Hemorrhagic Fevers and Bioterror

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In 1995, sarin gas was introduced in the Tokyo subway system by the Japanese "Aum Shinrikyo" cult. It was subsequently claimed that members of the cult had traveled to Zaire (now the Democratic Republic of Congo) in an attempt to obtain Ebola virus for use as a bioterror agent. Ebola virus is one of several agents that produce hemorrhagic fever, a syndrome characterized by severe multisystem disease and high mortality. Several of these diseases are highly contagious and would have a devastating impact in the setting of a bioterror attack. Although some hemorrhagic fevers are treatable by ribavirin, the medication is not generally available and would have little effect in a scenario of such magnitude.

The specific laboratory diagnosis of these diseases requires highly specialized biohazard laboratories. The actual tests employed are beyond the scope of this review. Clinicians encountering a suspect case are advised to immediately isolate the patient and his/her secretions to the highest degree possible, and consult local state authorities concerning further treatment and disposition of specimens.

The use of hemorrhagic fever viruses as agents of bioterrorism carries a number of advantages and disadvantages. These organisms are highly contagious, often lethal and, for the most part, untreatable. Their short incubation period and devastating psychological impact would further exacerbate their effect on any civilian population. Although vaccines are available for only three of these agents (yellow fever, Argentine hemorrhagic fever, and Old World hantaviruses), an invading army is not likely to encounter residual infection because of the transient nature of recorded outbreaks.

Notwithstanding their effectiveness as agents of death, the viruses are difficult to obtain, propagate and distribute, and would require high level sophisticated laboratories equipped with advanced protection procedures to prevent infection of personnel and the surrounding community. Unlike the modest requirements needed to produce anthrax, the existence of such a facility would be extremely difficult to camouflage.

We performed an exercise in data mining of the clinical and epidemiologic features of 12 viral hemorrhagic fevers [Table 1]. Any one of them could be used as an agent of bioterror. Many are extremely dangerous and life-threatening, and most are unfamiliar – even to specialists in infectious diseases. Epidemiologic data were abstracted from relevant documents (standard and electronic), published by the World Health Organization and a commercial informatics software program that abstracts peer-reviewed journals and texts (GIDEON, CY Informatics, Ramat Hasharon, Israel)

Hopefully, this review will add to the growing awareness of the potential use of hemorrhagic fever viruses as agents of bioterror.

Argentine hemorrhagic fever [1–4]

Argentine hemorrhagic fever occurs only in Argentina, with most cases reported from Cordoba, Santa Fe and Buenos Aires provinces (the causative virus is named for Junin, a town near Buenos Aires). The local reservoir is *Calomys musculinus* (7.9% of *Calomys* in endemic areas are seropositive). Disease rates peak during late summer to autumn and primarily affect individuals engaged in harvesting corn. Nosocomial transmission has been documented.

Clinical presentation

The onset of the illness is gradual, with progressive fever, malaise and myalgia (notably in the lower back). Additional findings include epigastric pain, retro-orbital headache, dizziness, photophobia and constipation. Conjunctival injection, erythema of the face and upper portion of the trunk, and orthostatic hypotension are common. Petechiae (notably in the axillae), generalized lymphadenopathy, and an enanthem consisting of petechiae and/or small vesicles on the palate and fauces are found in most patients. Affected individuals become progressively ill with vascular and/or neurologic disease. Complications at this point may include mucosal bleeding, shock, pulmonary infiltration and edema, secondary bacterial infection, gait disturbances, tremors, cerebellar dysfunction, clonic seizures and coma. The case-fatality rate is 30–40%. Convalescence is slow but leaves no sequelae. Note that Bolivian hemorrhagic fever (below) is clinically similar to Argentine hemorrhagic fever, however neurologic signs are more common in the Argentinian while hemorrhagic diatheses are more common in the Bolivian hemorrhagic fever.

Bolivian hemorrhagic fever [5–7]

Bolivian hemorrhagic fever was first identified in 1959 as a sporadic hemorrhagic illness in rural areas of the Beni district, Bolivia. The disease is most common during April to July in the upper savanna region of eastern Bolivia (Beni). Principal exposure occurs through rodents (*Calomys callosus*) that enter homes in this region. Nosocomial and human-to-human spread have been documented. Infection of *C. callosus* results in asymptomatic viral shedding in saliva, urine and feces; 50% of experimentally infected *C. callosus* are chronically viremic and shed virus in their bodily excretions or secretions.

