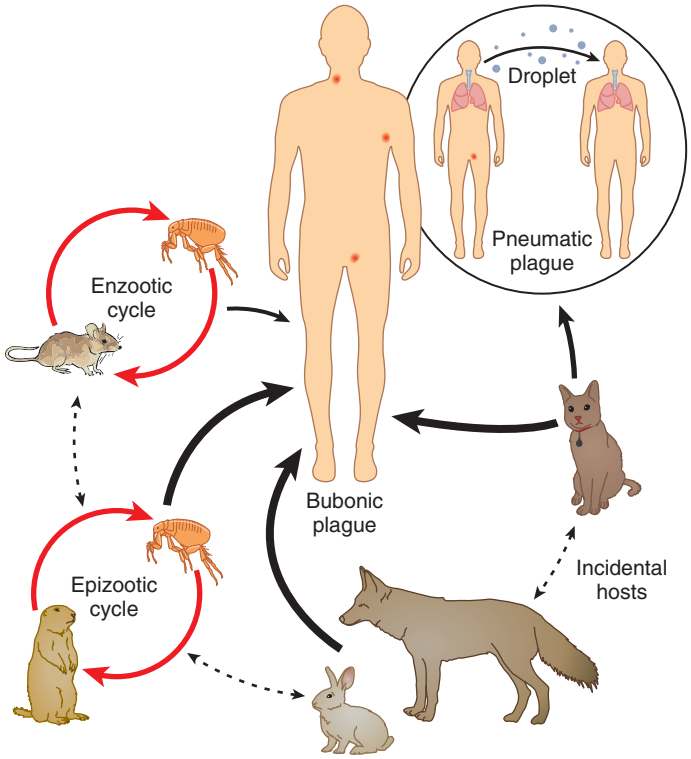

FIG. 229A.3 Ecology and transmission of plague. Red arrows indicate zoonotic cycles.

spp.), prairie dogs (*Cynomus* spp.), and chipmunks (*Tamias* spp.), as well as less familiar rodent species.

How *Y. pestis* survives in nature between epizootics is uncertain. One hypothesis holds that the organism continues to circulate slowly and undetected in enzootic cycles involving rodent species that are less susceptible to fulminant infection.[39] An alternative hypothesis holds that although the organism dies rapidly on inanimate surfaces, it may be able to survive in a niche within the soil, periodically infecting

burrowing rodent hosts.[6] This second hypothesis has received support recently by the demonstration that *Y. pestis* can replicate within certain free-living ameba,[40] an ability that may also relate to the organism's capacity as a facultative intracellular pathogen.

TRANSMISSION TO HUMANS

Humans become infected with *Y. pestis* through flea bites, direct contact with tissues or secretions of infected animals, or rarely through inhalation of infectious aerosols (see Fig. 229A.3). Flea-borne transmission is especially common during epizootics when large numbers of rodents die and their fleas seek alternative sources for a blood meal. Hunters become infected through direct inoculation while skinning or handling carcasses of infected rodents, rabbits and hares, wild cats, and coyotes.[41] Direct inoculation is associated with an increased risk for septicemia and death, possibly because the bacterium, coming directly from a warm-blooded host, is already expressing F1 antigen and thus less susceptible to phagocytosis. Consumption of uncooked meat from camels, goats, and other ungulates, which are also susceptible to infection, has been identified as the source of small outbreaks in northern Africa, the Middle East, and Central Asia.[42] Aerosols generated while handing infected animals can also pose a risk, as demonstrated by the case of a US wildlife biologist who developed primary pneumonic plague after necropsying an infected mountain lion.[43] Although generally "dead-end" hosts, humans who develop pneumonic plague can transmit the infection to close contacts through respiratory droplets.

Domestic pets are also an important source of potential exposure. Domestic cats that eat infected rodents develop pharyngeal infections that can be transmitted directly to humans through respiratory droplets, causing primary pneumonic plague.[44] Although dogs appear less likely to become clinically ill when infected, fulminant pneumonia in dogs with transmission to owners has been reported.[45] In addition, dogs may play a role in increasing human exposure by transporting rodent fleas into the home, especially if they are allowed to sleep on their owner's bed at night.[34] Laboratory infections, once common, are rare under current practices. Nevertheless, in 2009 a US laboratory researcher died of sepsis caused by an attenuated strain of *Y. pestis* that lacked the virulence genes necessary for iron absorption. Postmortem evaluation revealed that the worker had undiagnosed hemochromatosis.[46,47]

PATHOGENESIS

Fleas become infected when feeding on a bacteremic host. In the cooler environment of the flea, the bacillus expresses a variety of factors that facilitate colonization of the flea midgut, replication, and blockage of the flea intestine (see Table 229A.1).[21] Starved of sustenance, "blocked" fleas feed aggressively, regurgitating bacteria into the bite wound. Many of the inoculated bacteria are likely phagocytized and killed by polymorphonuclear lymphocytes; however, a few are taken up by mononuclear cells and carried via lymphatics to the regional lymph nodes.[19] Growing at 37°C, the bacteria begin expressing F1 envelope antigen, enhancing their ability to resist subsequent phagocytosis by polymorphonuclear lymphocytes.[2,19] Within the lymph node, the bacilli stimulate an intense inflammatory response that is detectable clinically as a bubo. Microscopic examination of the fully developed bubo reveals invasion by polymorphonuclear leukocytes, hemorrhagic necrosis with destruction of normal architecture, and dense concentrations of extracellular bacilli. Bacteremia is common and, in the absence of specific therapy, can lead to secondary pneumonia, disseminated intravascular coagulation, acute renal failure, and irreversible shock.[48] Blockage of vessels in cooler acral sites, including fingers, toes, ears, and nose, can lead to gangrene (Fig. 229A.4), a startling feature that may have given rise to the name "Black Death."[49] Pathogenesis of pneumonic plague is marked by a rapid, destructive proinflammatory phase that results in rapid death.[50]

CLINICAL MANIFESTATIONS

Plague takes several different clinical forms, depending in part on the route of exposure. In the United States 80% to 85% of patients present with primary bubonic plague, 15% with septicemic plague, and 1% to 3% with pneumonic or other forms of plague. The usual incubation period is 2 to 7 days but can be as short as 1 day for patients with primary pneumonic plague.

