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216 The Filovirids: Orthoebolavirus and Orthomarburgvirus Infections

public health impact while reducing potential risk in seronegative individuals. Further postmarket evaluation is ongoing. More recently, a phase 3 trial of Butantan-DV, a single-dose tetravalent vaccine, was shown to prevent symptomatic DENV-1 and DENV-2 infection; in the absence of DENV-3 and DENV-4 infections during the trial, efficacy against these serotypes is unknown. TV003, a single-dose vaccine designed to balance DENV serotype-specific components, is currently undergoing phase 3 clinical evaluation; similar concerns about safety are being addressed. YELLOW FEVER YFV had caused major epidemics in Africa and Europe before its transmission by YF mosquitoes was discovered in 1900. Urban YF became established in the Americas because of colonization with YF mosquitoes—originally an African mosquito. Subsequently, different types of mosquitoes and nonhuman primates were found to maintain YFV in Africa and in Central and South American rain forests. Transmission to humans is incidental, occurring via bites from mosquitoes that have fed on viremic monkeys. After the identification of *Ae. aegypti* as the vector of YF, containment strategies were aimed at increased mosquito control. Today, urban YFV transmission occurs only in some African cities, but the threat exists in the cities of South America, where reinfestation by YF mosquitoes has taken place, and DENV-1–4 transmission by these mosquitoes is common. Despite the existence of a highly effective and safe vaccine, several hundred jungle cases of YF occur annually in South America, and 84,000–170,000 severe jungle and urban cases (resulting in 29,000–60,000 fatal outcomes) occurred in Africa in 2013 alone. In 2016, a large urban outbreak (Luanda, Angola) spilled over to generate local transmission in large cities in neighboring countries (e.g., Kinshasa, Democratic Republic of the Congo) as well as travel-related cases in China; the signal of a global threat that included exportation to Asia stimulated ongoing efforts to identify and vaccinate highest-risk populations in 40 targeted countries in Africa and South America, to reactively vaccinate people in outbreak settings, and to increase measures to prevent

exportation. YF is a typical VHF notable for prominent hepatic necrosis. After an incubation period of 3–6 days, patients present with a nonspecific febrile illness (fatigue, myalgia, backache, headaches, photophobia, anorexia, nausea or vomiting) associated with viremia typically lasting 3–4 days. After defervescence, 10–15% of patients develop recrudescent fever and “intoxication” characterized by severe dysfunction of the liver and other organs. Hepatic failure leads to the characteristic jaundice, bleeding (gastrointestinal tract, nasopharyngeal mucosa), abdominal pain with nausea and vomiting, and hyperammonemic encephalopathy; acute kidney injury leads to oliguria, azotemia, and marked albuminuria; and myocardial injury and encephalitis have been described. Abnormalities in liver function tests range from modest elevations of hepatic aminotransferase activities in mild cases to severe liver injury, hyperbilirubinemia, and the synthetic dysfunction of acute hepatic failure. After early leukopenia, leukocytosis occurs as disease progresses, and coagulation abnormalities are common. Treatment is supportive only. Although most infections are subclinical, 50% of patients who enter the toxic phase die in the next 7–10 days. Urban YF can be prevented by the control of YF mosquitoes. The continuing sylvatic cycles require vaccination of all visitors to areas of potential transmission with live-attenuated variant 17D vaccine virus, which cannot be transmitted by mosquitoes. With few exceptions, reactions to the vaccine are minimal; immunity is provided within 10 days and lasts for at least 25–35 years. Recent meta-analytic review of 39 clinical studies suggests seroprotection is high (>90%) and perhaps lifelong after one vaccine dose in adults from nonendemic areas, raising questions about the utility of further boosting in this population. An egg allergy mandates caution in vaccine administration. Although fetal harm has not been documented, pregnant women should be immunized only if they are at risk of exposure to YFV. Because vaccination has been associated with several cases of encephalitis in children <6 months of age, it is contraindicated in this age group and not recommended for infants 6–8 months of age unless the risk of exposure is very high. Rare, serious, multisystemic adverse reactions (occasionally fatal), including vaccine-associated

“viscerotropic” YF, have been reported, particularly affecting the elderly and those with congenital (mutations affecting interferon α [IFN α] signaling) or acquired (autoantibodies to IFN α , thymoma) impairment affecting viral control. The risk-to-benefit ratio should be weighed before vaccine administration to individuals ≥ 60 years of age. Nevertheless, the number of deaths of unvaccinated travelers with YF exceeds the number of deaths from vaccination, and a liberal vaccination policy for travelers to involved areas should be pursued. Timely information on changes in YF distribution and YF vaccine requirements can be obtained from the U.S. Centers for Disease Control and Prevention (<https://wwwnc.cdc.gov/travel/yellowbook/2024/preparing/yellow-fever-vaccine-malaria-prevention-by-country>).