Although the infectious dose of Machupo virus in humans is unknown, exposed persons may become infected by inhaling the virus in aerosolized secretions or excretions of infected rodents, ingestion of food contaminated with rodent excreta, or by direct contact of excreta with abraded skin or oropharyngeal mucous membranes. While reports of person-to-person transmission are uncommon, hospital contact with a patient has resulted in person-to-person spread of Machupo virus to nursing and pathology laboratory staff. In 1994, the fatal secondary infection of six family members in Magdalena from a single naturally acquired infection further suggested the potential for person-to-person transmission.

Clinical presentation

Early clinical manifestations consist of non-specific signs and symptoms including fever, headache, fatigue, myalgia and arthralgia. Within 7 days, patients may develop hemorrhagic signs, including bleeding from the oral and nasal mucosa and from the bronchopulmonary, gastrointestinal and genitourinary tracts. The case-fatality rate is 18%.

Brazilian hemorrhagic fever ("Sabia") [8,9]

To date, only three cases (one fatal) of Sabia have been described – two of which were acquired in laboratories. The first case was reported in Sao Paulo, Brazil in 1990, and infection was thought to have originated in a community called "Sabia." The most recent case occurred among university personnel in Connecticut who were working with a patient's specimen from Brazil. Clinically, Sabia is similar to Argentine hemorrhagic fever, with natural infection limited to Brazil.

Crimean Congo hemorrhagic fever [10–13]

This is also known as acute infectious capillary toxinosis and Xinjiang hemorrhagic fever. Crimean Congo hemorrhagic fever was first described in the Crimea in 1944, and later equated with an illness that occurred in the Congo in 1956. Widely scattered cases were subsequently confirmed in Europe and Asia, most commonly among adult males engaged in the livestock industry. Evidence for the virus has been found among ticks in Africa, Asia, the Middle East and Eastern Europe. The virus is transmitted to humans through the bites of ixodid ticks (*Hyalomma*) or contact with infected blood and tissues from livestock. Person-to-person transmission also occurs.

This CCHF virus may infect a wide range of domestic and wild animals. Many bird species are resistant to infection, but ostriches are susceptible and may show a high prevalence of infection in endemic areas. Animals become infected from the bite of infected ticks. A number of tick genera are capable of becoming infected with CCHF virus, but the most efficient and common vectors appear to be members of the genus *Hyalomma*. Transovarial (transmission of the virus from infected female ticks to offspring via eggs) and venereal transmission have been demonstrated among some vector species. The most important source for acquisition of the virus by ticks is believed to be infected small vertebrates on which immature *Hyalomma* ticks feed. Once infected, the tick remains infected through its developmental stages, and the mature tick may transmit the infection to large vertebrates, such as livestock. Domestic ruminants are viremic for one week after becoming infected.

Humans who become infected with CCHF acquire the virus from a tick bite or through direct contact with blood or other infected tissues from livestock. The majority of cases occur in individuals involved with the livestock industry, such as agricultural workers, slaughterhouse workers and veterinarians. The virus has been found in cattle, goats, sheep, hares and hedgehogs.

Clinical presentation

The incubation period following tick bite is usually 1–3 days, with a maximum of 9 days. The incubation period following contact with infected blood or tissues is usually 5–6 days, with a maximum of 13 days. Onset of illness is sudden, with fever, myalgia, vertigo, neck pain and stiffness, backache, headache and photophobia. There may be initial nausea, vomiting and sore throat accompanied by diarrhea and generalized abdominal pain. Later, the patient may experience sharp mood swings and may become confused and aggressive.

After 2–4 days, agitation is replaced by somnolence, depression and lassitude, and the abdominal pain may localize to the right upper quadrant with detectable hepatomegaly. Other clinical signs at this stage include tachycardia, lymphadenopathy and a petechial rash that progresses to ecchymoses and other bleeding diatheses. There is usually evidence of hepatitis. The severely ill may develop hepatorenal and pulmonary failure after the fifth day of illness. The case-fatality rate is approximately 30%, with death occurring in the second week of illness. In those patients who recover, improvement generally begins on the ninth or tenth day after onset of illness.