Bubonic Plague

Bubonic plague results from cutaneous exposure and is characterized by the sudden onset of high fever, chills, weakness, and headache. A bubo or swelling of regional lymph nodes becomes apparent in the groin, axilla, or neck within the first day. Buboes vary from 1 to 10 cm and elevate the overlying skin, which may be warm and erythematous. Palpation typically elicits extreme tenderness. Bubonic plague is distinguished from other forms of lymphadenitis by its sudden onset, the intensity of inflammation in the bubo, and the usual absence of obvious skin lesions or associated ascending lymphangitis (Fig. 229A.5). Nevertheless, careful examination distal to the bubo will occasionally reveal a small papule or scab demarcating the site of the flea bite.[48,51] Rarely, ulcers or eschars may develop, which can be confused with those of anthrax or tularemia (Fig. 229A.6). The differential diagnostic possibilities for bubonic plague include cat-scratch disease, staphylococcal or streptococcal lymphadenitis, tularemia, filarial lymphadenitis, chancroid and other sexually transmitted diseases, and strangulated hernia.

Septicemic Plague

Septicemic plague is characterized by the sudden onset of high fever without associated bubo or other obvious localizing signs. Illness is rapidly progressive, leading to overwhelming sepsis and organ failure within a few days. Typically, the diagnosis is not considered until *Y.*

FIG. 229A.4 Hand of a patient with plague displaying acral gangrene, a manifestation that may have given rise to the name "Black Death." *(Courtesy Centers for Disease Control and Prevention.)*

FIG. 229A.5 Femoral and inguinal buboes in a boy showing marked edematous swelling, erythema, and overlying desquamation. *(Courtesy Centers for Disease Control and Prevention.)*

FIG. 229A.6 Axillary bubo with ulceration and small eschar at the site of an infective flea bite. *(Courtesy Centers for Disease Control and Prevention.)*

pestis is isolated from blood cultures. Some patients have gastrointestinal symptoms of nausea, vomiting, diarrhea, or abdominal pain, which may further complicate the diagnostic workup.[52] Because of delays in diagnosis and treatment, the case-fatality rate for septicemic plague in the United States is approximately 28%, three times higher than for bubonic plague.[53,54]

Pneumonic Plague

Pneumonic plague occurs in two forms, secondary and primary, both of which are frequently fatal and potentially contagious to close contacts.[55,56] Secondary pneumonic plague is the more common form and arises through hematogenous spread of bacteria from a bubo or other source. Approximately 10% of all plague patients in the United States develop secondary pneumonic plague, usually as a result of delayed treatment of bubonic infections. Secondary pneumonic plague begins as an interstitial process with cough productive of scant, tenacious sputum, typically beginning 5 to 6 days after illness onset. Chest radiographs reveal diffuse alveolar infiltrates that are almost always bilateral and often accompanied by pleural effusions.[57] If untreated, sputum will become more copious and eventually bloody, and death will often occur within 3 to 4 days.

Primary pneumonic plague is a fulminant condition that results from direct inhalation of bacteria into the lungs. This can occur through contact with another patient with pneumonic plague, exposure to animals (especially cats) with respiratory or pharyngeal plague, laboratory exposures, or, potentially, as a result of intentional aerosol release for purposes of terrorism. Symptoms begin within 1 to 4 days after exposure. Patients experience sudden onset of fever, chills, headache, malaise, and rapidly advancing tachypnea, dyspnea, hypoxia, chest pain, cough, hemoptysis, and general signs of endotoxemia. Chest radiographs demonstrate a lobar pneumonia initially (Fig. 229A.7), followed by dense consolidation and bronchopneumonic spread to other lobes of the same or opposite lung.[44,58] Sputum is often purulent but may be watery, frothy, and copious and also may be blood tinged or grossly hemorrhagic, at which point it may contain large numbers of plague

FIG. 229A.7 Chest radiograph of patient with primary pneumonic plague. *(Courtesy Centers for Disease Control and Prevention.)*

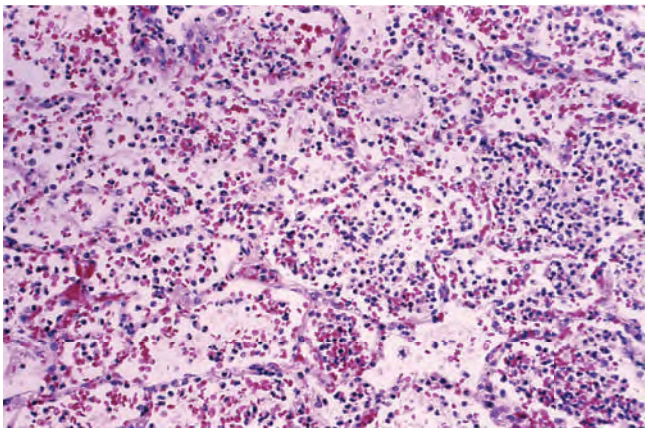

FIG. 229A.8 Photomicrograph of lung tissue from fatal case of primary pneumonic plague and septicemic plague. Note filling of alveolar spaces with inflammatory cells and debris. *(Courtesy Centers for Disease Control and Prevention.)*

bacilli.[55] Histologically, numerous bacilli and inflammatory cells fill the alveolar space[50] (Fig. 229A.8). Untreated pneumonic plague is almost always fatal, and mortality is very high in persons whose treatment is delayed beyond 24 hours after symptom onset. The case-fatality rate for pneumonic plague in the United States since 1950 approaches 25%.

