cases of tularemia in which the patient becomes afebrile within the first 48–72 h of gentamicin treatment, a 5- to 7-day course has been successful.

If available, streptomycin given intramuscularly is also effective. The dosage for adults is 2 g/d in two divided doses. For children, the dosage is 30 mg/kg daily in two divided doses (maximal daily dose, 2 g). After a clinical response is demonstrated at 3–5 days, the dosage for children can be reduced to 10–15 mg/kg daily in two divided doses. The total duration of streptomycin therapy in both adults and children is usually 10 days. Unlike streptomycin and gentamicin, tobramycin is ineffective in the treatment of tularemia and should not be used.

Because doxycycline is bacteriostatic against *F. tularensis*, there is a risk of relapse if the patient is not treated for a long enough period. Therefore, if doxycycline is used, it should be given for at least 14 days. The lack of availability of chloramphenicol limits the utility of this agent as a viable treatment option. Fluoroquinolones—specifically, ciprofloxacin and levofloxacin—have been used with good outcomes to treat infections caused by subspecies *holarctica*, which is most often found in Europe. The lack of data on the efficacy of these agents against subspecies *tularensis* limits their use in North America at this time.

F. tularensis cannot be subjected to standardized antimicrobial susceptibility testing because the organism will not grow on the media used. A wide variety of antibiotics, including all β-lactam antibiotics and the cephalosporins, are ineffective for the treatment of tularemia. Several studies indicated that third-generation cephalosporins were active against *F. tularensis* in vitro, but clinical case reports suggested nearly universal failure of ceftriaxone in pediatric patients with tularemia. Although in vitro data indicate that imipenem may be active, therapy with imipenem, sulfanilamides, and macrolides is not presently recommended because of the lack of relevant clinical data.

Virtually all strains of *F. tularensis* are susceptible to streptomycin and gentamicin. Hearing screening should be considered before initiation of streptomycin or gentamicin therapy. In successfully treated patients, defervescence usually occurs within 2 days, but skin lesions and lymph nodes may take 1–2 weeks to heal. When therapy is not initiated within the first several days of illness, defervescence may be delayed. Relapses are uncommon with streptomycin or gentamicin therapy. Late lymph-node suppuration, however, occurs in ~40% of children, regardless of the treatment received. These nodes have typically been found to contain sterile necrotic tissue without evidence of active infection. Patients with fluctuant nodes should receive several days of antibiotic therapy before drainage to minimize the risk to hospital personnel.

PROGNOSIS

If tularemia goes untreated, symptoms usually last 1–4 weeks but may continue for months. The mortality rate from severe untreated infection (including all cases of untreated pulmonary and typhoidal tularemia) can be as high as 30%. However, the overall mortality rate for untreated tularemia is <8%. With appropriate treatment, the mortality rate is <1%. Poor outcomes are often associated with long delays in diagnosis and treatment. Lifelong immunity usually follows tularemia.

PREVENTION

The prevention of tularemia is based on avoidance of exposure to biting and blood-sucking insects, especially ticks and deerflies. A wide range of approaches to vaccine development are being evaluated, but no vaccine against tularemia is yet licensed. Prophylaxis of tularemia has not proved effective in patients with embedded ticks or insect bites. However, in patients who are known to have been exposed to large quantities of organisms (e.g., in the laboratory) and who have incubating infection with *F. tularensis*, early treatment can prevent the development of significant clinical disease.

196 Plague and Other *Yersinia* Infections

Michael B. Prentice

PLAGUE

Plague is a systemic zoonosis caused by *Yersinia pestis*. It predominantly affects small rodents in rural areas of Africa, Asia, and the Americas and is usually transmitted to humans by an arthropod vector (the flea). Less often, infection follows contact with animal tissues or respiratory droplets. Plague is an acute febrile illness that is treatable with antimicrobial agents, but mortality rates among untreated patients are high. Ancient DNA studies have confirmed that the fourteenth-century "Black Death" in Europe was *Y. pestis* infection. Patients can present with the bubonic, septicemic, or pneumonic form of the disease. Although there is concern among the general public about epidemic spread of plague by the respiratory route, this is not the usual route of plague transmission, and established infection-control measures for respiratory plague exist. However, the fatalities associated with plague and the capacity for infection via the respiratory tract mean that *Y. pestis* fits the profile of a potential agent of bioterrorism. Consequently, measures have been taken to restrict access to the organism, including legislation affecting diagnostic and research procedures in some countries (e.g., the United States).

ETIOLOGY

The genus *Yersinia* comprises gram-negative bacteria of the family Enterobacteriaceae (gamma proteobacteria). Overwhelming taxonomic evidence showing *Y. pestis* strains as a clonal group within *Yersinia pseudotuberculosis* suggests recent evolution from the latter organism—an enteric pathogen of mammals that is spread by the fecal-oral route and thus has a phenotype distinctly different from that of *Y. pestis*. When grown in vivo or at 37°C, *Y. pestis* forms an amorphous capsule made from a plasmid-specified fimbrial protein, Caf or fraction 1 (F1) antigen, which is an immunodiagnostic marker of infection.

EPIDEMIOLOGY

Human plague generally follows an outbreak in a host rodent population (epizootic). Mass deaths among the rodent primary hosts lead to a search by fleas for new hosts, with consequent incidental infection of other mammals. The precipitating cause for an epizootic may ultimately be related to climate or other environmental factors. The reservoir for *Y. pestis* causing enzootic plague in natural endemic foci between epizootics (i.e., when the organism may be difficult to detect in rodents or fleas) is a topic of ongoing research and may not be the same in all regions. The enzootic/epizootic pattern may be the result of complex dynamic interactions of host rodents that have different plague susceptibilities and different flea vectors; alternatively, an environmental reservoir may be important.

In general, the enzootic areas for plague are lightly populated regions of Africa, Asia, and the Americas **(Fig. 196-1)**. Between 2004 and 2009, 12,503 cases of plague, with a global case-fatality rate of 6.7%, were recorded by the World Health Organization (WHO); these figures were obtained by combining cases notified under the International Health Regulations with data from national surveillance programs and publications. More than 97% of these cases were in Africa; the majority of cases were reported from the Democratic Republic of the Congo and the island of Madagascar. The period covered spans a change in the International Health Regulations from a requirement for nations to notify the WHO of all cases of plague to a requirement to report pneumonic plague or any suspected case of plague in an area not known to be endemic for plague. In the past decade, outbreaks of pneumonic plague have been recorded in the Democratic Republic of the Congo, Uganda, Algeria, Madagascar, China, and Peru.