Diagnosis of suspected CCHF is performed in specially equipped, high biosafety level laboratories. Immunoglobulin G and M antibodies may be detected in serum by enzyme-linked immunoassay from day 6 of illness. IgM remains detectable for up to 4 months, and IgG levels decline but remain detectable for up to 5 years. Although an inactivated, mouse brain-derived vaccine against CCHF has been developed and used on a small scale in Eastern Europe, there is no safe and effective vaccine widely available for human use.

Ebola [14–18]

Ebola was first identified in June 1976 during an outbreak in Sudan, which involved 284 cases with a case-fatality ratio of 53%. In September 1976, a separate outbreak (318 cases, 88% fatal) was reported from Zaire (Democratic Republic of the Congo). An additional fatal case was identified in that country in June 1977. An outbreak (34 cases, 64% fatal) was reported in Sudan in 1979. The disease was not identified again until 1994 when two outbreaks occurred, one in the Ivory Coast (12 chimpanzees and one human) and the other in Gabon (49 humans, 59% fatal).

CCHF = Crimean Congo hemorrhagic fever

IgM = immunoglobulin

Table 1. The hemorrhagic fever viruses

Disease	Agent	Reservoir	Vector	Vehicle	Incubation period	Typical therapy	Disease distribution
Argentine hemorrhagic fever	Virus (RNA: arenaviridae, tacaribe complex), arenavirus, Junin virus	Rodent (*Colomys musculinus*)	None	Air, dust, excreta	7–16 days	Strict isolation; specific immune plasma; suggest ribavirin 2.0 g IV, then 1.0 g IV, q 6 hr x 4 days, then 0.5 g q 8 hr x 6 days	Argentina
Bolivian hemorhagic fever	Virus (RNA: arenaviridae, tacaribe complex), arenavirus, Machupo virus	Rodent (*Calomys callosus*)	None	Food, water, direct patient contact	5–19 days	Strict isolation; specific immune plasma; suggest ribavirin 2.0 g IV, then 1.0 g IV, q 6 hr x 4 days, then 0.5 g q 8 hr x 6 days	Bolivia
Brazilian hemorrhagic fever	Virus (RNA: arenaviridae, tacaribe complex), arenavirus, Sabia virus	Rodent (presumed)	None	Excretions	7 days	Strict isolation; no therapy proven; suggest IV ribavirin 2 g, then 1g q 6 hr x 4 days, then 0.5 g q 8 hr x 6 days	Brazil
Crimean-Congo hemorrhagic fever	Virus (RNA: bunyaviridae) nairovirus	Hare, bird, tick, cattle, sheep, goat	Tick (*Hyalomma*, over 30 potential vectors in this genus)	Infected secretions from patient or livestock	1–6 days (range 2–12)	Isolation; supportive; ribavirin: 1 g p.o. QID x 4 days, then 0.5 g QID x 6 days	Disease is endemic or potentially endemic to 35 countries
Ebola fever	Virus (RNA: filoviridae) filovirus. Four species of the virus have been described: Ivory Coast, Reston, Sudan and Zaire	? guinea pig, ? bat	None	Secretions, contact, needle, syringe	5–12 days (range 2–21)	Strict isolation; supportive	Disease is endemic or potentially endemic to 14 countries
Hantavirus infections	Virus (RNA: bunyaviridae) hantavirus (Hantaan, Puumala, Dobrava/ Belgrade & Seoul viruses)	Field mice (*Apodemus agrarius* – Hantaan), vole (*Clethrionomys glareolus* – Puumala), rat (*Rattus norvegicus* -Seoul), ? bat, ? bird	None	Animal excreta	12–21 days (range 4–42)	Supportive; ribavirin: 1 g IV, q 6 hr x 4 days, then 0.5 g q 6 hr x 6 days	Disease is endemic or potentially endemic to 70 countries
Lassa fever	Virus (RNA: arenaviridae), arenavirus	Multimammate mouse (*Mastomys huberti* and *M. erythroleucus*)	None	Rodent secretions, dust, food, patient secretions	8–14 days (range 3–21)	Strict isolation; IV ribavirin 2 g, then 1 g q 6 hr x 4 days, then 0.5 g q 8 hr x 6 days	Disease is endemic or potentially endemic to 15 countries
Marburg virus disease	Virus (RNA: filoviridae) filovirus. Marburg virus	? African green monkey, ? bat	None	Secretions, contact, syringe, needle	5–7 days (range 3–13)	Strict isolation; supportive	Disease is endemic or potentially endemic to 10 countries
Omsk hemorrhagic fever	Virus (RNA: flaviviridae) flavivirus	Rodent, muskrat (*Ondrata zibethica*), tick	Tick (*Dermacentor pictus* and *D. marginatus*)	None	3–9 days (range 2–12)	Supportive	Romania, Russia (former USSR)
Rift Valley fever	Virus (RNA: bunyaviridae) phlebovirus	Sheep, ruminant	Mosquito (*Culex, Aedes, Anopheles, Erethmapodite, Mansonia, Culicoides, Coquillettidia* spp.)	None	3–5 days (range 2–7)	Supportive	Disease is endemic or potentially endemic to 33 countries
Venezuelan hemorrhagic fever	Virus (RNA: arenaviridae, tacaribe complex), arenavirus, Guanarito virus	Rodent (cane mouse = *Zygodontomys brevicauda*), ? other rodents (cotton rat = *Sigmodon alstoni*	None	? excretions	Not known	Strict isolation; supportive	Venezuela
Yellow fever	Virus (RNA: flaviridae), flavivirus	Humans, mosquito, monkey, ? marsupial	Mosquito (*Aedes, Haemagogus, Sabethes*)	None	3–6 days (range 2.5–14)		Disease is endemic or potentially endemic to 43 countries