To prevent person-to-person transmission, patients with suspected pneumonic plague should be managed in isolation under respiratory droplet precautions.[13,59] Strict isolation under negative pressure and filtering exhaust is not necessary because infectious dispersal by fine aerosol or dried droplet nuclei does not occur. Person-to-person transmission of pneumonic plague requires close contact, typically with a patient who is in the late stages of infection and coughing copious amounts of bloody sputum.[60] The last confirmed outbreak of person-to-person respiratory spread in the United States occurred in Los Angeles in 1924, and there have been at least nine subsequent cases of primary pneumonic plague without secondary transmission.[44] Nevertheless, in 2014 three persons in Colorado developed primary pneumonic plague after exposure to an ill, infected dog. Although it could not be proven, one of the patients may have acquired the infection while caring for an infected family member in the hospital.[45]

Other Syndromes

Plague meningitis is a rare complication that can occur acutely or as a delayed manifestation of inadequately treated bubonic plague. Symptoms include fever, headache, sensorial changes, and meningismus. Examination of cerebrospinal fluid (CSF) reveals a pleocytosis with predominance

of polymorphonuclear leukocytes. Bacteria are frequently demonstrable with a Gram or Wayson stain of CSF sediment. Another rare presentation is pharyngeal plague, which resembles acute tonsillitis. The anterior cervical lymph nodes are usually inflamed, and *Y. pestis* may be recovered from a throat culture or by aspiration of a cervical bubo. Asymptomatic pharyngeal colonization with *Y. pestis* has also been reported among close contacts of patients with pneumonic plague. Osteomyelitits involving both skull and long bones has been reported.[61]

LABORATORY FINDINGS

Laboratory findings in patients with plague are similar to those of patients with other serious gram-negative infections. Peripheral white blood cell counts generally range from 10,000 to 25,000 cells/mm^3 with a predominance of immature neutrophils. Leukemoid reactions with counts as high as 50,000/mm^3 or greater can occur. Platelet counts may be normal or low in the early stages of bubonic plague. Bacteremia is common; in one series, single blood cultures obtained at the time of hospital admission were positive in 27% of cases.[51] Without prompt treatment, patients develop such high-level bacteremia that bipolar staining bacilli can be seen in the peripheral blood smear, a finding that strongly suggests the diagnosis of plague and is associated with a poor outcome (Fig. 229A.9). Disseminated intravascular coagulation, thrombocytopenia, elevated results of liver function tests, and impaired renal function are all common in advanced stages of illness.[51]

DIAGNOSIS

Plague should be considered in any patient with an acute febrile illness and a risk for exposure to infected animals or fleas in a plague-endemic area. A careful history and thorough physical examination are required to make a timely diagnosis; a delayed or missed diagnosis of plague is associated with a high case-fatality rate. In the United States the Laboratory Response Network provides upgraded, standardized diagnostic testing for *Y. pestis* and other select agents.[14,62] All state public health laboratories have the ability to conduct rapid and confirmatory testing or, if necessary, forward materials to the CDC for confirmation and advanced procedures, including molecular subtyping.[63]

When plague is suspected, diagnostic specimens should be obtained promptly and effective antimicrobial therapy initiated immediately thereafter.[13] Chest radiographs should be obtained to rule out pneumonia. Appropriate diagnostic specimens include blood cultures and bubo aspirates, sputum, tracheobronchial washes, swabs of skin lesions or pharyngeal mucosa, and CSF, as indicated by signs and symptoms. Bubo aspirates are especially useful and can be obtained by inserting a 20-gauge needle on a 10-mL syringe containing 2 mL of sterile saline solution into the bubo and withdrawing the plunger several times until the saline becomes blood tinged.

Primary specimens can be stained with Wayson or Giemsa stain and with Gram stain, and then examined using light microscopy. In the case of pneumonic plague, stain and culture of bronchial washings or expectorated sputum may yield a putative diagnosis quickly. With Wayson staining, *Y. pestis* appears as light blue bacilli with dark blue polar bodies, giving the organisms a closed safety-pin appearance that is characteristic of, but not pathognomonic for, *Y. pestis*. If possible, the specimens should also be examined using direct fluorescent antibody (DFA) testing. Presumptive identification of *Y. pestis* can be made by polymerase chain reaction assay.[16,63,64]

Laboratory confirmation is best achieved through the isolation of *Y. pestis* from body fluids or tissues. Samples should be inoculated onto suitable culture media (e.g., brain-heart infusion broth, sheep blood agar, chocolate agar, or MacConkey agar) and held for 5 to 7 days.[16] Plague bacilli are readily distinguished from other gram-negative bacteria by staining properties, growth characteristics, and biochemical profiles. Nevertheless, automated identification systems frequently misidentify *Y. pestis* as other species, an error that frequently delays diagnosis.[65] Isolates are confirmed in reference laboratories by lysis with *Y. pestis*–specific bacteriophage.

In patients with negative cultures, plague can be confirmed serologically by passive hemagglutination testing for antibodies to *Y. pestis* F1 antigen. A fourfold or greater change in titer between an acute serum and a convalescent serum collected 3 to 4 weeks later is considered diagnostic, as is a single titer greater than or equal to 1:128 in an unvaccinated patient with compatible illness.[16] A small percentage of plague patients will develop diagnostic antibody levels within 5 days after illness onset, most seroconvert within 1 to 2 weeks, a few seroconvert more than 3 weeks after onset, and less than 5% fail to seroconvert.[66] Rapid, handheld chromatographic assays designed to detect *Y. pestis* F1 antigen in patient samples are being evaluated for rapid presumptive diagnosis at the bedside.[67]

For diagnosis in fatal cases, samples of lymph nodes, liver, spleen, lungs, and bone marrow should be collected at autopsy for culture, DFA antibody testing, and histologic studies, including immunohistochemical staining. Cary-Blair or a similar holding medium can be used to transport swabs or tissues for culture.

