genetic modification of this organism to yield antibiotic-resistant strains, broad-spectrum coverage should be the rule until sensitivities have been determined. As mentioned above, special isolation procedures for patients are not required.

Vaccination and Prevention There are no vaccines currently licensed for the prevention of tularemia. Although a live, attenuated strain of the organism has been used in the past with some reported success, there are inadequate data to support its widespread use at this time. Development of a vaccine for this agent is an important part of the current biodefense research agenda. In the absence of an effective vaccine, postexposure chemoprophylaxis with either doxycycline or ciprofloxacin appears to be a reasonable approach (Table 261e-3).

VIRAL HEMORRHAGIC FEVERS

See also Chaps. 233 and 234.

Hemorrhagic Fever Viruses as Bioweapons Several of the hemorrhagic fever viruses have been reported to have been weaponized by the Soviet Union and the United States. Nonhuman primate studies indicate that infection can be established with very few virions and that infectious aerosol preparations can be produced. Under the guise of wanting to aid victims of an Ebola outbreak, members of the Aum Shinrikyo cult in Japan were reported to have traveled to central Africa in 1992 in an attempt to obtain Ebola virus for use in a bioterrorist attack. Thus, although there has been no evidence that these agents have ever been used in a biologic attack, there is clear interest in their potential for this purpose.

Microbiology and Clinical Features The viral hemorrhagic fevers are a group of illnesses caused by any one of a number of similar viruses (Table 261e-2). These viruses are all enveloped, single-strand RNA viruses that are thought to depend on a host reservoir for long-term survival. Although rodents or insects have been identified as the hosts for some of these viruses, for others the hosts are unknown. These viruses tend to be geographically restricted according to the migration patterns of their hosts. Great apes are not a natural reservoir for Ebola virus, but large numbers of these animals in sub-Saharan Africa have died from Ebola infection over the past decade. Humans can become infected with hemorrhagic fever viruses if they come into contact with an infected host or other infected animals. Person-to-person transmission, largely through direct contact with virus-containing body fluids, has been documented for Ebola, Marburg, and Lassa viruses and rarely for the New World arenaviruses. Although there is no clear evidence of respiratory spread among humans, these viruses have been shown in animal models to be highly infectious by the aerosol route. This, coupled with mortality rates as high as 90%, makes them excellent candidate agents of bioterrorism.

The clinical features of the viral hemorrhagic fevers vary depending on the particular agent (Table 261e-3). Initial signs and symptoms typically include fever, myalgia, prostration, and disseminated intravascular coagulation with thrombocytopenia and capillary hemorrhage. These findings are consistent with a cytokine-mediated systemic inflammatory syndrome. A variety of different maculopapular or erythematous rashes may be seen. Leukopenia, temperature-pulse dissociation, renal failure, and seizures may also be part of the clinical presentation.

Outbreaks of most of these diseases are sporadic and unpredictable. As a consequence, most studies of pathogenesis have been performed using laboratory animals. The diagnosis should be suspected in anyone with temperature >38.3°C for <3 weeks who also exhibits at least two of the following: hemorrhagic or purpuric rash, epistaxis, hematemesis, hemoptysis, or hematochezia in the absence of any other identifiable cause. In this setting, samples of blood should be sent after consultation to the CDC or the USAMRIID for serologic testing for antigen and antibody as well as reverse transcriptase polymerase chain reaction (RT-PCR) testing for hemorrhagic fever viruses. All samples should be handled with double-bagging. Given how little is known regarding the human-to-human transmission of these viruses, appropriate isolation measures would include full barrier precautions with negative-pressure rooms and use of powered air-purifying respirators (PAPRs). Unprotected skin contact with cadavers has been implicated in the transmission of certain hemorrhagic fever viruses such as Ebola, so it is recommended that autopsies of suspected cases be performed using the strictest measures for protection and that burial or cremation be performed promptly without embalming.

TREATMENT VIRAL HEMORRHAGIC FEVERS

There are no approved and effective antiviral therapies for this class of viruses (Table 261e-3). Although there are anecdotal reports of the efficacy of ribavirin, interferon-α, or hyperimmune immunoglobulin, definitive data are lacking. The best data for ribavirin are in arenavirus (Lassa and New World) infections. In some in vitro systems, specific immunoglobulin has been reported to enhance infectivity, and thus these potential treatments must be approached with caution.

Vaccination and Prevention There are no licensed and effective vaccines for these agents. Studies are currently under way examining the potential role of DNA, recombinant viruses, and attenuated viruses as vaccines for several of these infections. Among the most promising at present are vaccines for Argentine, Ebola, Rift Valley, and Kyasanur Forest viruses. A series of monoclonal antibodies directed against the envelope glycoproteins of Ebola have demonstrated protection against infection in a postexposure setting in nonhuman primates and are being further developed for human use.

BOTULISM TOXIN (*CLOSTRIDIUM BOTULINUM*)

See also Chap. 178.

Botulinum Toxin as a Bioweapon In a bioterrorist attack, botulinum toxin would likely be dispersed as an aerosol or as contamination of a food supply. Although contamination of a water supply is possible, it is likely that any toxin would be rapidly inactivated by the chlorine used to purify drinking water. Similarly, toxin can be inactivated by heating any food to >85°C for >5 min. Without external facilitation, the environmental decay rate is estimated at 1% per minute, and thus the time interval between weapon release and ingestion or inhalation needs to be rather short. The Japanese biologic warfare group, Unit 731, is reported to have conducted experiments on botulism poisoning in prisoners in the 1930s. The United States and the Soviet Union both acknowledged producing botulinum toxin, and there is some evidence that the Soviet Union attempted to create recombinant bacteria containing the gene for botulinum toxin. In records submitted to the United Nations, Iraq admitted to having produced 19,000 L of concentrated toxin—enough toxin to kill the entire population of the world three times over. By many accounts, botulinum toxin was the primary focus of the pre-1991 Iraqi bioweapons program. In addition to these examples of state-supported research into the use of botulinum toxin as a bioweapon, the Aum Shinrikyo cult unsuccessfully attempted on at least three occasions to disperse botulinum toxin into the civilian population of Tokyo.

Microbiology and Clinical Features Unique among the category A agents for not being a live microorganism, botulinum toxin is one of the most potent toxins ever described and is thought by some to be the most poisonous substance in existence. It is estimated that 1 g of botulinum toxin would be sufficient to kill 1 million individuals if adequately dispersed. Botulinum toxin is produced by the gram-positive, spore-forming anaerobe *C. botulinum* (Chap. 178). Its natural habitat is soil. There are seven antigenically distinct forms of botulinum toxin, designated A–G. The majority of naturally occurring human cases are of types A, B, and E. Antitoxin directed toward one of these will have little to no activity against the others. The toxin is a 150-kDa zinc-containing protease that prevents the intracellular fusion of acetylcholine vesicles with the motor neuron membrane, thus preventing the release of acetylcholine. In the absence of acetylcholine-dependent triggering of muscle fibers, a flaccid paralysis develops. Although botulism does