In 1995, an outbreak was reported in the Democratic Republic of the Congo (315 cases, 77% fatal). In 1996, two outbreaks were reported in Gabon (31 cases, 68% fatal; and 60 cases, 75% fatal). In 2000, an outbreak (428 cases, 160 fatal) was reported in Uganda. Subsequent outbreaks occurred in the Republic of Congo and Gabon in 2001 and 2002, as of this writing. In 1989, Ebola virus (Reston strain) was identified in monkeys (cynomolgus macaques) imported from the Philippines to the United States: at least four human contacts seroconverted without clinical illness. Two imported monkeys died of Ebola in Texas in 1996.

Clinical presentation

The symptoms and signs of Marburg (see below) and Ebola virus infections are similar. Following an incubation period of 4–16 days, onset is sudden, marked by anorexia, fever, chills, headache and myalgia. Later, the patient develops nausea, vomiting, sore throat, abdominal pain and diarrhea. Patients are dehydrated, apathetic and disoriented and exhibit pharyngeal and conjunctival infection. Most develop severe hemorrhagic manifestations between days 5 and 7. Bleeding is often from multiple sites, most commonly from the gastrointestinal tract, lungs and gingiva. Hemorrhage and oropharyngeal lesions carry a particularly poor prognosis. Death occurs between days 7 and 16.

Hantaviruses [19–21]

Other names for this group of viruses include: acute epidemic hemorrhagic fever, Bosnian hemorrhagic fever, Churilov disease, endemic benign nephropathy, epidemic hemorrhagic fever, Far Eastern hemorrhagic fever, hemorrhagic nephrosonephritis, hemorrhagic fever and renal syndrome, infectious hemorrhagic fever, Korean hemorrhagic fever, muroid virus nephropathy, nephropathia epidemica, rodent-borne viral nephropathy, Scandinavian epidemic nephropathy, and Songo fever.

Hantavirus infections are most common among agrarian and military populations. Each year 150,000 victims are hospitalized, and 4,500 to 22,550 die of these infections, over 50% of them in China. Approximately 200,000 cases are estimated each year for Eurasia. There were 293 cases officially reported by the European Region (not including the Russian Republic) in 1998 (227 of these in Norway) and 114 in 1999 (64 in Norway).