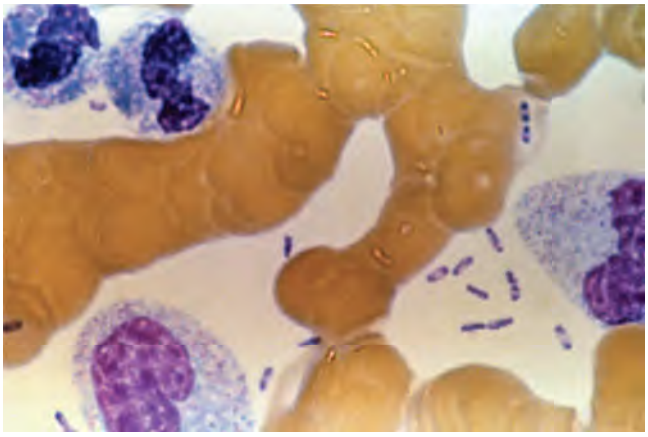

FIG. 229A.9 Peripheral blood smear of septicemic plague patient showing large numbers of bipolar-staining bacilli. *(Courtesy Centers for Disease Control and Prevention.)*

THERAPY

Antimicrobial Agents

Without treatment, 50% of patients with bubonic plague and nearly all patients with septicemic or pneumonic plague will die. Effective antibiotic therapy should be given immediately after obtaining diagnostic specimens. Although fluoroquinolones may offer a less toxic alternative (see later), streptomycin has been considered the drug of choice since its introduction in the 1940s, and prompt administration can reduce the mortality rate in bubonic plague to 5% or less. Streptomycin should be administered intramuscularly twice daily, in a dose for adults of 15 mg/kg/dose (maximum, 1 g) for 7 days or at least 3 days after remission of fever and other symptoms. Most patients improve rapidly and become afebrile after approximately 3 days of therapy.[48] Streptomycin is ototoxic and nephrotoxic and should be used cautiously in pregnant women, older patients, and patients with hearing difficulty.

Although not approved by the US Food and Drug Administration (FDA) for treatment of plague, gentamicin has been proposed as an acceptable alternative based on in vitro susceptibility studies, animal models, and reports of efficacy in treating humans with plague.[13,68–72] A retrospective analysis of 50 plague patients treated in New Mexico between 1985 and 1999 suggests that gentamicin, or a combination of gentamicin and doxycycline, is at least as efficacious as streptomycin.[73] All 36 gentamicin-treated patients survived without complications. In a randomized trial of 65 patients with plague in Tanzania, 94% of patients treated with gentamicin recovered.[74] Gentamicin is considered to be safer than streptomycin for use in pregnant women and children.

For patients with contraindications to the use of aminoglycosides, tetracycline and its congeners are satisfactory alternatives. Doxycycline is the tetracycline of choice in treating plague because of the convenience of its twice-daily dose schedule, its rapid absorption from the gut, and its superior ability to achieve peak serum concentrations. 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[75] and is followed by a daily dose

of 100 mg every 12 hours. 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 to 10 days or for at least 3 days after fever and other symptoms have subsided.

Levofloxacin, ciprofloxacin, and moxifloxicin have been approved recently by the FDA for treatment of plague, based on studies showing the efficacy in vitro and in animal models, including African green monkeys.[76–82] Published information on successful treatment of human plague is limited, however.[83] In a small case series from Uganda, six patients with culture-confirmed plague, including one with secondary pneumonic plague, were treated successfully with oral ciprofloxacin.[84] Based on FDA approval and pharmacologic properties, either levofloxicin or chloramphenicol should be used for conditions in which high tissue penetration is important, such as plague meningitis, pleuritis, or myocarditis.[13,68,80] It may be used separately or in combination with an aminoglycoside. Chloramphenicol is given as a loading dose of 25 to 30 mg/kg, followed by 50 to 60 mg/kg/day in four divided doses. As indicated by clinical response, the chloramphenicol dose may be reduced to a daily dose of 25 to 30 mg/kg/day to lessen the magnitude of bone marrow suppression, which is reversible. 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. Trimethoprim-sulfamethoxazole (cotrimoxazole) has been used successfully to treat bubonic plague, but responses may be delayed and incomplete, and it is not considered a first-line choice. Penicillins, cephalosporins, and macrolides have a suboptimal clinical effect and are not recommended for use in treating plague.

Strains of *Y. pestis* that are resistant to antimicrobial agents have only rarely been isolated from humans. Usually these strains have shown partial resistance to a single agent only 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 and the second resistant to multiple drugs, including streptomycin, chloramphenicol, ampicillin, tetracycline, and sulfonamides.[68] Nevertheless, both patients recovered when treated per protocol with streptomycin and trimethoprim-sulfamethoxazole. Molecular studies have identified very different plasmids in the two strains, and they are believed to have arisen independently, possibly through horizontal gene transfer in the flea midgut.[68] It is unclear whether such resistance would be expected to propagate in nature in the absence of antibiotic pressure on wild rodent populations, and to date these remain the only such natural isolates identified among thousands tested worldwide. Antimicrobial resistance is not known to have emerged during the treatment of plague in humans, and relapses after recommended courses of treatment are virtually unknown.

Supportive Therapy

The hemodynamic status of patients with plague should be monitored closely and shock managed according to general principles used to combat endotoxic shock.[85] There is no evidence that corticosteroids are beneficial in treating plague. Buboes usually recede during the first week of antibiotic treatment, but it may be several weeks before they completely resolve; on occasion, they enlarge or become fluctuant, requiring incision and drainage.

PREVENTION

Infection Control

All suspected plague cases should be reported immediately to state health department authorities for assistance with confirmation of microbiologic diagnosis, epidemiologic investigation, and protection of the public's health. Patients with uncomplicated infections who are treated promptly do not present a hazard to others. Those with cough or other signs of pneumonia should be placed in isolation and managed under respiratory droplet precautions for at least 48 hours after the initiation of antibiotic therapy or until the sputum culture is negative. Respiratory droplet precautions include the use of masks, gowns, gloves, and protective eyewear when providing direct patient care.[59] Cultures of clinical materials are usually negative after 24 hours of treatment. Patients without respiratory plague can be managed under standard precautions. Potentially infective clinical fluids should be handled with gloves and with care to avoid aerosolization, as could result from dropping a specimen or by breakage of a container during centrifugation. Routine clinical specimens are managed in the laboratory under Biosafety Level 2 precautions, but manipulation of cultures should be performed in a negative-pressure hood using Biosafety Level 3 procedures.

