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type A variety. For the type B F. tularensis variety, the same surveillance data from 1964–2004 showed a 7% fatality outcome. Caution in inter preting these latter data is warranted, as they likely are overestimates of mortality due to selected reporting and disease severity bias from the inclusion of culture-positive cases only. Recent analyses of patients with respiratory/pneumonic type B tularemia in Sweden revealed a 1.5% fatality. Outcome analyses considering all clinical forms of tulare mia suggest an overall type B tularemia fatality rate of <1% in Sweden. The frequency of disease complications, including lymphadenopathy, among 327 patients was <10%, much lower than previously reported for tularemia, likely because appropriate antibiotics were often given early, at a median of 7 days after disease onset. ■ ■PREVENTION Standard precautions are recommended for infection control and pre vention in the clinic. Face protection using goggles or a face shield and a fluid-resistant medical mask should be used in procedures with a risk of splashes from potentially infected body fluids. Only procedures with a very high risk of aerosol formation that may contain live F. tularensis, such as the surgical evacuation of pus from an abscess by applying high pressure or autopsy work with rotating tools, warrant respiratory protec tion with an N95 mask. Tularemia patients do not need to be isolated, given there is no human-to-human transmission. Because F. tularensis is a known risk for laboratory-acquired infection, suspected isolates should, at a minimum, be manipulated at BSL-2 using BSL-3 precautions in a biosafety cabinet. In the United States, specialized reference labora tories should always be consulted and involved in attempts for complete identification and antimicrobial susceptibility testing of F. tularensis. Vaccination is a potentially important measure for preventing tularemia. However, no U.S. Food and Drug Administration (FDA)-approved F. tularensis vaccines exist. The efficacy of the only available vaccine, LVS, is uncertain given concerns about adverse reactions to the vaccine, potential for reversion, unknown correlates of protection, and variable immunogenicity. Prevention strategies for the public include measures to avoid F. tularensis exposure. It is advised to avoid tick-infested areas and mosquito bites in tularemia-endemic areas, wear trousers and longsleeved shirts, use arthropod repellants, and remove attaching ticks promptly. Exposure to and touching dead or sick wild mammals should be avoided. If touching the mammal is necessary, gloves should be worn and hands should be washed thoroughly after removing the gloves. In addition to avoiding direct contact, exposure to potentially F. tularensis–contaminated aerosols should also be avoided, e.g., from handling dry hay or grain where carcasses of rodents are found. ■ ■GLOBAL CONSIDERATIONS Due to its past development as a biologic weapon, there is a risk that

F. tularensis could be used as a biothreat agent. F. tularensis is considered an HHS Tier 1 Select Agent in the United States because it presents the greatest risk of deliberate misuse with the most significant potential for mass casualties or devastating effects to the economy, critical infra structure, or public confidence. From 1932 to 1945, Japanese research units examined the utility of F. tularensis as a biologic weapon. After World War II, there were continuous military studies of tularemia. In the United States, there were federally funded biologic warfare pro grams from 1943 to 1969, with the development of weapons to dissemi nate type A F. tularensis aerosols. By 1973, the entire F. tularensis weapon arsenal of the United States had been destroyed. The former Soviet Union, as part of the civilian component of its offensive Biopreparat program, also incorporated F. tularensis into weapons. In 1970, the World Health Organization published a report estimating that an aero sol dispersal of 50 kg of virulent type A F. tularensis over a metropolitan area with 5 million inhabitants would result in 250,000 incapacitating causalities, including 19,000 deaths. Efficacy trials of tularemia vaccines in humans against highly viru lent type A tularemia are not feasible, and animal studies are judged to be the best option for screening and evaluating new vaccine candidates. There is ongoing research on the matter, including evaluating vaccines under the FDA “Animal Rule,” aimed at bridging the outcomes in ani mals to use in humans.

New tularemia treatment options with promising results, tested in experimentally infected animals, include the use of passive immuniza tion by F. tularensis–specific antibodies and a new triazaacenaphthylene antibiotic, gepotidacin. This new antibiotic class blocks bacterial DNA replication via inhibition of DNA gyrase and topoisomerase IV and is claimed to have no cross-resistance with the fluoroquinolones. Impor tantly, experience from treatment of humans with tularemia is lacking for both these treatments.

Considerations for tularemia in pregnant women include a recom mendation to use antibiotic treatment to avoid a risk of loss of preg nancy. Literature is scarce, but the available data suggest that the risk of adverse outcomes, including lymph node complications in the mother, maternal bleeding, spontaneous abortion, intrauterine fetal death, and preterm birth, is lowered with prompt institution of antibiotic treat ment. F. tularensis findings in transplacental villi and transplacental transmission to the fetus have been reported without treatment. ■ ■FURTHER READING
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antimicrobial treat ment, and outcomes: An analysis of US surveillance data, 2006–2021. Clin Infect Dis 78:S29, 2024. Yanes H et al: Evaluation of in-house and commercial serological tests for diagnosis of human tularemia. J Clin Microbiol 56:e01440, 2017. Michael B. Prentice

Plague and Other

Yersinia Infections 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 antimi crobial agents, but mortality rates among untreated patients are high.

Ancient DNA studies have confirmed that both the fourteenth-century Black Death and the sixth-century Plague of Justinian in Europe were due to Y. pestis infection. Patients can present with the bubonic, sep ticemic, or pneumonic form of the disease. Although there is concern about epidemic spread of plague by the respiratory route, this is not the most common route of plague transmission, and established infectioncontrol 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 bioter rorism (Chap. S4). 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 order Enterobacterales (class Gammaproteobacteria). Overwhelming taxo nomic and paleogenomic evidence shows Y. pestis recently evolved from Yersinia pseudotuberculosis, an enteric pathogen of mammals spread by the fecal–oral route, and thus has a phenotype distinctly dif ferent 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 popula tion (epizootic). Mass deaths among the rodent primary hosts lead to a search by fleas for new hosts, with consequent incidental infec tion 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 with different flea vectors; alternatively, an envi ronmental reservoir may be important. PART 5 Infectious Diseases ■ ■GLOBAL FEATURES In general, the enzootic areas for plague are lightly populated regions of Africa, Asia, and the Americas (Fig. 176-1). Between January 2013 and December 2018, 2886 cases of plague with a global case-fatality rate of 17% were notified to the World Health Organization (WHO) under the International Health Regulations. More than 97% of these Countries reporting human plague cases, 1970−2005 Probable sylvatic foci FIGURE 176-1 Approximate global distribution of Yersinia pestis. (Compiled from WHO, CDC, and country sources. Reprinted with permission from DT Dennis, GL Campbell: Plague and other Yersinia infections, in Harrison’s Principles of Internal Medicine, 17th ed, AS Fauci et al [eds]. New York, McGraw-Hill, Chap. 152, 2008.)