Hantaan virus causes epidemic hemorrhagic fever ("Korean hemorrhagic fever" or "hemorrhagic fever with renal syndrome"). The striped field mouse (*Apodemus agrarius*) reservoir is found in Central Europe south of Thrace, the Caucasus and Tien Shan Mountains, the Amur River to East Xijiang and East Hunnan, West Sichuan, Fujian and Taiwan. The Dobrava/Belgrade virus causes severe hemorrhagic fever with renal syndrome. The yellow-necked mouse (*Apodemus flavicolis*) reservoir is found from England and Wales, through northwest Spain, France, southern Scandinavia, European Russia to the Urals, southern Italy, the Balkans, Syria, Lebanon and Israel. The Seoul virus causes less severe hemorrhagic fever with renal syndrome. The reservoir rat (*Rattus norvegicus*) is found worldwide.

Puumala virus causes nephropathia epidemica. The reservoir, the bank vole (*Clethrionomys glariolus*), is found in the West Palearctic from France and Scandinavia to Lake Baikal, south of northern Spain, northern Italy, the Balkans, Western Turkey, northern Kazakhstan, the Altai and Sayan mountains, Great Britain and southwestern Ireland. The house mouse (*Mus musculus*) is implicated in Serbia, and *Clethrionomys rutilis* in western Russia. The muskrat (*Ondatra zibethicus*) has been implicated as a disease reservoir in Germany.

There are no proven cases of Hantaan or Seoul infections either from Europe or from western Russia (west of the Urals) as of the year 2000: all the claimed cases turned out to be caused by the Dobrava virus. The latter has been confirmed in the former Yugoslavia, Albania, Greece, Germany, Estonia and Russia. In contrast to the Balkan region where the Dobrova virus seems to be carried mainly *by Apodemus flavicollis*, the virus has only been found in *Apodemus agrarius* in Estonia and Russia. Notably, two outbreaks in the Ryazan and Tula regions in Russia, previously reported as caused by the Seoul virus, were later proven to be caused solely by Dobrava virus. Simultaneous HFRS epidemics in Bashkortostan (Bashkiria), Samara and Tatarstan appear to have been related. Recent increases in the number of human cases have been ascribed to a construction boom in forests during the last decade.

Clinical presentations

The course of severe HFRS involves five overlapping stages: febrile, hypotensive, oliguric, diuretic, and convalescent, although it is not uncommon for one or more of these stages to be inapparent or absent. The onset of the disease is sudden, with intense headache, backache, fever and chills. Hemorrhage is manifested during the febrile phase as a flushing of the face or infection of the conjunctiva and mucous membranes. A petechial rash may appear on the palate and axillary skin folds. Extreme albuminuria, typically appearing on the fourth day, is characteristic of severe HFRS.

As the febrile stage ends, hypotension may develop and last for hours to days, accompanied by nausea and vomiting. One-third of deaths occur during this phase and are related to vascular leakage and shock. Approximately 50% of deaths occur during the subsequent (oliguric) phase. Patients who survive and progress to the diuretic phase show improved renal function but may still die of shock or pulmonary complications. The final (convalescent) phase can last for weeks to months. Case-fatality rates range from less than 0.1% for HFRS caused by Puumala virus to approximately 5–10% for HFRS caused by the Hantaan virus.

Lassa fever [22–26]

Lassa fever is thought to occur in all of West Africa, from Nigeria to Senegal. As many as 500,000 cases may occur yearly according to some estimates. Disease rates peak during January to April (i.e., the dry season). Twelve cases of Lassa fever were imported into Europe and North America during 1970–2000, with no secondary cases among medical staff or patients. Four cases were imported into Europe during January to July 2000. A single imported case (from Sierra Leone) was reported in Israel in 1987.

HFRS = hemorrhagic fever with renal syndrome

The disease is transmitted to humans from wild rodents (the multimammate rat *Mastomys natalensis*). Lassa infection in rodents persists and the virus is shed throughout the life of the animal. Disease transmission is primarily through direct or indirect contact with excreta of infected rodents deposited on surfaces such as floors and beds, or in food or water. All age groups are susceptible to Lassa infection. Person-to-person and laboratory infections occur, especially in the hospital environment, by direct contact with blood (including inoculation with contaminated needles), pharyngeal secretions or urine, or by sexual contact. Person-to-person spread may occur during the acute phase of fever when the virus is present in the throat. The virus may be excreted in the urine of patients for 3–9 weeks from the onset of illness. The virus can be transmitted via semen for up to 3 months. Nosocomial outbreaks have been described in Nigeria, Liberia and Sierra Leone.