Chemoprophylaxis

Antibiotics can be used for chemoprophylaxis against plague in persons believed to have had an infective exposure within the previous 7 days, such as family members, care providers, and others with a close and direct contact with a patient having pneumonic plague or a laboratory worker exposed to an accident that may have created an infective aerosol.[13] Doxycycline, given in an adult dose of 100 mg twice daily for 7 days, or ciprofloxacin, 500 mg twice daily for 7 days, are appropriate choices for prophylaxis.

Vaccination

Historically, two types of plague vaccine have been available for use in humans, a killed whole-cell vaccine (KWC) and a live-attenuated vaccine (LWC). Neither vaccine is currently licensed for use in the United States, although LWC is reportedly available in Russia.[86] The KWC vaccine is not effective against respiratory exposures and has no usefulness in combating epidemic disease in a setting of modern sanitation and prophylactic antibiotics.[87] Nevertheless, concern for bioterrorism and the possibility of engineered, multidrug resistance have maintained interest in the development of effective vaccines for plague. A series of candidate vaccines have been developed using recombinant capsular subunit protein F1 and the low-calcium response V antigen (LcrV), either as a mixture of the two antigens or as a fusion of the two antigens. Both types of vaccine have shown promise in animal models against subcutaneous, intranasal, or aerosol challenge, and various constructs have been evaluated in phase I and phase II trials.[86] Other recent approaches toward immunization include development of DNA vaccines, expression of protective antigens in live bacterial, viral, and plant carriers; passive immunization with aerosolized monoclonal antibodies; and vaccines based on attenuated *Y. pseudotuberculosis*.[86]

Environmental Control

Persons living in endemic areas should take precautions to reduce exposure to rodents and fleas, including rat-proofing dwellings, removing food and harborage for rodents, using repellents, and applying insecticides on their pets.[32] Local or state health authorities should be consulted for regionally appropriate advice on rodent and vector control. If killing of rodents is considered, flea control should be performed before or at the same time to reduce the chances that infected fleas will feed on humans.

BIOTERRORISM

Y. pestis is designated a Tier 1 select agent, reflecting its high potential for use as a biological weapon. The organism is found naturally in many parts of the world, is relatively easy to manipulate in the laboratory, including the introduction of antimicrobial resistance, and has been previously developed and used as a biological weapon. Furthermore, because of its rich history, plague has a cultural cachet that amplifies its effect as an agent of social disruption well beyond its direct medical impact.[88]

Intentional release of *Y. pestis* could be achieved through several routes; however, an aerosol release is generally considered the most deadly and therefore the most likely. Aerosol exposure would be expected to cause an outbreak of primary pneumonic plague, which is rapidly fatal and has the potential for secondary person-to-person transmission. WHO estimates that a release of 50 kg of *Y. pestis* over a city of 5 million people could result in 150,000 cases of pneumonic plague and 36,000 deaths.[89] Clinicians and hospital laboratorians would almost certainly be the first to recognize an outbreak and should be familiar with the clinical features of pneumonic plague (see earlier discussion).[90,91] The appearance of multiple patients with fulminant pneumonia, especially

if characterized by bloody sputum containing gram-negative rods, should raise consideration of a bioterrorist attack.

To aid in the laboratory recognition of bioterrorism events, the American Society of Microbiology, in coordination with the CDC and the Association of Public Health Laboratories (APHL), has developed protocols designed to assist Sentinel Level Clinical Microbiology Laboratories with information and techniques to evaluate microorganisms that might be suspected as agents of bioterrorism or to refer specimens to public health laboratories for confirmation.[63] In addition, the Working Group on Civilian Biodefense has published recommendations for treatment and postexposure prophylaxis of plague in the setting of a bioterrorism event (Table 229A.2).[13] These recommendations predate FDA approval of fluoroquinolones for treatment of plague, and concerns for engineered multidrug resistance may dictate the use of multiple agents until results of antimicrobial resistance testing are available. Treatment recommendations for contained casualty settings are similar to those listed earlier for naturally occurring plague. In a mass casualty setting, medication shortages may increase the need for use of non–FDA-approved agents. For example, gentamicin is recommended by the Working Group on Civilian Biodefense but has not been approved by the FDA for treatment or prevention of plague. Individual physicians can decide to use these agents from local sources off label; however, use of these drugs from the US government's Strategic National Stockpile (SNS) would require either an Emergency Use Authorization (EUA) issued by the Secretary of Health and Human Services or an Investigational New Drug (IND) application.[92] In anticipation, the CDC has submitted IND and pre-EUA applications for the use of the agents for plague in the event of a bioterrorist attack. WHO has published additional guidance for the public health officials.[93]

MASS PROPHYLAXIS

Mass chemoprophylaxis is a likely public health response after an intentional release of *Y. pestis* and could be a valuable control measure. Although prevention of illness in patients exposed to the primary release would be logistically challenging, given the short incubation period of 1 to 4 days between exposure and illness onset, prophylaxis of their contacts to prevent secondary transmission may be achievable. Nevertheless, recent modeling suggests that the risk for secondary transmission is quite low for most patients and that droplet precautions and social distancing may be quite effective at preventing subsequent transmission.[94] Plague vaccines are not currently available in the United States and, given the short incubation period, would not have a role in an immediate response. A variety of tools have been developed to assist the health care community prepare for a bioterrorism or mass casualty event.[95,96]

OCCUPATIONAL EXPOSURE

A minimum of Biosafety Level 3 PPE (i.e., Tyvek outer clothing, gloves, booties, and positive-pressure high-efficiency particulate air [HEPA]-filtered respirators) should be used for field work involving necropsy of infected animals.[97] Morticians, forensic personnel, and veterinarians should follow precaution standards published for other health care workers.[59] Recommendations on biosafety practices for laboratory workers have been published.[98]

ENVIRONMENTAL PERSISTENCE

Y. pestis does not form spores and is highly susceptible to desiccation and damage by ultraviolet radiation in sunlight. As a general rule, the majority of organisms released into the environment are expected to become nonviable within 1 hour.[89] Nevertheless, plague bacilli can survive in the soil for prolonged periods under certain circumstances and might serve as a source of infection for rodents.[99] Standard treatment of sewage would decrease but not eliminate contamination.[100] Monitoring of animal populations may be a useful tool to assess the geographic extent of environmental contamination and ongoing risk for human infection after an intentional release.