cases were in Africa. The majority of cases in each year were from the island of Madagascar, which in 2017 experienced an urban outbreak of over 2400 clinically suspected cases, with an unusually high proportion of pneumonic plague (78%). A decline in reports from the Democratic Republic of the Congo (DRC) may reflect ongoing conflict in that country affecting surveillance rather than a true decrease. In the past decade, outbreaks of pneumonic plague have been recorded in the DRC, Uganda, Algeria, Madagascar, China, and Peru. Plague was introduced into North America via the port of San Francisco in 1900 as part of the Third Pandemic, which spread around the world from Hong Kong. The disease is presently enzootic on the western side of the continent from southwestern Canada to Mexico. Most human cases in the United States occur in two regions: “Four Corners” (the junction point of New Mexico, Arizona, Colorado, and Utah), especially northern New Mexico, northern Arizona, and south ern Colorado; and further west in California, southern Oregon, and western Nevada (https://www.cdc.gov/plague/maps-statistics/). From 1970 to 2020, 496 cases of plague were reported in the United States; in recent decades, incidence has fallen to an average of seven cases per year. Most cases occur from May to October—the time of year when people are outdoors and rodents and their fleas are most plentiful. Prior animal contact occurs in at least 50% of cases, and about 60% of these include domestic animals (usually dogs or cats) that brought wild animals or plague-infected fleas home. Infected cats or dogs may transmit plague directly to humans by the respiratory route. A slightly lower percentage of prior animal contacts involve direct handling of living or dead wild small mammals (e.g., rabbits, hares, prairie dogs) or wild carnivores (e.g., wildcats, coyotes, or mountain lions). In 2014, an outbreak of nonfatal pneumonic plague in Colorado affected four people exposed to an infected dog, with possible interhuman transmis sion in one case. Prior to this report, the most recent case of person-toperson transmission in the United States occurred in the Los Angeles pneumonic plague outbreak of 1924. Plague most often develops in areas with poor sanitary conditions and infestations of rats—in particular, the widely distributed roof rat Rattus rattus and the brown rat Rattus norvegicus (which serves as a laboratory model of plague). Rat control in warehouses and shipping facilities has been recognized as important in preventing the spread of plague since the early twentieth century and features in the current WHO International Health Regulations. Urban rodents acquire infec tion from wild rodents, and the proximity of the former to humans increases the risk of transmission. The oriental rat flea Xenopsylla cheopis is the most efficient vector for transmission of plague among rats and onward to humans in Asia, Africa, and South America.

Worldwide, bubonic plague is the predominant form reported. A minority of patients (10–20%) present with primary septicemic plague (i.e., systemic Y. pestis sepsis with no bubo; see “Clinical Manifestations,” below) or pneumonic disease. Primary pneumonic plague is generally the least common and most fatal of the main plague presentations, but, as in the 2017 Madagascar outbreak, it is occasionally predominant. Rare outbreaks of pharyngeal plague following consumption of raw or undercooked camel or goat meat have been reported. A total of 744 (82%) of the 913 plague cases with clinically docu mented features (out of 1006 cases reported in total) in the United States from 1900 to 2012 were bubonic disease, 87 (10%) were septice mic disease, and 74 (8%) were pneumonic disease; 6 cases (1%) were pharyngeal. Sixteen percent of cases were fatal in the postantibiotic era from 1942 onward compared with 66% in the period 1900–1941. This century (2000–2018), mortality in the United States has been 8% in patients receiving any antimicrobial and 4% in patients receiving one of the high-efficacy antimicrobials currently recommended as therapy. A systematic review and meta-analysis of the worldwide literature estimated a death rate for treated pneumonic plague of 17%, compared with 98% for untreated

pneumonic plague. ■ ■PATHOGENESIS As mentioned earlier, genetic evidence shows Y. pestis is a clone derived from the enteric pathogen Y. pseudotuberculosis in the recent evolutionary past (7000–50,000 years ago). The change from infection by the fecal–oral route to a two-stage life cycle, with alternate parasitization of arthropod and a wide range of mammalian hosts, occurred as a result of two plasmid gene acquisitions (pla on pPCP1/pPst and ymt on pFra/pMT1), and the inactivation of a handful of Y. pseudotuberculosis genes, in conjunction with preexisting proper ties of the Y. pseudotuberculosis ancestor, including the presence of a virulence plasmid, pYV, and the capacity to cause septicemia. In the arthropod-parasitizing portion of its life cycle, Y. pestis multiplies and forms biofilm-embedded aggregates in the flea midgut after ingestion of a blood meal containing bacteria. In some fleas, biofilm-embedded bacteria eventually fill the proventriculus (a valve connecting the esophagus to the midgut) and block normal blood feeding. Both “blocked” fleas and those containing masses of biofilm-embedded Y. pestis without complete blockage inoculate Y. pestis into each bite site. The ability of Y. pestis to colonize and multiply in fleas fed on infected blood from most hosts requires phospholipase D encoded by the ymt gene on the pFra (pMT1) plasmid, and biofilm synthesis requires the chromosomal hms locus shared with Y. pseudotuberculosis. Recently, it has been shown Y. pestis does not require an intact ymt gene to infect and be transmitted from fleas fed on blood from the brown rat (Rattus norvegicus), although this is required for blood from the black rat (Rattus rattus). Three Y. pseudotuberculosis genes inhibiting biofilm formation or promoting its degradation are inactivated in Y. pestis, together with urease (urease activity otherwise causes acute flea gastrointestinal toxicity). Blockage takes days or weeks to come about after initial infec tion of the flea and is followed by the flea’s death. Many flea vectors (including X. cheopis) are also able to transmit plague in an early-phase unblocked state for up to a week after feeding, but 10 fleas in this state are required to infect a mammalian host (mass transmission). Y. pestis disseminates from the site of inoculation in the mammalian host in a process initially dependent on plasminogen activator Pla, which is encoded by the small pPCP1 (pPst) plasmid. This surface protease activates mammalian plasminogen, degrades complement, and adheres to the extracellular matrix component laminin. Pla is essential for the high-level virulence of Y. pestis in mice by subcutane ous or intradermal injection (laboratory proxies for fleabites) and for the development of primary pneumonic plague. When actual fleabite inoculation is used in mouse models, the fimbrial capsule-forming protein (Ca1 or fraction 1; F1 antigen) encoded on pFra increases the efficiency of transmission, and plasminogen activator is required for the formation of buboes. Paleogenomics (sequencing of DNA extracts from teeth of ancient human remains) shows that the 14th-century Black Death and the 6thcentury Plague of Justinian were caused by Y. pestis and suggests Black

Death mortality selected for protective immune response gene variants now associated with autoimmune disease. It has also revealed that Y. pestis infection was a common cause of death in Eurasia in the Bronze Age and Neolithic period. Remarkably, the ymt gene is absent from the pFra (pMT1) plasmid in Y. pestis sequences from some remains >4000 years old, whereas pla is present with intact urease and biofilm regulatory genes. This suggests that plague was a common fatal human infection before flea-borne transmission was fully optimized, possibly spread by the pneumonic or gastrointestinal route.