Acknowledgment The authors gratefully acknowledge the major contributions of Clarence J. Peters and additional contributions by Rémi N. Charrel to this chapter in previous editions and thank Anya Crane (IRF-Frederick) for editing the manuscript. ■ ■ **FURTHER READING** Centers for Disease Control and Prevention: Arbovirus catalog. Available at <https://wwwn.cdc.gov/arbocat/>. Accessed February 4, 2024. Howley PM, Knipe DM (eds): Fields Virology. Volume 1: Emerging Viruses, 7th ed. Philadelphia, Wolters Kluwer/Lippincott Williams & Wilkins, 2020. International Committee on Taxonomy of Viruses (ICTV): Virus taxonomy: The ICTV report on virus classification and nomenclature. Available at <https://ictv.global/report>. Accessed February 4, 2024. Lvov DK et al: Zoonotic Viruses of Northern Eurasia: Taxonomy and CHAPTER 216 Ecology. London, Elsevier/Academic Press, 2015. Singh SK, Ruzek D (eds): Viral Hemorrhagic Fevers. Boca Raton, FL,

CRC Press, 2013. Vasilakis N, Gubler DJ (eds): Arboviruses: Molecular Biology, Evolution and Control. Haverhill, UK, Caister Academic Press, 2016. Filovirids: Orthoebolavirus and Orthomarburgvirus Infections ■ ■WEBSITE International Committee on Taxonomy of Viruses (ICTV). <https://ictv.global/>. Accessed February 4, 2024. Jens H. Kuhn, Ian Crozier

Filovirids: Orthoebolavirus

and Orthomarburgvirus Infections Several viruses in the family Filoviridae cause severe infections in humans that are often fatal. Introduction of filovirids into human populations is an extremely rare event that most likely occurs by direct or indirect contact with reservoir hosts (known and unknown) or by contact with sick or deceased filovirid-infected mammals. Filovirids are highly infectious but not exceptionally contagious. Human-to-human transmission occurs through direct person-to-person contact or exposure to infected bodily fluids or tissues; there is no evidence of aerosol or respiratory droplet transmission in natural outbreak settings. Infections manifest initially with a nonspecific influenza-like febrile illness that rapidly progresses to commonly include gastrointestinal manifestations and, in severe illness, coagulopathy, multiple-organ dysfunction syndrome, shock, and death. Although the prevalence and source remain controversial, serologic footprints of subclinical

acute filovirid infections have been identified since the first descriptions of filovirid disease outbreaks. Filovirid disease survivors may be persistently infected in immune-privileged tissue compartments, commonly in the male reproductive tract, but also in the central nervous system (CNS), and in intraocular tissues and fluids; notably, filoviral persistence has been rarely associated with the re-ignition of outbreaks. Historically, the prevention of filovirid infections has consisted primarily of tried-and-true epidemiologic approaches (e.g., isolation of cases, contact tracing, effective infection prevention and control, and safe burial practices). Treatment of disease traditionally consisted only of limited supportive clinical care (often constrained by in-field capacity); indeed, filovirid-specific vaccines or therapeutic agents had not been rigorously evaluated in humans prior to the 2013–2016/2021 outbreaks of Ebola virus disease (EVD) that occurred in Western Africa. Building on the knowledge gained in Western Africa and during the 2018–2020 EVD outbreak in the Democratic Republic of the Congo, prevention and treatment strategies now include the widespread deployment of an effective vaccine specific to Ebola virus (EBOV); the use of effective therapeutics based on virus-specific monoclonal antibodies (mAbs), which were identified in a first-of-its-kind randomized controlled trial; and the delivery of improved supportive care. Although these advances have essentially become new standards for prevention and treatment of EVD, the same cannot yet be said for other filovirid diseases.

Filovirids are categorized as World Health Organization (WHO) Risk Group 4 pathogens. Consequently, all work with material potentially containing replicating filovirids should be conducted in maximum containment (biosafety level 4) laboratories, or the viruses should be inactivated prior to activities in biosafety level 2/3 laboratories. These viruses must be handled by experienced personnel wearing appropriate personal protective equipment (PPE; see “Control and Prevention,” below) and following rigorous standard operating procedures. In addition, when filovirid disease outbreaks are suspected or confirmed, the appropriate national authorities and WHO reference laboratories should be contacted immediately. PART 5 Infectious Diseases ■ ■ETIOLOGY The family Filoviridae includes nine official genera (Figs. 216-1 and 216-2). Human