TABLE 229A.2 Working Group on Civilian Biodefense Recommendations for Treatment of Pneumonic Plague[a]

Contained Casualty Setting	
Adults	Preferred choices: Streptomycin: 1 g IM twice daily Gentamicin: 5 mg/kg IM or IV once daily or 2 mg/kg loading dose followed by 1.7 mg/kg IM or IV 3 times daily[b] Alternative choices: Doxycycline; 100 mg IV twice daily or 200 mg IV once daily Ciprofloxacin: 400 mg IV twice daily[c] Chloramphenicol: 12–25 mg/kg IV 4 times daily[d]
Children[e]	Preferred choices: Streptomycin: 15 mg/kg IM twice daily (maximum daily dose, 2 g) Gentamicin: 2.5 mg/kg IM or IV 3 times daily[b] Alternative choices: Doxycycline: if ≥45 kg, give adult dosage; if <45 kg, give 2.2 mg/kg IV twice daily (maximum, 200 mg/day) Ciprofloxacin: 15 mg/kg IV twice daily[c] Chloramphenicol: 12–25 mg/kg IV 4 times daily[d]
Pregnant women[f]	Preferred choice: Gentamicin: 5 mg/kg IM or IV once daily or 2 mg/kg loading dose followed by 1.7 mg/kg IM or IV 3 times daily[b] Alternative choices: Doxycycline: 100 mg IV twice daily or 200 mg IV once daily Ciprofloxacin: 400 mg IV twice daily[c]
Mass Casualty Setting and Postexposure Prophylaxis[g]	
Adults	Preferred choices: Doxycycline: 100 mg PO twice daily[i] Ciprofloxacin: 500 mg PO twice daily[c] Alternative choice: Chloramphenicol: 12–25 mg/kg PO 4 times daily[i]
Children[e]	Preferred choices: Doxycycline[h]: if ≥45 kg, give adult dosage; if <45 kg, give 2.2 mg/kg PO twice daily Ciprofloxacin: 20 mg/kg PO twice daily Alternative choice: Chloramphenicol: 12–25 mg/kg PO 4 times daily[i]
Pregnant women[f]	Preferred choices: Doxycycline: 100 mg PO twice daily[h] Ciprofloxacin: 500 mg PO twice daily Alternative choice: Chloramphenicol: 12–25 mg/kg PO 4 times daily[i]

[a] *Modified from Inglesby TV, Dennis DT, Henderson DA, et al. Plague as a biological weapon: medical and public health management. Working Group on Civilian Biodefense.* JAMA. *2000;283:2281–2290.* After publication of these recommendations, the US Food and Drug Administration (FDA) approved levofloxacin, ciprofloxacin, and moxifloxacin for treatment of plague. Therapy continued for 10 days. Oral therapy can be substituted when the patient's condition improves.

[b] Gentamicin is not FDA-approved for treatment of plague, although animal and limited human studies support its use (see text). Evidence suggests that once-daily dosing may be efficacious with lower toxicity. Aminoglycoside dosages should be adjusted for renal function.

[c] Other fluoroquinolones can be substituted at doses appropriate for age. Ciprofloxacin dosage should not exceed 1 g/day in children.

[d] See text regarding loading dose. Concentration should be maintained between 5 and 20 μg/mL; concentrations >25 μg/mL can cause reversible bone marrow suppression.

[e] In children, the ciprofloxacin dose should not exceed 1 g/day.

[f] All recommended antibiotics for plague have relative contraindications for use in children and pregnant women; however, use is justified in life-threatening situations.

[g] The duration of postexposure prophylaxis to prevent plague infection is 7 days.

[h] Tetracycline can be substituted for doxycycline.

[i] Children younger than 2 years should not receive chloramphenicol. Chloramphenicol dose should not exceed 4 g/day. An oral formulation is available only outside the United States.

IM, Intramuscular; *IV,* intravenous; *PO,* oral.

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229B *Yersinia enterocolitica* and *Yersinia pseudotuberculosis*

Richard R. Watkins

SHORT VIEW SUMMARY

Definition
- Zoonoses with multiple animal hosts; widespread in environment
- Display tropism for lymph nodes

Epidemiology
- Fecal-oral transmission; enteric pathogens; more common in children
- Worldwide distribution but most common in northern Europe; infections frequently occur in winter months; *Yersinia enterocolitica* serogroup O:3 causes most disease in the United States

Microbiology
- Aerobic and anaerobic growth, non–spore forming, pleomorphic, non–lactose fermenting gram-negative bacilli; members of family Enterobacteriaceae
- Motile at 25°C but nonmotile at 37°C; growth at 37°C on MacConkey agar, *Salmonella-Shigella* agar (*Y. enterocolitica*), and brain-heart infusion; CIN (cefsulodin, irgasan, novobiocin) agar is selective medium
- Distinguished from other enteric pathogens and from *Yersinia pestis* by biochemical profiles

Clinical Manifestations
- Enterocolitis, mesenteric lymphadenitis, and pseudoappendicitis are most common
- Risk for sepsis is increased in those with iron overload or treated with iron-chelating agents (e.g., deferoxamine)
- Reactive arthritis, erythema nodosum, and Graves disease may follow gastrointestinal illness

Diagnosis
- Can be cultured from stool, blood, bile, wounds, throat, mesenteric lymph nodes, cerebrospinal fluid, and peritoneal fluid
- Acute and convalescent serology; molecular methods are becoming more widespread
- Automated systems can misidentify

Therapy
- Antimicrobial agents generally unnecessary for enteritis or mesenteric lymphadenitis in immunocompetent patients; do not reduce risk for postinfectious complications
- For extraintestinal symptoms, aminoglycosides, tetracycline, and fluoroquinolones are effective; *Y. enterocolitica* often produce β-lactamases, precluding the use of penicillin and lower-generation cephalosporins

