relative remission separating the two phases. The first phase (disease onset until around day 5–7) resembles influenza and is characterized by sudden onset of fever and chills, severe headaches, cough, myalgia, pharyngitis, arthralgia of the larger joints, development of a maculopapular rash, and other signs/symptoms (Table 234-2). The second phase (approximately 5–7 days after disease onset and thereafter) involves the gastrointestinal tract (abdominal pain with vomiting and/or diarrhea), respiratory tract (chest pain, cough), vascular system (postural hypotension, edema), and central nervous system (confusion, coma, headache). Hemorrhagic manifestations such as subconjunctival injection, nosebleeds, hematemesis, hematuria, and melena are typical (Table 234-2).

Typical laboratory findings are leukopenia (with cell counts as low as 1000/μL) with a left shift prior to leukocytosis, thrombocytopenia (with counts as low as 50,000/μL), increased concentrations of liver and pancreatic enzymes (aspartate aminotransferase > alanine aminotransferase, γ-glutamyltransferase, serum amylase), hypokalemia, hypoproteinemia, increased creatinine and urea concentrations with proteinuria, and prolonged prothrombin and partial thromboplastin times.

Patients usually succumb to disease 4–14 days after infection. Patients who survive experience prolonged and sometimes incapacitating sequelae such as arthralgia, asthenia, iridocyclitis, hearing loss, myalgia, orchitis, parotitis, psychosis, recurrent hepatitis, transverse myelitis, or uveitis. Temporary hair loss and desquamation of skin areas previously affected by a typical maculopapular rash are visible consequences of the disease. Rarely, filoviruses can persist in the liver, eyes, or testicles of survivors and may cause recurrent disease months after convalescence.

DIAGNOSIS

Filovirus infections cannot be diagnosed on the basis of clinical presentation alone. Numerous diseases typical for Equatorial Africa need to be considered in the differential diagnosis of a febrile patient. Almost all of these diseases occur at a much higher incidence than filovirus infections and are therefore the more likely candidates during differential diagnostic deliberations. The most important of the infectious diseases that closely mimic EVD and MVD are falciparum malaria and typhoid fever; also important are enterohemorrhagic *Escherichia coli* enteritis, gram-negative septicemia (including shigellosis), meningococcal septicemia, rickettsial infections, fulminant viral hepatitis, leptospirosis, measles, and all other viral hemorrhagic fevers (in particular, yellow fever). Other ailments, such as venomous snakebites, warfarin intoxication, and the many transient or inherited platelet and vascular disorders, also must be considered. Visits to caves or mines and direct contact with bats, nonhuman primates (especially apes), or bush meat should raise suspicion of filovirus infection, as should admission to or treatment in rural hospitals or direct contact with severely ill local residents.

If EVD or MVD is suspected on the basis of epidemiologic history, exposure history, and/or clinical manifestations, infectious disease specialists and the proper public health authorities, including the WHO, should be notified immediately. Laboratory diagnosis of EVD and MVD is relatively straightforward but requires maximal containment (biosafety level 4), which usually is not available in filovirus-endemic countries, or the involvement of on-site personnel trained in the use of diagnostic assays adapted for field use. Consequently, diagnostic samples should be collected with great caution and with use of proper personal protective equipment and strict barrier nursing techniques. With adherence to established biosafety precautionary measures, samples should be sent in suitable transport media to national or international WHO reference laboratories. Acute-phase blood/serum is the preferred diagnostic specimen because it usually contains high titers of filovirions and filovirion-specific antibodies.

The current methods of choice for the diagnosis of filovirus infection are reverse-transcription polymerase chain reaction (detection limit, 1000–2000 virus genome copies per milliliter of serum) and antigen capture enzyme-linked immunosorbent assay (ELISA) for the detection of filovirus genomes and filovirion components, respectively. Direct IgM and IgG or IgM capture ELISA is used for the detection of filovirion-targeting antibodies from patients in later stages of disease—i.e., those who have been able to mount a detectable immune response, including survivors. All these assays can be conducted on samples treated with guanidinium isothiocyanate (for polymerase chain reaction) or cobalt-60 irradiation (for ELISA) or subjected to other effective measures that render filoviruses noninfectious. Virus isolation in cell culture and plaque assays for quantification or diagnostic confirmation is relatively easy but must be performed in maximal-containment laboratories. If available, electron microscopic examination of properly inactivated samples or cultures can confirm the diagnosis because filovirions have unique filamentous shapes (Fig. 234-2). Formalin-fixed skin biopsies can be useful for safe postmortem diagnoses.

TREATMENT FILOVIRUS INFECTIONS

Any treatment of patients with suspected or confirmed filovirus infection must be administered under increased safety precautions by experienced specialists using appropriate personal protective equipment (see "Prevention," below). Treatment of EVD and MVD is entirely supportive because no accepted/approved, efficacious, specific antiviral agents or vaccines are yet available. The one exception is hyperimmune equine immunoglobulin, which has been approved in Russia—in the absence of convincing efficacy data—for emergency treatment of laboratory infections. Given the extraordinarily high lethality of filoviruses, special protocols may be established by ad hoc expert groups to outline treatment of exposed individuals with one of several regimens that have shown promise in experimental nonhuman primates. Current options include postexposure vaccination with filovirus $GP_{1,2}$-expressing recombinant replicating vesicular stomatitis Indiana virus; administration of specific filovirus genome- or transcript-targeting small interfering RNAs or phosphorodiamidate morpholino oligomers; administration of filovirus-specific antibodies or antibody cocktails (convalescent sera have not yet been proven effective); and use of a synthetic adenosine analog (BCX4430) that acts as a non-obligate RNA chain terminator. In the absence of these candidate treatments, measures to stabilize patients include those generally recommended for severe septicemia/sepsis/shock. Countermeasures should address hypotension and hypoperfusion, vascular leakage in the systemic and pulmonary circulatory system, disseminated intravascular coagulation and overt hemorrhaging, acute kidney failure, and electrolyte (especially potassium) imbalances. Pain management and administration of antipyretics and antiemetics should always be considered.

COMPLICATIONS

Given the severe immunosuppression induced by filovirus infection, secondary infections should be kept in mind and appropriately treated as early as possible. Pregnancy and labor cause severe and frequently fatal complications in filovirus infections due to clotting factor consumption, fetal loss, and/or severe blood loss during birth.

PROGNOSIS

The prognosis of filovirus infections is generally poor, although outcome probably depends somewhat on which particular virus causes the infection (Fig. 234-3). Convalescence may take months, with skin peeling, alopecia, prostration, weight loss, orchitis, amnesia, confusion, and anxiety as typical sequelae. Rarely, filoviruses persist in apparently healthy survivors and are either reactivated by unknown means at a later point or transmitted sexually. Condom use or abstinence from sexual activity for at least 3 months after disappearance of clinical signs is therefore recommended for survivors.

CONTROL AND PREVENTION

Currently, filovirus vaccines are not available. Prevention of filovirus infection in nature is difficult because the ecology of the viruses is not completely understood. As stated above, frugivorous cave-dwelling