Clinical presentation

The onset of symptoms is gradual, with fever, malaise, headache, sore throat, cough, nausea, vomiting, diarrhea, myalgia and chest and abdominal pain. The fever may be either constant or intermittent with spikes. Inflammation of the throat and eyes is commonly observed. In severe cases, hypotension or shock, pleural effusion, hemorrhage, seizures, encephalopathy, and swelling of the face and neck are frequent.

Approximately 15% of hospitalized cases die. The disease is more severe in pregnancy, with fetal loss occurring in more than 80% of cases. Alopecia and loss of coordination may occur in convalescence. Sensorineural deafness occurs in 29% of cases, making this the most common cause of deafness in West Africa. The clinical syndrome of Lassa fever is difficult to distinguish from severe malaria, septicemia, yellow fever and other viral hemorrhagic fevers (e.g., Ebola). Inflammation of the throat with white tonsillar patches is an important distinguishing feature.

Marburg disease [27–31]

Marburg disease was first described in 1967 in laboratories in Marburg (Germany) and the former Yugoslavia among workers handling vervet monkeys originating from Uganda. The disease did not reappear again until 1975 when several Australians trekking in Zimbabwe were infected, resulting in additional secondary infections while under treatment in South Africa. Subsequent cases were described in Kenya in 1980 and 1987. A tourist returning to Sweden from Kenya in 1990 was also found to have the disease (diagnosis speculative). A case report of laboratory infection with Marburg virus in Russia was published in 1994. The world's first extensive outbreak of Marburg fever occurred in the Democratic Republic of Congo during 1998–1999, with additional cases in the area reported during 2000. The clinical presentation is the same as for Ebola (above).

Omsk hemorrhagic fever [32]

Also known as Muskrat fever and spring-autumn fever, Omsk hemorrhagic fever was first reported during an outbreak in Omsk district, Russia (1943–44). The virus was first isolated in 1947. Disease incidence peaks in April to June and September to November, and is limited to western and northwestern Siberia. Cases during the winter are associated with hunting activities. Most patients are rural residents, hunters and agricultural workers. The local vectors are *Dermacentor pictus* (north) and *D. marginatus* (south).

Clinical presentation

The onset of illness is abrupt, with fever, headache, myalgia, nausea, facial flushing, and a papulovesicular enanthem of the soft palate progressing to hemorrhage from multiple mucosal surfaces. A biphasic fever course is noted in 30–50% of cases, with meningitis, renal dysfunction or pneumonia during the second stage. Gastrointestinal symptoms, cough, relative bradycardia, leukopenia, thrombocytopenia and lymphadenopathy are common, as are such sequelae as alopecia and hearing loss. The case-fatality rate ranges between 0.5% and 2.5%.

Rift Valley fever [33–35]

The Rift Valley fever virus was first isolated during an outbreak among sheep in the Rift Valley (Kenya) in 1931. An outbreak in Egypt during 1977–78 involved 18,000 human cases (598 fatalities). Outbreaks in Kenya, Somalia and Tanzania during 1997–98 involved an estimated 89,000 people. The virus was first reported in West Africa in 1974 (among mosquitoes in Senegal), however large outbreaks in the area had not been reported prior to an epidemic in southern Mauritania in 1987. The first outbreak outside of sub-Saharan Africa occurred in Egypt in 1977 (serologic surveys indicate that the virus did not exist in Egypt prior to that year). Rift Valley fever was first reported outside of the African continent (Saudi Arabia and Yemen) in 2000.

During epizootics, disease usually occurs first in animals, then in humans. Man is infected either through mosquito bites or contact with the body fluids or organs of infected animals and possibly by aerosol or by ingestion of contaminated milk. Human infection occurs mainly among farmers and others who are at occupational risk. Sheep are more susceptible than cattle, while goats are least susceptible. Outbreaks are often portended by increasing numbers of unexplained abortion among livestock. Infected bats have been identified in Guinea.