Macrophages, neutrophils, and dendritic cells are all involved in the innate immune response to flea-transmitted Y. pestis. The organ ism is taken up by macrophages but avoids being killed by autophagy and can also survive and replicate in neutrophils. Rapid transport of the bacteria to

regional lymph nodes occurs. Y. pestis then undergoes extracellular replication with full expression of its antiphagocytic sys tems: the type III secretion machines and their effectors encoded by pYV as well as the F1 capsule. These factors prevent neutrophil uptake, and the type III secretion effectors also block extrusion of microbicidal DNA by neutrophils and trigger apoptotic cell death. Immune cell targeting follows binding of the N-formylpeptide receptor (FPR1) on phagocytic cells by LcrV, the needle cap protein of the type III secre tion system. Overproduction of LcrV also exerts an anti-inflammatory effect, reducing host immune responses. Likewise, Y. pestis lipopolysac charide is modified to minimize stimulation of host Toll-like receptor 4, thereby reducing protective host inflammatory responses during peripheral infection and prolonging host survival with high-grade bacteremia—an effect that probably enhances the pathogen's subse quent transmission by fleabite. CHAPTER 176 Replication of Y. pestis in a regional lymph node results in the local swelling of the lymph node and periglandular region known as a bubo. On histology, the node is found to be hemorrhagic or necrotic, with thrombosed blood vessels, and the lymphoid cells and normal architec ture are replaced by large numbers of bacteria and fibrin. Periglandular tissues are inflamed and also contain large numbers of bacteria in a serosanguineous, gelatinous exudate. Plague and Other Yersinia Infections Continued spread through the lymphatic vessels to contiguous lymph nodes produces second-order primary buboes. Infection is initially contained in the infected regional lymph nodes, although transient bacteremia can be detected. As infection progresses, spread via efferent lymphatics to the thoracic duct produces high-grade bacte remia. Hematogenous spread to the spleen, liver, and secondary buboes follows, with subsequent uncontrolled septicemia leading to death. In some patients, this septicemic phase occurs without obvious prior bubo development or lung disease (septicemic plague). Hematogenous spread to the lungs results in secondary plague pneumonia, with bac teria initially more prominent in the interstitium than in the air spaces (the reverse being the case in primary plague pneumonia). Hematog enous spread to other organs, including the meninges, can occur. ■ ■CLINICAL MANIFESTATIONS Bubonic Plague After an incubation period of 2–6 days, the onset of bubonic plague is sudden and is characterized by fever (>38°C), malaise, myalgia, dizziness, and increasing pain due to progressive lymphadenitis in the regional lymph nodes near the fleabite or other inoculation site. Lymphadenitis manifests as a tense, tender swelling (bubo) that, when palpated, has a boggy consistency with an underly ing hard core. Generally, there is one painful and erythematous bubo with surrounding periganglionic edema. The bubo is most commonly inguinal but can also be crural, axillary (Fig. 176-2), cervical, or sub maxillary, depending on the site of the bite. Abdominal pain from intraabdominal node involvement can occur without other visible signs. Children are most likely to present with cervical or axillary buboes. The differential diagnosis includes acute focal lymphadenopathy of other etiologies, such as streptococcal or staphylococcal infection, tularemia, cat-scratch disease, tick typhus, infectious mononucleosis, or lymphatic filariasis. These infections do not progress as rapidly, are not as painful, and are associated with visible cellulitis or ascending lymphangitis—both of which are absent in plague.

FIGURE 176-2 Plague patient in the southwestern United States with a left axillary bubo and an unusual plague ulcer and eschar at the site of the infective flea bite. (Reprinted with permission from DT Dennis, GL Campbell: Plague and other Yersinia infections, in Harrison's Principles of Internal Medicine, 17th ed, AS Fauci et al [eds]. New York, McGraw-Hill, Chap. 152, 2008.) PART 5 Infectious Diseases Without treatment, Y. pestis dissemination occurs and causes seri ous illness, including pneumonia (secondary pneumonic plague) and meningitis. Secondary pneumonic plague can be the source of personto-person transmission of respiratory infection by productive cough

(droplet infection), with the consequent development of primary plague pneumonia. Appropriate treatment of bubonic plague results in fever resolution within 2–5 days, but buboes may remain enlarged for

> 1 week after initial treatment and can become fluctuant. Primary Septicemic Plague A minority (10–25%) of infections with Y. pestis present as gram-negative septicemia (hypotension, shock) without preceding lymphadenopathy. Septicemic plague occurs in all age groups, but persons >40 years of age are at elevated risk. Some chronic conditions may predispose to septicemic plague: in 2009 in the United States, a fatal laboratory-acquired infection with an attenu ated Y. pestis strain manifested as septicemic plague in a 60-year-old FIGURE 176-3 Sequential chest radiographs of a patient with fatal primary plague pneumonia. Left: Upright posteroanterior film taken at admission to hospital emergency department on third day of illness, showing segmental consolidation of right upper lobe. Center: Portable anteroposterior film taken 8 h after admission, showing extension of pneumonia to right middle and right lower lobes. Right: Portable anteroposterior film taken 13 h after admission (when patient had clinical acute respiratory distress syndrome), showing diffuse infiltration throughout right lung and patchy infiltration of left lower lung. A cavity later developed at the site of initial right-upper-lobe consolidation. (Reprinted with permission from DT Dennis, GL Campbell: Plague and other Yersinia infections, in Harrison's Principles of Internal Medicine, 17th ed. AS Fauci et al [eds]. New York, McGraw-Hill, Chap. 152, 2008.)

researcher with diabetes mellitus and undiagnosed hemochromato sis. These conditions also carry an increased risk of septicemia with other pathogenic Yersinia species. The term septicemic plague can be confusing since most patients with buboes have detectable bacteremia at some stage, with or without systemic signs of sepsis. In laboratory experiments, however, septicemic disease without histologic changes in lymph nodes is seen in a minority of mice infected via fleabites. Pneumonic Plague Primary pneumonic plague results from inha lation of infectious bacteria in droplets expelled from another person or an animal with primary or secondary plague pneumonia. This syndrome has a short incubation period, averaging from a few hours to 2–3 days (range, 1–7 days), and is characterized by a sudden onset of fever, headache, myalgia, weakness, nausea, vomiting, and diz ziness. Respiratory signs—cough, dyspnea, chest pain, and sputum production with hemoptysis—typically arise after 24 h. Progression of initial segmental pneumonitis to lobar pneumonia and then to bilat eral lung involvement may occur (Fig. 176-3). The possible release of aerosolized Y. pestis bacteria in a bioterrorist attack, manifesting as an outbreak of primary pneumonic plague in nonendemic regions or in an urban setting where plague is rarely seen, has been a source of public health concern. Secondary pneumonic plague is a consequence of bacteremia occurring in ~10–15% of patients with bubonic plague. Bilateral alveolar infiltrates are seen on chest x-ray, and diffuse intersti tial pneumonitis with scanty sputum production is typical. Meningitis Meningeal plague is uncommon, occurring in ≤6% of plague cases reported in the United States. Presentation with headache and fever typically occurs >1 week after the onset of bubonic or sep ticemic plague and may be associated with suboptimal antimicrobial therapy

(delayed therapy, penicillin administration, or low-dose tetra cycline treatment) and cervical or axillary buboes. Pharyngitis Symptomatic plague pharyngitis can follow the con sumption of contaminated meat from an animal dying of plague or contact with persons or animals with pneumonic plague. This condi tion can resemble tonsillitis, with peritonsillar abscess and cervical lymphadenopathy. Asymptomatic pharyngeal carriage of Y. pestis can also occur in close contacts of patients with pneumonic plague. ■ ■LABORATORY DIAGNOSIS Because of the scarcity of laboratory facilities in regions where human Y. pestis infection is most common, and because of the potential sig nificance of Y. pestis isolation in a nonendemic area or an area from which human plague has been absent for many years, the WHO recom mends an initial presumptive diagnosis followed by reference labora tory confirmation (Table 176-1). In the United States, comprehensive national diagnostic facilities for plague have been in place since 1999 (Laboratory Response Network for Biological Threats [LRN-B];

https://emergency.cdc.gov/lrn/index.asp) to detect possible use of bio logical terrorism agents, including Y. pestis. Routine diagnostic clinical

