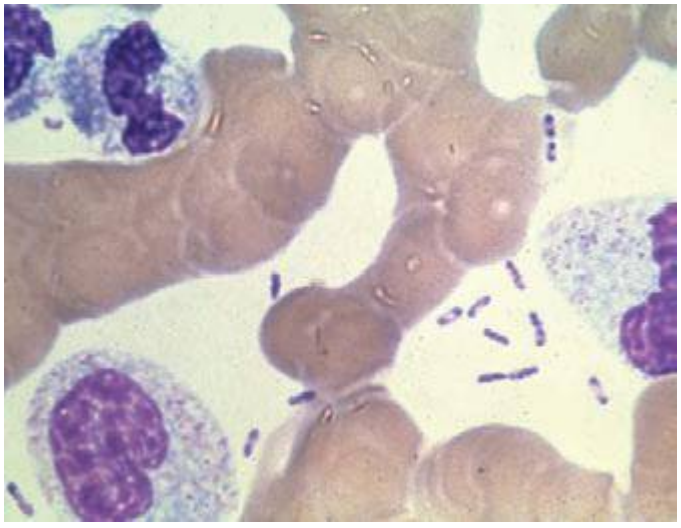

FIGURE 196-4 Peripheral blood smear from a patient with fatal plague septicemia and shock, showing characteristic bipolar-staining *Yersinia pestis* bacilli (Wright's stain, oil immersion). *(Reprinted with permission from DT Dennis, GL Campbell: Plague and other Yersinia infections, in Harrison's Principles of Internal Medicine, 17th ed, AS Fauci et al [eds]. New York, McGraw-Hill, Chap. 152, 2008.)*

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 can also 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. Gram's staining of these specimens may reveal gram-negative 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. 196-4); this finding indicates very high numbers of circulating bacteria and a poor prognosis.

Y. pestis grows on nutrient agar and other standard laboratory media but forms smaller colonies than do other Enterobacteriaceae. Specimens 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 specimens, 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, urea-negative, indole-negative, and lactose-negative. Automated biochemical identification systems can misidentify *Y. pestis* as *Y. pseudotuberculosis* or other bacterial species.

Reference laboratory tests for definitive identification of isolates include direct immunofluorescence for F1 antigen; specific polymerase chain reaction (PCR) for targets such as F1 antigen, the pesticin gene, and the plasminogen activator gene; 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 immunochromatographic test strip for F1 antigen detection by monoclonal antibodies in clinical specimens has been devised in Madagascar. This method is effective for both laboratory and near-patient use and is now widely used in endemic countries. A similar test strip for Pla antigen has recently been developed and could be used to detect wild-type or engineered F1-negative virulent strains. Many other rapid diagnostic kits for possible bioterrorism pathogens, including *Y. pestis*, have been described in recent years, but none is widely used for primary or reference laboratory identification, and only one (a field real-time PCR for a range of potential bioterrorism agents) is approved by the U.S. Food and Drug Administration (FDA). Detailed phylogeographic DNA sequence data based on culture collections have been accumulated to trace plague evolution, and this system could be adapted in the future to determine real-time clinical plague epidemiology.

In the absence of other positive laboratory diagnostic tests, a retrospective serologic diagnosis may be made on the basis of rising titers of hemagglutinating antibody to F1 antigen. Enzyme-linked immunosorbent assays (ELISAs) for IgG and IgM antibodies to F1 antigen are also available.

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 platelet counts are usually normal or low-normal. However, disseminated intravascular coagulation, with low platelet counts, prolonged prothrombin times, reduced fibrinogen, and elevated fibrinogen degradation product levels, occurs in a significant minority of patients.

TREATMENT PLAGUE

Guidelines for the treatment of plague are given in **Table 196-2**. A 10-day course of antimicrobial therapy is recommended. Streptomycin 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 proven safe and effective in clinical trials in Tanzania and Madagascar

TABLE 196-2 GUIDELINES FOR THE TREATMENT OF PLAGUE

Drug	Daily Dose	Interval, h	Route
Gentamicin			
Adult	5 mg/kg[a]	24	IM/IV
	3–5 mg/kg	8 (2 mg/kg loading dose followed by 1.7 mg/kg tid, reduced)	IM/IV
Child	5 mg/kg[a]	24	IM/IV
	7.5 mg/kg	8 (2.5 mg/kg tid)	IM/IV
Streptomycin			
Adult	2 g	12	IM
Child	30 mg/kg	12	IM
Levofloxacin			
Adult and child >50 kg	500 mg	24	PO/IV
Child <50 kg and ≥6 months	8 mg/kg (not to exceed 250 mg/dose)	12	PO/IV
Doxycycline			
Adult	200 mg	12 or 24	PO/IV
Child >8 y	4.4. mg/kg	12 or 24	PO/IV
Tetracycline			
Adult	2 g	6	PO/IV
Child >8 y	25–50 mg/kg	6	PO/IV
Chloramphenicol			
Adult	50 mg/kg	6	PO/IV
Child >1 y	50 mg/kg	6	PO/IV

[a]Aminoglycoside dose should be adjusted in light of renal function. There are no published trial data for once-daily gentamicin as plague therapy in adults or children, but this regimen is efficacious in gram-negative sepsis of other causes and was 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 (2.5 mg/kg IV bid).

Source: Dennis DT, Campbell GL: Plague and other *Yersinia* infections, in AS Fauci et al (eds): *Harrison's Principles of Internal Medicine,* 17th ed. 2008, p. 980; Inglesby TV et al: Plague as a biological weapon: medical and public health management. Working Group on Civilian Biodefense. JAMA 283:2281, 2000; and FDA Product Label Reference ID 3123374 *(www.accessdata.fda.gov/drugsatfda_docs/label/2012/020634s061,020635s067,021721s028lbl.pdf).*