Prevention
- Follow safe food handling practices; avoid undercooked meat (especially pork), unwashed vegetables, and unpasteurized dairy products
- Vaccine development is in early stages, none is available for humans or animals

First discovered in 1894 in Hong Kong by Alexandre Yersin and Shibasaburo Kitasato, the genus *Yersinia* currently includes 18 species. Of these, only three have been identified as human pathogens: *Y. pestis, Y. pseudotuberculosis,* and *Y. enterocolitica*. While *Y. pestis* causes plague and is responsible for one of the greatest calamities in human history, the Black Death of mid-14th century Europe, infections from *Y. pseudotuberculosis* and *Y. enterocolitica* generally cause a self-limited gastrointestinal illness. Genetic analysis has shown that *Y. pseudotuberculosis* is the direct evolutionary ancestor of *Y. pestis* and the two organisms have approximately 98% identity at the DNA level.[1] The contrast in lifestyle and virulence between *Y. pestis* and *Y. pseudotuberculosis* is mainly due to the presence of two additional plasmids that *Y. pestis* possesses, as well as minor genomic differences.[2] *Yersinia pseudotuberculosis* and *Y. enterocolitica* are among the most divergent of the species and gained their pathogenicity independently, yet they share pathogenicity islands and other virulence factors and cause similar gastrointestinal diseases. Although gastroenteritis is the most common presentation of yersiniosis, other clinical features include mesenteric adenitis, terminal ileitis, septicemia, and reactive arthritis. All *Yersinia* species are zoonotic, with humans being accidental hosts. The modes of transmission are primarily fecal-oral, by hand-to-mouth transfer of organisms following handling of contaminated animals and animal carcasses, and by ingestion of contaminated food or water. Patients who are immunodeficient, recipients of blood transfusions, and those with iron overload treated with deferoxamine are at particular risk of *Yersinia* sepsis.

MICROBIOLOGY

As members of the family Enterobacteriaceae, *Y. enterocolitica* and *Y. pseudotuberculosis* are non–spore forming, pleomorphic, non–lactose fermenting gram-negative bacilli that grow under aerobic and anaerobic conditions. They are urease-positive organisms, which distinguishes them from urease-negative *Y. pestis*. Both *Y. enterocolitica* and *Y. pseudotuberculosis* are motile at 25°C but not at 37°C. They grow on brain heart infusion agar, MacConkey agar, and *Salmonella-Shigella* agar at room temperature and at 37°C and in buffered saline at 4°C. Culture on specific selective media (cefsulodin irgasan novobiocin [CIN] agar), with or without preenrichment in broth or phosphate-buffered saline at 4°C or 16°C, is one protocol for isolating *Y. enterocolitica* and *Y. pseudotuberculosis* from stool and other nonsterile sites. They form 2- to 4-mm colonies with a characteristic deep red center (bull's-eye) and a transparent margin on CIN agar. The colonies are difficult to detect after incubation for 24 hours but are easily visible at 48 hours (Fig. 229B.1). *Yersinia enterocolitica* and *Y. pseudotuberculosis* can be distinguished from other enteric pathogens and from *Y. pestis* by biochemical profiles. Strains are differentiated by combined biochemical reactions and serogroups. Six biotypes (1A, 1B, 2, 3, 4, 5) and 60 serogroups of *Y. enterocolitica* have been described; not all strains are pathogenic for humans. Clinical infections are mostly associated with serogroups O:3, O:9, and O:5,27 and biotypes 2, 3, and 4. The previously dominant serogroup O:8 has been declining in North America.[3] There is a separate system for serotyping *Y. pseudotuberculosis,* which is also based on somatic antigens. Fourteen serotypes of *Y. pseudotuberculosis* have been identified, five of which (O:1 to O:5) are considered pathogenic for humans. Serotype O:1 accounts for approximately 80% of isolates from humans.

A multitude of virulence factors allow *Y. enterocolitica* and *Y. pseudotuberculosis* to adhere to host cells and tissues and undermine immunologic defenses. The most extensively studied is the type III secretion system (T3SS) that is carried on the pYV virulence plasmid.

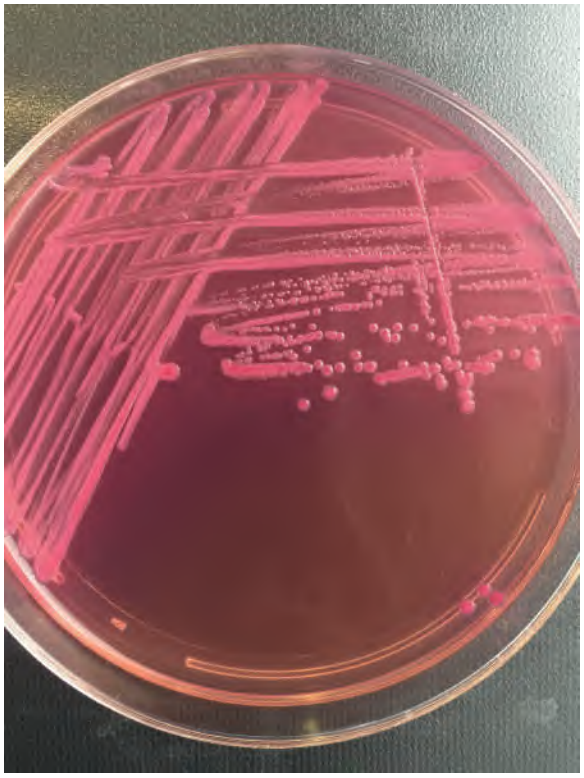

FIG. 229B.1 Yersinia enterocolitica growing on cefsulodin irgasan novobiocin agar. *(Courtesy Drs. Sandra Richter and Joshua Otiso.)*