TABLE 176-1 World Health Organization Case Definitions of Plague Suspected Case Clinical presentation suggestive of plague And Epidemiological context suggesting possible exposure to plague (exposure to infected humans or animals, or residence in or travel to a known endemic focus within 10 days prior to onset of the disease) Probable Case Meeting the definition of a suspected case plus 1 of the following • F1 antigen detected in bubo aspirate, sputum, blood, or postmortem tissues by rapid antigen test or direct immunofluorescence • A single anti-F1 serology without evidence of previous Yersinia pestis infection or immunization • Direct microscopy in a clinical sample: gram-negative coccobacilli that display bipolar staining with Wayson or Wright-Giemsa stain Confirmed Case Meeting the definition of a suspected case Plus at least 1 of the following • Isolation of Y. pestis from a clinical sample (based on appropriate colonial morphology and at least 2 of the following tests positive: phage lysis of cultures at 20–25°C and 37°C; biochemical profile; F1 antigen detection) • Seroconversion or a fourfold difference in anti-F1 antibody titer in paired serum samples drawn at least 2 weeks apart • Y. pestis DNA positive by species-specific PCR on either clinical sample or culture Not a case (exclusion of diagnosis) Meeting the definition of a suspected case And either of the following • At least two laboratory tests (rapid antigen test or direct immunofluorescence against F1 antigen, direct microscopy, convalescent serology, culture, PCR) are conducted AND they are negative • When no confirmatory tests can be performed, 2 negative rapid antigen tests for F1 antigen on 2 clinical specimens collected at 24-h intervals Abbreviation: PCR, polymerase chain reaction. Source: Reproduced with permission from E Bertherat, S Jullien. Revision of the international definition of plague cases. Wkly Epidemiol Rec 24:238, 2021. microbiology laboratories that are included in this network as sentinellevel laboratories use joint protocols from the Centers for Disease Control and Prevention (CDC) and the American Society for Micro biology (https://asm.org/Articles/Policy/Laboratory-Response-NetworkLRN-Sentinel-Level-C) to identify suspected Y. pestis isolates and to refer these specimens to LRN-B reference laboratories for confirmatory tests. Y. pestis is designated a “Tier 1 select agent” under the Public Health Security and Bioterrorism Preparedness and Response Act of 2002 and subsequent executive orders; the provisions of this act, the Patriot Act of 2001, and related executive orders apply to all U.S. labo ratories and individuals working with Y. pestis. Details of the applicable regulations are available from the CDC (www.selectagents.gov). Yersinia species are gram-negative coccobacilli (short rods with rounded ends) 1–3 μm in length and 0.5–0.8 μm in

diameter. Y. pestis in particular appears bipolar (with a “closed safety pin” appearance) and pleomorphic when stained with a polychromatic stain (Wayson or Wright-Giemsa; Fig. 176-4). Its lack of motility distinguishes Y. pestis from other Yersinia species, which are motile at 25°C and nonmotile at 37°C. Transport medium (e.g., Cary-Blair medium) preserves the viability of Y. pestis if transport is delayed. The appropriate specimens for diagnosis of bubonic, pneumonic, and septicemic plague are bubo aspirate, bronchoalveolar lavage fluid or sputum, and blood, respectively. Culture of postmortem organ biopsy samples also can be diagnostic. A bubo aspirate is obtained by injection of 1 mL of sterile normal saline into a bubo under local anesthetic and aspiration of a small amount of (usually blood-stained) fluid. The WHO has provided guidance on how to aspirate buboes and

FIGURE 176-4 Peripheral-blood smear from a patient with fatal plague septicemia and shock, showing characteristic bipolar-staining Yersinia pestis bacilli (Wright’s stain, oil immersion). (Reprinted with permission from DT Dennis, GL Campbell: Plague and other Yersinia infections, in Harrison’s Principles of Internal Medicine, 17th ed, AS Fauci et al [eds]. New York, McGraw-Hill, Chap. 152, 2008.) collect sputum from patients with suspected pneumonic plague (https:// www.who.int/emergencies/outbreak-toolkit/disease-outbreak-toolboxes/ plague-outbreak-toolbox; https://www.who.int/publications/i/item/ operational-guidelines-on-plague-surveillance-diagnosis-preventionand-control). Gram’s staining of these specimens may reveal gramnegative rods, which are shown by Wayson or Wright-Giemsa staining to be bipolar. These bacteria may even be visible in direct blood smears in septicemic plague (Fig. 176-4); this finding indicates very high num bers of circulating bacteria and a poor prognosis. CHAPTER 176 Plague and Other Yersinia Infections Y. pestis grows on nutrient agar and other standard laboratory media but forms smaller colonies than do other Enterobacteriaceae. Speci mens should be inoculated onto nutrient-rich media such as sheep blood agar (SBA), into nutrient-rich broth such as brain-heart infusion broth, and onto selective agar such as MacConkey or eosin methylene blue (EMB) agar. Yersinia-specific CIN (cefsulodin, triclosan [Irgasan], novobiocin) agar can be useful for culture of contaminated speci mens, such as sputum. Blood should be cultured in a standard blood culture system. The optimal growth temperature is <37°C (25–29°C), with pinpoint colonies only on SBA at 24 h. Slower growth occurs at 37°C. Y. pestis is oxidase-negative, catalase-positive, urease-negative, indole-negative, and lactose-negative. Automated biochemical or mass spectrometry identification systems can misidentify Y. pestis as Y. pseu dotuberculosis or other bacterial species. Reference laboratory tests for definitive identification of isolates include direct immunofluorescence for F1 antigen; polymerase chain reaction (PCR) for specific Y. pestis targets (see below); and specific bacteriophage lysis. PCR can also be applied to diagnostic specimens, as can direct immunofluorescence for F1 antigen (produced in large amounts by Y. pestis) by slide microscopy. An immunochromato graphic test strip for F1 antigen detection by monoclonal antibodies in clinical specimens (rapid diagnostic test based on the F1 antigen [F1RDT]) has been devised in Madagascar. This method is effective for both laboratory and near-patient use on bubo aspirates and sputum and is now widely used in endemic countries. A similar test strip for Pla antigen has been developed and could be used to detect wild-type or engineered F1-negative virulent strains. Recent clinical experience, including the 2017 Madagascar outbreak, found F1RDT to be at least as sensitive as laboratory culture for diagnosis of bubonic or pneumonic plague. However, there was a low diagnostic yield of culture in this outbreak, possibly due to widespread prehospital use of antimicrobials. The specificity of F1RDT for pneumonic plague diagnosed by culture was 71%; thus, while a positive sputum test is useful in determining whether a symptomatic patient in an endemic

area is a probable case requiring treatment, additional laboratory tests are required to confirm

a diagnosis of pneumonic plague. F1RDT had a high negative predic tive value in the limited studies available; thus, when other laboratory tests are unavailable, two negative F1RDT tests on clinical specimens 1 day apart can help exclude a diagnosis of plague in a symptomatic patient. This use of F1RDT has been incorporated in the revised WHO international definition of plague introduced following the 2017 Mada gascar outbreak.