Vectors include *Eretmapodites chrysogaster, Aedes caballus*, *Ae. circumluteolus*, *Ae. lineatopennis*, *Ae. cumminsii* (in Burkina Faso), *Culex theileri*, *Culex antennatus* (Nigeria), *Mansonia africana*, *Ma. uniformis* (Burkina Faso) and *Culicoides* spp. Inter-epizootic vectors belong to the *Aedes* subgenera: *Neomelaniconion* in East Africa, Aedimorphus in West Africa, *Culex theileri* in South Africa, *Aedes dalzieli*, *Ae. ochraceus* and *Ae. vexans* in Senegal, and *Culex pipiens* in Egypt. Transovarial transmission has been found in *Aedes*, and epidemics may occur when high rainfall favors hatching and development of transovarially infected offspring.

Clinical presentation

Disease is preceded by a flu-like illness with sudden onset of fever, headache, myalgia and back pain. Nucchal rigidity and photophobia may also be present at this time. Complications include hemorrhagic fever on the second to fourth day of illness, or retinal

hemorrhage or meningoencephalitis appearing after the first week. Retinitis occurs in 15% of patients. Hemorrhagic phenomena and fatal encephalitis have been observed in approximately 1–2% of patients during epidemics and account for much of the mortality. The overall case-fatality rate is estimated at 0.5– 2%.

Venezuelan hemorrhagic fever [36–38]

Also known as guanarito virus infection and pirital virus, Venezuelan hemorrhagic fever was first reported as an outbreak (15 cases, 9 fatal) in Portuguesa State during 1989. Subsequent cases were reported from Barinas State. To date, this disease has been limited to Venezuela. Highest rates (41% of cases) are reported during December to January. The local reservoir appears to be the cane rat (*Zygodontomys brevicada*). Cotton rats (*Sigmodon alstoni*) are infected by a related arenavirus (Pirital virus) of unknown significance to humans.

Clinical presentation

The clinical features are similar to those of Argentine hemorrhage fever (see above), with the exception that pharyngitis is common in Venezuelan hemorrhagic fever. The case-fatality rate is 19–33%.

Yellow fever [39,40]

Transmission of yellow fever follows three patterns: sylvatic (or jungle), intermediate, and urban.

- *Sylvatic yellow fever*: In tropical rain forests, yellow fever occurs in monkeys that are infected by mosquitoes. The infected monkeys can then pass the virus onto other mosquitoes that feed on them. These infected mosquitoes bite humans who enter the forest, resulting in sporadic cases of yellow fever. The majority of cases are young males working in the forest (logging, etc.). On occasion, the virus spreads beyond the affected individual.
- *Intermediate yellow fever*: Small-scale epidemics occur in humid or semi-humid savannas of Africa. These behave differently from urban epidemics: i.e., many separate villages in an area suffer cases simultaneously but fewer people are infected. Semi-domestic mosquitoes infect both monkey and human hosts. This area is often called the "zone of emergence," where increased contact between humans and infected mosquitoes leads to disease. This is the most common type of outbreak seen in recent decades in Africa. It can shift to a more severe urban-type epidemic if the infection is carried into a suitable environment (with the presence of domestic mosquitoes and unvaccinated humans).
- *Urban yellow fever*: Large epidemics can occur when migrants introduce the virus into areas with a high human population density. Domestic mosquitoes (of one species, *Aedes aegypti*) carry the virus from person to person; no monkeys are involved in transmission. These outbreaks tend to spread outwards from one source to cover a wide area. Nigeria accounted for 90.8% of all yellow fever cases during 1989–1993. In 1995, Peru accounted for 50% of the world's cases; in 1996, Senegal accounted for 30.2% of the world's cases, and Benin for 28.3%; in 1997, Bolivia accounted for 33.2% of the world's cases, and Peru for 23.2%; in 1998, Peru accounted for 54.5% of the world's cases. Africa reported 29,525 (23% fatal) cases during the period 1950–99. Mass vaccination in Africa was introduced during 1934–35, when 5,699 persons were given vaccine in French sub-Saharan Africa. Subsequent campaigns to vaccinate 25 million persons every 4 years were initiated in the same area in 1940, resulting in a reduction in local incidence. A total of 289,697,881 persons were vaccinated during the campaigns of 1939–53. Latin America reported 8,503 cases and 4,694 (62% fatal) during the periods 1950–99 and 1971–99, respectively. The last case of urban yellow fever in the Americas was reported in 1954.