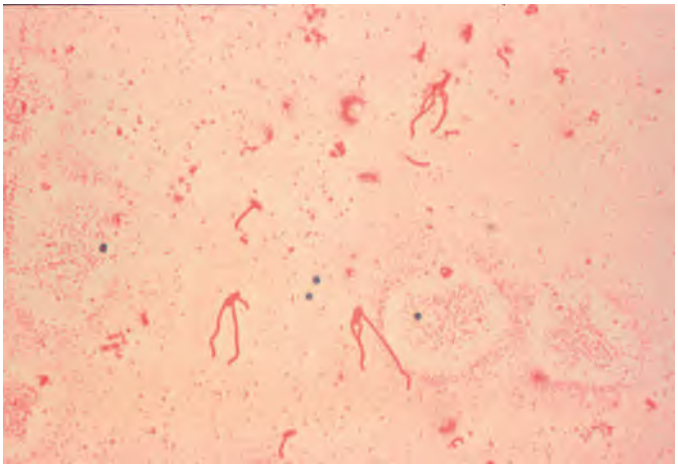

FIG. 229B.2 Photomicrograph of Yersinia enterocolitica using a flagella-staining technique. *(From the Public Health Images Library, Centers for Disease Control and Prevention.)*

The T3SS injects *Yersinia* outer proteins (Yops) directly into the host cell, causing subversion of signaling pathways that suppresses transcription of genes of the innate immune response, inhibition of phagocytosis, and blockage of cytokine production.[4] Chromosomal virulence factors include adhesion proteins YadA (previously known as Yop1), invasin (Inv), Ail, and MyfA; the heat-stable enterotoxin Yst; and the *myf* operon that encodes genes of a fimbria similar to the CS3 fimbria of enterotoxigenic *Escherichia coli*.[4] Furthermore, 1B/O:8 strains of *Y. enterocolitica* contain a high-pathogenicity island that encodes yersiniabactin, a siderophore that enhances iron acquisition. Serogroup O:3 and O:9 isolates of *Y. enterocolitica* lack this siderophore for iron transport and are less invasive in normal hosts. However, in the setting of iron overload or treatment with therapeutic chelating agents (e.g., deferoxamine), these strains can achieve virulence similar to O:8 strains. *Yersinia enterocolitica* use flagella (Fig. 229B.2) to help establish contact with the intestinal epithelium.[4] The role that Yst plays in gastroenteritis is controversial. Yst is not detectable in diarrheal stool samples in infected animal models, and some strains carry the *yst* gene but do not produce the enterotoxin, suggesting the presence of silent genes. Nevertheless, noninvasive 1A strains that cause diarrhea often carry the *yst* gene as their only virulence factor.[5] *Yersinia pseudotuberculosis* produces *Y. pseudotuberculosis*–derived mitogen (YPM), a superantigenic toxin that induces proliferation of human T lymphocytes and causes toxic shock. The genes that code for YPM are not carried by plasmids but are inserted in an unstable locus of the genome.[6]

EPIDEMIOLOGY

The reservoirs for *Y. enterocolitica* and *Y. pseudotuberculosis* are diverse and include soil, water, and the intestinal tracts of wild and domestic animals. Most of the environmental strains are avirulent, but those in pigs and their food products are the major source for pathogenic *Y. enterocolitica* in humans.[7] Yersiniosis has a global distribution and is the third most common zoonosis in Europe. Germany accounts for over half of the reported cases, with an annual incidence of 7.2 per 100,000 population.[8] This may be due to a higher prevalence of *Y. enterocolitica* and *Y. pseudotuberculosis* in animal reservoirs, as well as higher pork consumption in Germany compared to other European nations. In the United States, the average annual incidence of yersiniosis is 0.16 cases per 100,000 population.[9] There has been a significant decrease in infections among African Americans less than 5 years of age but an increasing incidence among whites ages 19 to 64 years and Hispanics. This decline in African-American children may be due to educational efforts in the state of Georgia.[10] Infections have been reported in other parts of the world, including South America, Africa, and Asia, but yersiniosis is not considered an important cause of tropical diarrhea. In 2014, a sustained outbreak of yersiniosis from *Y. pseudotuberculosis* occurred in all the major cities of New Zealand, with 220 laboratory-confirmed cases.[11] Genomic and epidemiologic data suggested a single point-source contamination of the food chain, with subsequent nationwide distribution of contaminated produce. Unlike other enteropathogens, *Yersinia* infections often occur during winter months and in cold climates.

The majority of cases of gastrointestinal illness occur in children under 5 years of age, whereas mesenteric adenitis and terminal ileitis are more common among older children and adults. In the United States, yersiniosis is more likely to be diagnosed in young children compared with the general population.[12] Transmission of infection occurs by ingestion of contaminated food or water and, less often, by direct contact with infected animals or patients (Fig. 229B.3). The zoonotic reservoirs of *Y. enterocolitica* are diverse and include pigs, dogs, cats, rodents, bats, sheep, deer, horses, rabbits, cows, beavers, and muskrats. Flies can also be carriers and might facilitate the spread of yersiniosis from animals to humans.[13] In France, *Y. pseudotuberculosis* tends to be more common in wild animals, particularly birds, rodents, hares, and rabbits, compared to domesticated ones.[14] *Yersinia enterocolitica* is frequently present on the tonsils and in the alimentary tract of pigs, and transmission can occur by ingesting incompletely cooked pork and by contamination of other foods by pork products. Outbreaks of yersiniosis have been associated with contaminated milk and milk products[15]; contaminated produce such as bean sprouts, carrots, and lettuce[16]; and foods contaminated with spring water.[17] The ability of the organisms to grow at 4°C means that refrigerated meats can be sources of infection. Cases of sepsis due to *Y. enterocolitica* have occurred following transfusion of blood stored between 2°C and 6°C.[18] Occupational exposure to pigs increases the risk of infection in farmers,[19] slaughterhouse workers,[19] and butchers.[20] Among pregnant Danish women with occupational exposures, elevated immunoglobulin G to *Y. enterocolitica* serogroup O:3 was not a risk factor for adverse pregnancy outcomes.[21] Household transmission likely occurs through the fecal-oral route since children with yersiniosis may excrete the organism in their stool for several weeks. The cecum may become chronically colonized and serve as a reservoir for dissemination of infection to extraintestinal sites.[22]