The WHO requires diagnostic PCR or real-time PCR (RT-PCR) assays to show positivity for at least two different targets specific for Y. pestis from a short list comprising the plasmid-based caf1 (specifying the F1 antigen) and pla (specifying plasminogen activator) genes and three other chromosomal genes. Y. pestis is included in the U.S. Food and Drug Administration (FDA)-authorized Biofire FilmArray Next Generation Diagnostic System (NGDS) Warrior Panel for use with the FilmArray 2.0 system (Biomérieux) as a medical diagnostic device suit able for whole blood (ethylenediaminetetraacetic acid [EDTA]), blood cultures, and sputum specimens used by U.S. Department of Defense laboratories and laboratories in the CDC-managed LRN-B network. It is also one of 14 viral, bacterial, and protozoan pathogens diagnosable from blood samples with the BioFire Global Fever Special Pathogens Panel recently authorized by the FDA. Detailed phylogeographic DNA sequence data based on culture collections have been accumulated to trace plague evolution, and this approach could be adapted in the future to real-time clinical plague epidemiology. In the absence of other positive laboratory diagnostic tests, a retro spective serologic diagnosis may be made on the basis of rising titers of hemagglutinating antibody to F1 antigen. Enzyme-linked immuno sorbent assays (ELISAs) for IgG and IgM antibodies to F1 antigen are also available. PART 5 Infectious Diseases The white blood cell (WBC) count is generally raised (to 10,000– 20,000/μL) in plague, with neutrophilic leukocytosis and a left shift (numerous immature neutrophils); in some cases, however, the WBC count is normal or leukopenia develops. WBC counts are occasionally very high, especially in children (>100,000/μL). Levels of fibrinogen degradation products are elevated in a majority of patients, but plate let counts are usually normal or low-normal. However, disseminated intravascular coagulation, with low platelet counts, prolonged pro thrombin times, reduced fibrinogen, and elevated fibrinogen degrada tion product levels, occurs in a significant minority of patients. TREATMENT Plague Guidelines for the treatment of plague are given in Table 176-2. A 10- to 14-day course of antimicrobial therapy (or a course con tinued until 2 days after fever subsides) is recommended. Strepto mycin has historically been the parenteral treatment of choice for plague and is approved for this indication by the FDA. Although not yet approved by the FDA for plague, gentamicin has proved safe and effective in clinical trials in Tanzania and Madagascar and in retrospective reviewed cases in the United States. In view of streptomycin’s adverse-reaction profile and limited availability, some experts now recommend gentamicin over streptomycin. The FDA has approved levofloxacin, moxifloxacin, and ciprofloxacin for prophylaxis and treatment of plague (including septicemic and pneumonic plague) under a regulatory approach based on animal studies alone, known as the Animal Rule. Levofloxacin has more efficacy than ciprofloxacin in postexposure prophylaxis of inhalational anthrax in animal models and has also received FDA approval for this indication (Chap. S4); thus, it is a suitable agent for prophylaxis against two diseases in possible bioterrorism expo sures. The WHO issued new guidelines in 2021 adding these three fluoroquinolones to the recommended list of first-line medicines for treating bubonic, pneumonic, or septicemic plague. It also rec ommended moxifloxacin and ofloxacin for plague meningitis, and ciprofloxacin for postexposure prophylaxis.

While systemic chloramphenicol therapy is available in the resource-poor countries primarily affected by plague, it is less

TABLE 176-2 Guidelines for the Treatment of Plague DOSING INTERVAL, h ROUTE DRUG DAILY DOSE Gentamicin Adult 5 mg/kga

IM/IV Child 4.5–7.5 mg/kga

IM/IV Streptomycin Adult 2 g

IM Child 30 mg/kg (maximum 1 g per dose)

IM Levofloxacin Adult (child >50 kg) 750 (500–750) mg

PO/IV Child <50 kg and ≥6 months of age 16 mg/kg (maximum, 250 mg/ dose)

PO/IV Ciprofloxacin Adult 1500 mg

PO 1200 mg

IV Child 30–45 mg/kg (maximum, 500 mg/dose) 8–12 PO 20–30 mg/kg (maximum, 400 mg/dose) 8–12 IV Moxifloxacin Adult 400 mg

PO/IV Doxycycline Adult and child ≥45 kg 200 mg (200 mg loading dose)

PO/IV Child <45 kg 4.4 mg/kg (maximum, 100 mg/ dose, 4.4 mg/kg loading dose)

PO/IV Tetracycline Adult 2 g

PO/IV Child >8 y 40–50 mg/kg

PO/IV Chloramphenicol Adult 50–100 mg/kg

PO/IV Child >2 y 50–100 mg/kg (maximum, 4 g)

PO/IV aAminoglycoside dose is adjusted with impaired renal function. No trial data have been published for once-daily gentamicin therapy for plague in adults or children, but this regimen is efficacious in gram-negative sepsis of other etiologies and has been successful in a recent outbreak of pneumonic plague in the Democratic Republic of the Congo. Neonates (up to 1 week of age) and premature infants should receive gentamicin at 4 mg/kg IV once daily. Source: CA Nelson et al: Antimicrobial treatment and prophylaxis of plague: Recommendations for naturally acquired infections and bioterrorism response. MMWR Recomm Rep 70(No. RR-3):1, 2021. Provides detailed guidelines on recommended regimens for pneumonic versus bubonic plague, plague meningitis, treatment during pregnancy and lactation, and neonatal infection. Recommends dual therapy with two different classes of antimicrobials for initial treatment of patients with severe pneumonic or septicemic plague and patients infected after intentional release of Yersinia pestis. likely to be available or used in high-income countries because of its adverse effect profile. Tetracyclines are

also effective and can be given by mouth but are not generally recommended for children age <7 years because of tooth discoloration. Doxycycline is the tet racycline of choice; at an oral dosage of 100 mg twice daily, this drug was as effective as intramuscular gentamicin (2.5 mg/kg twice daily) in a trial in Tanzania. There is recent evidence that doxycycline does not cause dental staining in children because it binds calcium less readily than other tetracyclines. Although Y. pestis is sensitive to β-lactam drugs in vitro and these drugs have been efficacious against plague in some animal models, the response to penicillins has been poor in some clinical cases; thus β-lactams and macrolides are not generally recom mended as first-line therapy. Chloramphenicol, alone or in com bination, is recommended for some focal complications of plague (e.g., meningitis, endophthalmitis, myocarditis) because of its tis sue penetration properties. Fluoroquinolones, effective in vitro