Thirteen species of African mosquitoes are capable of transmitting yellow fever in the laboratory. The natural African vectors are *Aedes aegypti* (urban), *Ae. africanus* (jungle), *Ae. simpsoni* and *Ae. furcifer-taylori*. *Ae. simpsoni* is found only in South Africa and Zimbabwe, and could theoretically transmit disease. *Ae. bromeliae* is a vector to both humans and monkeys in Central and East Africa. Additional vectors implicated include *Ae. luteocephalus*, *Ae. metallicus*, *Ae. neoafricanus*, *A. opok* and *Ae. vittatus*. Vertebrate hosts in Africa include monkeys: *Colobus abyssinicus* (East and Central Africa), *Co. polykomos* and *Co. badius* (West Africa), *Cercopithecus* species, *Cerocebus* (mangabeys), *Erythrocebus* (red monkeys or patas) and *Papio papio, and P. anubis* (baboons) and Pan troglodytes (chimpanzees). Galagoes (bush babies) have also been implicated. Ixodid ticks (*Amblyomma*) may serve as reservoirs in West Africa; and vertical transmission among culicine mosquitoes may allow survival in inter-epidemic periods.

Aedes aegypti was eradicated from most of South America during the first half of the twentieth century but reappeared during the 1970s. Urban yellow fever had virtually disappeared from the continent, but was reported for the first time in Bolivia during 1997–98, following a hiatus of 44 years. The American vectors are *A. aegypti, Haemagogus janthinomys, H. spegazzinii, H. leucocelaenus, H. equinus, H. mesodentatus, H. lucifer, H. iridicolor, H. capricornii, H. albomaculatus* and *Sabethes chloropterus*. *Aedes aegypti* was eradicated from 21 countries in the Americas during 1948–62; however, as of 1996, the mosquito is found in all countries in the area, except for Bermuda, Canada, Chile and Uruguay. Vertebrate hosts in South America include *Alouatta* (howler monkeys), *Ateles* (spider monkeys), *Callithrix* (marmosets), *Cebus* (capuchin monkeys) and *Saimiri* (squirrel monkeys).

Clinical presentation

The clinical presentation of yellow fever can range from a self-limited flu-like illness to overwhelming hemorrhagic fever, with a case-fatality rate of 50%. As many as 50% of infections may be clinically inapparent. Signs of infection include abrupt onset of fever, headache and myalgias, associated with conjunctival infection, facial flushing, relative bradycardia (Faget's sign) and leukopenia.

Although most cases do not progress beyond this stage, remission of fever for a few hours to several days is followed by high fever, headache, lumbosacral pain, nausea, vomiting, abdominal pain and somnolence. At this stage, the patient exhibits icteric hepatitis and a hemorrhagic diathesis with prominent bleeding

from the gastrointestinal tract, epistaxis, bleeding gums, and petechial and purpuric hemorrhages. Weakness, prostration, protracted vomiting and albuminuria are prominent. Deepening jaundice and elevations in serum transaminase levels continue for several days, accompanied by azotemia and progressive oliguria. Direct bilirubin levels rise to 5–10 mg/dl, while alkaline phosphatase levels are only slightly elevated.

Eventually, hypotension, shock and metabolic acidosis develop, compounded by myocardial dysfunction and arrhythmias. Additional findings may include acute tubular necrosis, confusion, seizures and coma. Cerebrospinal fluid examination reveals an elevated protein level without pleocytosis. Ten to 60% of patients die, usually within 7–10 days after onset.

Conclusion

It is unlikely that healthcare workers practicing in most countries will ever encounter any of the diseases noted in this review. Nevertheless, the mass movement of tourists, immigrants and refugees could potentially result in the introduction of such "exotic" diseases into distant populations. The potential use of hemorrhagic fever viruses as agents of bioterror is a real threat, and it is incumbent on the clinician to maintain a high degree of suspicion whenever confronted with a patient exhibiting unusual or severe multisystem illness characterized by hemorrhagic diathesis.

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