and in animal models, are recommended in guidelines for possible bioterrorism-associated pneumonic plague and are increasingly used in plague therapy. ■ ■PREVENTION In endemic areas, the control of plague in humans is based on reduc tion of the likelihood of being bitten by infected fleas or exposed to infected droplets from either humans or animals with plague pneumo nia. In the United States, residence and outdoor activity or contact with wild or pet animals in rural areas of western states where epizootics occur are the main risk factors for infection. To assess potential risks to humans in specific areas, surveillance for Y. pestis infection among animal plague hosts and vectors is carried out regularly as well as in response to observed animal die-offs. Personal protective measures include avoidance of areas where a plague epizootic has been identified and publicized (e.g., by warning signs or closure of campsites). Sick or dead animals should not be handled by the general public. Hunters, zoologists, and pet owners should wear gloves if handling wild-animal carcasses in endemic areas. General measures to avoid rodent fleabite during outdoor activity are appropriate and include the use of insect repellent, insecticide, and protective clothing. General measures to reduce peridomestic and occupational human contact with rodents are advised and include rodent-proofing of buildings and food-waste stores and removal of potential rodent habitats (e.g., woodpiles and junk heaps). Flea control by insecticide treatment of wild rodents is an effective means of minimizing human contact with plague if an epizo otic is identified in an area close to human habitation. Any attempt to reduce rodent numbers must be preceded by flea suppression to reduce the migration of infected fleas to human hosts. An oral F1-V subunit vaccine using raccoon poxvirus (RCN) as a vector (sylvatic plague vac cine) is partially protective against plague when administered to wild prairie dogs in field trials and may in the future provide a means of reducing the risk of human exposure to Y. pestis. Patients in whom pneumonic plague is suspected should be managed in isolation (with negative pressure, if available), with droplet precau tions observed until pneumonia is excluded or effective antimicrobial therapy has been given for 48 h. Review of the literature published before the advent of antimicrobial agents suggests that the main infec tive risk is posed by patients in the final stages of disease who are cough ing up sputum with plentiful visible blood and/or pus. Cotton and gauze masks were protective in these circumstances. Current surgical masks capable of barrier protection against droplets, including large respira tory particles, are probably protective, but the differential diagnosis of fever and hemoptysis in plague-endemic areas includes small airborne particle-transmitted infections such as tuberculosis. In addition, WHO guidance recommends that personal protective equipment for potential aerosol-generating procedures (e.g., collection of respiratory samples from patients with suspected or confirmed plague) or handling the remains of someone who was infected with plague should include a fit-tested N95 face mask, a gown, gloves, and a face

shield or goggles. Antimicrobial Prophylaxis Postexposure antimicrobial prophy laxis lasting 7 days is recommended following household, hospital, or other close contact with persons with untreated pneumonic plague. (Close contact is defined as contact with a patient at <2 m.) In animal aerosol-infection studies, levofloxacin and ciprofloxacin are associated with higher survival rates than doxycycline (Table 176-3). Immunization Studies with candidate plague vaccines in animal models show that neutralizing antibody provides protection against exposure but that cell-mediated immunity is critical for protection and clearance of Y. pestis from the host. A killed whole-cell vaccine used in humans required multiple doses, caused significant local and systemic reactions, and was not protective against pneumonic plague; this vac cine is not currently available. A live attenuated vaccine based on strain EV76 is still used in countries of the former Soviet Union and China but has significant side effects. Different subunit vaccines devised by governmental agencies in the United States, United Kingdom, and China all comprising recombinant F1 (rF1) and various recombinant

TABLE 176-3 Guidelines for Plague Prophylaxis DOSING INTERVAL, h ROUTE DRUG DAILY DOSE Doxycycline Adult 200 mg 12 or 24 PO Child ≥8 y ≥45 kg: adult dose

PO ≤45 kg: 4.4 mg/kg (maximum, 200 mg)

PO Tetracycline Adult 2 g 6 or 12 PO Child ≥8 y 40 mg/kg (maximum 500 mg dose) 6 or 12 PO Levofloxacin Adult and child >50 kg 500–750 mg

PO Child <50 kg and ≥6 months of age 16 mg/kg (maximum, 250 mg/dose)

PO Ciprofloxacin Adult 1–1.5 g

PO Child 30 mg/kg (maximum 750 mg dose)

PO Source: TV Inglesby et al: Plague as a biological weapon: Medical and public health management. Working Group on Civilian Biodefense. JAMA 283:2281, 2000; https:// www.cdc.gov/plague/healthcare/clinicians.html; CA Nelson et al: Antimicrobial treatment and prophylaxis of plague: Recommendations for naturally acquired infections and bioterrorism response. MMWR Recomm Rep 70(No. RR-3):1, 2021. CHAPTER 176 V (rV) proteins produced in Escherichia coli, combined either as a fusion protein or as a mixture, purified, and adsorbed to aluminum hydroxide for injection are close to licensing. This combination pro tects mice and various nonhuman primates in laboratory models of bubonic and pneumonic plague and has been evaluated in phase 2 clinical trials. Prelicensing field-efficacy studies (phase 3 trials) are dif ficult to devise because of plague epidemiology. In the United States, the FDA will assess plague vaccines for human use under the Animal Rule, using efficacy data from animal studies and antibodies and other correlates of immunity from human vaccinees (https://www.fda.gov/ emergency-preparedness-and-response/mcm-regulatory-science/animal-rule-

information), and the rF1-V subunit vaccine has orphan drug status. The WHO has produced a Target Product Profile (TPP) for phase 3 trial design and prioritization of the vaccine candidates. Candidate vac cines include protein subunit, live-attenuated, and bacterial, viral, and bacteriophage vectors, DNA, and mRNA vaccines. Antigens other than F1 and V are being investigated because of the recovery of F1-negative Y. pestis strains from natural sources and the

observation that F1 antigen is not required for virulence in primate models of pneumonic plague. Plague and Other Yersinia Infections YERSINIOSIS Yersiniosis is a zoonotic infection with an enteropathogenic Yersinia species, usually Y. enterocolitica or Y. pseudotuberculosis. The usual hosts for these organisms are pigs and other wild and domestic ani mals; humans are usually infected by the oral route, and outbreaks from contaminated food occur. Yersiniosis is most common in child hood and in colder climates. Patients present with abdominal pain and sometimes with diarrhea (which may not occur in up to 50% of cases). Y. enterocolitica is more closely associated with terminal ileitis and Y. pseudotuberculosis with mesenteric adenitis, but both organisms may cause mesenteric adenitis and symptoms of abdominal pain and tenderness that result in pseudoappendicitis, with the surgical removal of a normal appendix. Diagnosis was historically based on culture of the organism or convalescent serology, but some proprietary multiplex PCR systems for gastrointestinal infection diagnosis now include Y. enterocolitica (but not Y. pseudotuberculosis). Y. pseudotuberculosis and some rarer strains of Y. enterocolitica are especially likely to cause systemic infection, which is also more likely in patients with diabetes or iron overload. Systemic sepsis is treatable with antimicrobial agents, but postinfective arthropathy responds poorly to such therapy. Over

twenty other Yersinia species lacking the virulence plasmid pYV com mon to Y. pestis, Y. pseudotuberculosis, and Y. enterocolitica are now recognized, primarily from genome sequencing. These are, at most, opportunistic pathogens of humans (including Y. aldovae, Y. aleksiciae, Y. bercovieri, Y. entomophaga, Y. frederiksenii, Y. hibernica, Y. interme dia, Y. kristensenii, Y. massiliensis, Y. mollaretii, Y. nurmii, Y. pekkanenii, Y. rohdei, Y. similis, Y. ruckeri, and Y. wautersii). Molecular phylogeny shows that Y. enterocolitica is more distantly related to Y. pseudotu berculosis than these other Yersinia species, and the similar virulence plasmid they share has probably been acquired independently by at least one of the two since the species diverged.

■ ■EPIDEMIOLOGY Y. enterocolitica Y. enterocolitica is found worldwide and has been isolated from a wide variety of wild and domestic animals and environ mental samples, including samples of food and water. In vitro, Y. entero colitica is resistant to predation by the protozoon Acanthamoeba castellani and can survive inside it, suggesting a possible mode of environmental persistence. Strains are classically differentiated by biochemical reactions (biovar or biotype) combined with serogroup and, increasingly, by whole genome sequence data used for core genome multilocus sequence typing (cgMLST) (see “Laboratory Diagnosis,” below). Yersiniosis, >99% due to Y. enterocolitica, remains the third most common bacterial food-borne zoonosis reported in Europe, especially prevalent in Germany and Scandinavia. The incidence is highest among children; children <4 years of age are more likely to present with diarrhea than are older children. Abdominal pain with mesenteric ade nitis and terminal ileitis is more prominent among older children and adults. Septicemia is more likely in patients with preexisting conditions such as diabetes mellitus, liver disease, any condition involving iron overload (including thalassemia and hemochromatosis), advanced age, malignancy, or HIV/AIDS. As in enteritis of other bacterial etiologies, postinfective complications such as reactive arthritis occur mainly in individuals who are HLA-B27 positive. Erythema nodosum (Fig. A1-39) following Yersinia infection is not associated with HLA-B27 and is more common among women than among men. PART 5 Infectious Diseases Consumption or preparation of raw pork products (such as chitter lings) and some processed pork products is strongly linked with infec tion because a high percentage of pigs carry pathogenic Y. enterocolitica strains. Outbreaks of Y. enterocolitica infection have been associated with

consumption of milk (pasteurized, unpasteurized, and chocolate-flavored) and various ready-to-eat vegetables including fresh spinach that were processed or washed with water. Person-to-person transmission is sus pected in a few cases (e.g., in nosocomial and familial outbreaks) but is much less likely with Y. enterocolitica than with other causes of gastro intestinal infection, such as Salmonella. A multivariate analysis indicates that contact with companion animals is a risk factor for Y. enterocolitica infection among children in Sweden, and low-level colonization of dogs and cats with Y. enterocolitica has been reported. Transfusion-associated septicemia due to Y. enterocolitica, while recognized as a very rare but frequently fatal event for >30 years, has been difficult to eradicate. Y. pseudotuberculosis Y. pseudotuberculosis is much less frequently reported as a cause of human disease than Y. enterocolitica, and infec tion with Y. pseudotuberculosis is more likely to present as fever and abdominal pain due to mesenteric lymphadenitis and be identified from a blood culture isolate. This organism is associated with wild mammals (rodents, rabbits, and deer), birds, and domestic pigs. Although outbreaks are generally rare, several have recently occurred associated by food culture or dietary history with consumption of lettuce or raw carrots (Finland, New Zealand), tomatoes (France), or unpasteurized milk (Finland). Strains have historically been differ entiated by combined biochemical reactions (biovar) and serogroup. cgMLST is now used for investigation of both Y. enterocolitica and Y. pseudotuberculosis outbreaks in several countries. ■ ■PATHOGENESIS The usual route of infection is oral. Studies with both Y. enterocolitica and Y. pseudotuberculosis in animal models suggest that initial replication

in the small intestine is followed by invasion of Peyer’s patches of the distal ileum via M cells, with onward spread to mesenteric lymph nodes. The liver and spleen can also be involved after oral infection. The characteristic histologic appearance of enteropathogenic Yersinia after invasion of host tissues is as extracellular microabscesses sur rounded by an epithelioid granulomatous lesion. Experiments involving oral infection of mice with tagged Y. entero colitica show that only a very small proportion of bacteria in the gut invade tissues. Individual bacterial clones from an orally inoculated pool give rise to each microabscess in a Peyer’s patch, and the host restricts the invasion of previously infected Peyer’s patches. A prior model positing progressive bacterial spread from Peyer’s patches and mesenteric lymph nodes to the liver and spleen appears to be inaccu rate: spread of Y. pseudotuberculosis and Y. enterocolitica to the liver and spleen of mice occurs independently of regional lymph node coloniza tion and in mice lacking Peyer’s patches. Invasion requires the expression of several nonfimbrial adhesins, such as invasin (Inv) and—in Y. pseudotuberculosis—Yersinia adhe sin A (YadA). Inv interacts directly with β1 integrins, which are expressed on the apical surfaces of M cells but not enterocytes. YadA of Y. pseudotuberculosis interacts with extracellular matrix proteins such as collagen and fibronectin to facilitate host cell integrin association and invasion. YadA of Y. enterocolitica lacks a crucial N-terminal region and binds collagen and laminin but not fibronectin and does not cause inva sion. Inv is chromosomally encoded, whereas YadA is encoded on the virulence plasmid pYV. YadA also helps to confer serum resistance in Y. enterocolitica by binding host complement regulators such as factor H and C4-binding protein. Another chromosomal gene, ail (attachment and invasion locus), encodes the extracellular protein Ail, which is the main factor conferring serum resistance in Y. pseudotuberculosis by bind ing these complement regulators. By binding to host cell surfaces, YadA allows targeting of immune effector cells by the pYV plasmid–encoded type III secretion system (injectisome). As a consequence, the host’s innate immune response is altered; toxins (Yersinia outer proteins, or Yops) are injected into host macrophages, neutrophils, and dendritic cells, affecting signal transduc tion pathways, resulting in reduced phagocytosis and inhibited

produc tion of reactive oxygen species by neutrophils, and triggering apoptosis of macrophages. Other factors functional in invasive disease include yersiniabactin (Ybt), a siderophore produced by some strains of Y. pseu dotuberculosis and Y. enterocolitica as well as other Enterobacterales. Ybt allows bacteria to access iron from saturated lactoferrin during infection and reduces production of reactive oxygen species by innate immune effector cells, thereby decreasing bacterial killing. Y. pseudotuberculosis and Y. pestis make other siderophores apart from Ybt. ■ ■CLINICAL MANIFESTATIONS Self-limiting diarrhea is the most common reported presentation in infection with pathogenic Y. enterocolitica, especially in children <4 years of age, who form the single largest group in most case series. Blood may be detected in diarrheal stool. Older children and adults are more likely than younger children to present with abdominal pain, which can be localized to the right iliac fossa—a situation that often leads to lapa rotomy for presumed appendicitis (pseudoappendicitis). Appendec tomy is not indicated for Yersinia infection causing pseudoappendicitis. Thickening of the terminal ileum and cecum is seen on endoscopy and ultrasound, with elevated round or oval lesions that may overlie Peyer's patches. Mesenteric lymph nodes are enlarged. Ulcerations of the mucosa are noted on endoscopy. Gastrointestinal complications include granulomatous appendicitis, a chronic inflammatory condition affecting the appendix that is responsible for ≤2% of cases of appendici tis; Yersinia is involved in a minority of cases. Y. enterocolitica infection can present as acute pharyngitis with or without other gastrointesti nal symptoms. Fatal Y. enterocolitica pharyngitis has been recorded. Mycotic aneurysm can follow Y. enterocolitica bacteremia, as can focal infection (abscess) in many other sites and body compartments (liver, spleen, kidney, bone, meninges, endocardium). Y. pseudotuberculosis infection is more likely to present as abdom inal pain and fever than as diarrhea. A superantigenic toxin—

Y. pseudotuberculosis mitogen (YPM)—is produced by strains seen in eastern Russia in association with Far Eastern scarlet-like fever (FESLF), a childhood illness with desquamating rash, arthralgia, and toxic shock. A similar illness is recognized in Japan (Izumi fever) and Korea. Similarities have been noted with Kawasaki disease, the idio pathic acute systematic vasculitis of childhood. There is an epidemio logic link between exposure of populations to superantigen-positive Y. pseudotuberculosis and an elevated incidence of Kawasaki disease. Y. enterocolitica or Y. pseudotuberculosis septicemia presents as a severe illness with fever and leukocytosis, often without localizing fea tures, and is significantly associated with predisposing conditions such as diabetes mellitus, liver disease, and iron overload. Hemochromatosis combines several of these risk factors. Administration of iron chela tors like desferrioxamine, which provide iron accessible to Yersinia (and have an inhibitory effect on neutrophil function), may result in Yersinia septicemia in patients with iron overload who presumably have an otherwise mild gastrointestinal infection. HIV/AIDS has been associated with Y. pseudotuberculosis septicemia. The unusual phe nomenon of transfusion-associated septicemia is linked to the ability of Y. enterocolitica to multiply at refrigerator temperature (psychrotro phy). Typically, the transfused unit has been stored for >20 days, and it is believed that small numbers of yersiniae from an apparently healthy donor with subclinical bacteremia are amplified to very high numbers by growth inside the bag at ≤4°C, with consequent septic shock after transfusion. Complete prevention of this very rare event (one case in several million transfused units in countries such as the United States and France) without unacceptable restriction in the blood supply has not yet been devised. ■ ■POSTINFECTIVE PHENOMENA As in other invasive intestinal infections (salmonellosis, shigellosis), reactive arthritis (articular arthritis of multiple joints developing within 2–4 weeks of a preceding infection) occurs as

a result of autoim mune activity initiated by the deposition of bacterial components (not viable bacteria) in joints in combination with the immune response to invading bacteria. The majority of individuals affected by reactive arthritis due to Yersinia are HLA-B27 positive. Myocarditis with elec trocardiographic ST-segment abnormalities may occur with Yersiniaassociated reactive arthritis. Most Yersinia-associated cases follow Y. enterocolitica infection (presumably because it is more common than infection with other species), but Y. pseudotuberculosis–associated reactive arthritis is also well documented in Finland, where sporadic and outbreak infections with Y. pseudotuberculosis are more common than in other countries. Of infected individuals identified in a recent Y. pseudotuberculosis serotype O:3 outbreak in Finland, 12% developed reactive arthritis affecting the small joints of the hands and feet, knees, ankles, and shoulders and lasting >6 months in most cases. Erythema nodosum (Fig. A1-39) occurs after Yersinia infection (more commonly in women) with no evidence of HLA-B27 linkage. There is a long-standing association between antithyroid and antiYersinia antibodies. Antibody evidence of prior Y. enterocolitica infec tion in Graves' disease and increased levels of antithyroid antibody in patients with Y. enterocolitica antibodies were first noted in the 1970s. Y. enterocolitica contains a thyroid-stimulating hormone (TSH)–binding site that is recognized by antibodies to TSH from Graves' disease patients. Raised titers of antibodies to Y. enterocolitica whole cells and Yops have been found in some series of Graves' disease patients but not in others. It remains unclear whether this cross-reactivity is significant in the etiology of Graves' disease. ■ ■LABORATORY DIAGNOSIS Standard laboratory culture methods can be used to isolate entero pathogenic Yersinia species from sterile samples, including blood and cerebrospinal fluid. Culture on specific selective media (CIN agar), with or without pre-enrichment in broth or phosphate-buffered saline at either 4°C or 16°C, is the basis of most schema for isolation of yersiniae from stool or other nonsterile samples. Outside known highincidence areas, specific culture may only be carried out by laboratories on request, or if a multiplex PCR screen detects Y. enterocolitica–specific

DNA in feces. Several CE-marked, FDA-approved kits for enteric pathogens now offer Y. enterocolitica detection (the precise assay targets are not disclosed), and their use has increased detection of Y. enterocolitica. These kits generally do not detect Y. pseudotuberculosis. A standard for PCR detection of pathogenic Y. enterocolitica and Y. pseudotuberculosis in food samples is available from the International Organization for Standardization.

Matrix-assisted laser desorption ionization time of flight (MALDITOF) mass spectrometry systems can speciate isolates of Y. enteroco litica and Y. pseudotuberculosis (but cannot separate Y. pestis from Y. pseudotuberculosis). Most clinical infections from typical presenta tions described above are associated with virulence plasmid-containing low-pathogenic strains, which genome sequencing has assigned to four phylogroups that correspond to the classical groups of Biotype 2/3 serogroup O:9 (BT2/3 O:9), BT4 O:3, BT2/3 O:5,27, and BT5. A highly pathogenic (mouse-lethal) virulence plasmid-containing phylogroup (BT1B O:8) used to be commonly reported from North America, where it is now rare, but occasional cases are now reported from Europe and Japan. A current area under active research is the clinical significance of a further phylogroup comprising Biotype 1A Y. enterocolitica strains of various serotypes. These comprise >50% of Y. enterocolitica fecal isolates in recent clinical studies from England, France, and China and >20% in New Zealand. They have generally been regarded as nonpathogenic because they lack the virulence plas mid and are not pathogenic in mouse-infection models. However, they do contain other genes associated with Yersinia pathogenesis, invade epithelial cells and macrophages in vitro, and are pathogenic in an insect model. They form the majority of Y. enterocolitica cultures from food sampled in the

United Kingdom and France. CHAPTER 176 Because of the frequency with which the virulence plasmid is lost on laboratory subculture, combined biochemical identification (with biotyping according to a standard schema) and serologic identification was usually required to interpret the significance of an isolate of Y. enterocolitica from a nonsterile site. Whole genome DNA sequenc ing applying a Yersinia genus wide seven-gene multilocus sequence typing (MLST) scheme can now speciate Y. enterocolitica, Y. pestis, and Y. pseudotuberculosis and differentiate Y. enterocolitica biotypes. A cgMLST scheme provides a more detailed population structure and has been used for outbreak tracing and revealing novel, as yet phenotypi cally undefined Yersinia species. Plague and Other Yersinia Infections Agglutinating or ELISA antibody titers to specific O-antigen types are used in the retrospective diagnosis of both Y. enterocolitica and Y. pseudotuberculosis infections. IgA and IgG antibodies persist in patients with reactive arthritis. Serologic cross-reactions between Y. enterocolitica serogroup O:9 and Brucella are due to the similarity of their lipopolysaccharide structures. Multiple assays are required to cover even the predominant serogroups (Y. enterocolitica O:3, O5,27, and O:9; Y. pseudotuberculosis O:1a, O:1b, and O:3), and these assays are generally available only in reference laboratories. ELISA and western blot tests for antibodies to Yops, which are expressed by all pathogenic strains of Y. enterocolitica and Y. pseudotuberculosis, are also available; most of the positivity in these assays probably relates to previous infection with Y. enterocolitica. TREATMENT Yersiniosis Most cases of diarrhea caused by enteropathogenic Yersinia are self-limiting. Data from clinical trials do not support antimicrobial treatment for adults or children with Y. enterocolitica diarrhea. Systemic infections with bacteremia or focal infections outside the gastrointestinal tract generally require antimicrobial therapy. Infants <3 months of age with documented Y. enterocolitica infec tion may require antimicrobial treatment because of the increased likelihood of bacteremia in this age group. Y. enterocolitica strains nearly always express β-lactamases. Because of the relative rarity of systemic Y. enterocolitica infection, there are no clinical trial data to guide antimicrobial choice or to suggest the optimal dose and

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