pathogens are found in two of these genera, Orthoebolavirus and Orthomarburgvirus. Collectively, these pathogens cause “filovirid” (“filovirus”) disease (FVD; International Classification of Diseases, Eleventh Revision [ICD-11], code 1D60). FVD is subdivided into “Ebola disease” (EBOD; ICD-11, code 1D60.0), caused by four of six classified orthoebolaviruses (Bundibugyo virus [BDBV], EBOV, Sudan virus [SUDV], and Taï Forest virus [TAFV]), and “Marburg disease” (MARD; ICD-11, code 1D60.1), caused by the two orthomarburgviruses, Marburg virus and Ravn virus. Accordingly, specific diseases are optimally named with the virus-specific cause such that, for example, “EVD” is distinguished from “Sudan virus disease (SVD).” Mammalian filovirids have linear, nonsegmented, negative-sense RNA genomes that are ≈ 19 kb in length. These genomes contain seven genes that encode seven structural proteins: a nucleoprotein (NP), a polymerase cofactor (VP35), a matrix protein (VP40), a glycoprotein (GP1,2), a transcriptional activator (VP30), a ribonucleoprotein complex-associated protein (VP24), and a large (L) protein that contains an RNA-directed RNA polymerase domain. Orthoebolaviruses, but not orthomarburgviruses, additionally encode three nonstructural proteins of unknown functions (sGP, ssGP, and Δ -peptide). Filovirions are unique among human virus particles in that they are predominantly pleomorphic filaments but also assume torus-like or 6-like shapes (width ≈ 91 – 98 nm; average length <1 μ m). These enveloped virions contain helical ribonucleoprotein capsids and are covered with GP1,2 spikes (Fig. 216-3). ■

■ **EPIDEMIOLOGY** The majority of recorded FVD outbreaks, including the 2013–2016 EVD outbreak, can be traced back to single index patients who transmitted the infection to others. Although small outbreaks may not have been recorded historically, the epidemiology of EVD transmission chains suggests that only ≈ 50 natural host-to-human spillover events

Realm Riboviria Kingdom Orthornavirae Phylum Negarnaviricota Subphylum Haploviricotina Class Monjiviricetes Order Mononegavirales Family Filoviridae Genus Cuevavirus Species Cuevavirus lloviuense Virus: Lloviu virus (LLOV) Genus Dianlovirus Species “Dianlovirus dehongense” (proposed) Virus: Dínhồng virus (DEHV) Species Dianlovirus menglaense Virus: Mễnglả virus (MLAV) Genus Loebevirus Species Loebevirus percae Virus: Lötschberg virus (LTBV) Genus Oblavirus Species Oblavirus percae Virus: Oberland virus (OBLV) Genus Orthoebolavirus Species Orthoebolavirus bombaliense Virus: Bombali virus (BOMV) Species Orthoebolavirus bundibugyoense Virus: Bundibugyo virus (BDBV) Species Orthoebolavirus restonense Virus: Reston virus (RESTV) Species Orthoebolavirus sudanense Virus: Sudan virus (SUDV) Species Orthoebolavirus taiense Virus: Taï Forest virus (TAFV) Species Orthoebolavirus zairense Virus: Ebola virus (EBOV) Genus Orthomarburgvirus Species Orthomarburgvirus marburgense Virus 1: Marburg virus (MARV) Virus 2: Ravn virus (RAVV) Genus Striavirus Species Striavirus antennarii Virus: Xìlǎng virus (XILV) Genus Tapjovirus Species Tapjovirus bothropis Virus: Tapajós virus (TAPV) Genus Thamnovirus Species Thamnovirus kanderense Virus: Kander virus (KNDV) Species Thamnovirus percae Virus: Fiwi virus (FIWIV) Species Thamnovirus thamnaconi Virus: Huángjiāo virus (HUJV) Filovirids that are known to infect humans are depicted in the same nonblack colors as in figures. FIGURE 216-1 Filovirid taxonomy (2024). have occurred since the discovery of filovirids in 1967. However, outbreaks associated with reignition of human-to-human transmission from a persistently infected survivor of a previous outbreak have more recently been described. Outbreak frequency, size, and overall

FJ217162 TAFV/H.sap/CIV/94/Pau-CI

FJ217161 BDBV/H.sap/UGA/07/But-811250

AF086833 EBOV/H.sap/COD/76/Yam-May 0.96 MF319185 BOMV/M.con/SLE/16/Nor-
PREDICT_SLAB000156

AY729654 SUDV/H.sap/UGA/00/Gul-808892 0.96 AF522874 RESTV/M.fas/USA/89/Phi89-Pen
KX371873 "Bat2162"

KP233864 "BtFV/WD04" MW775011 LLOV/M.sch/HUN/19/378

DQ217792 MARV/H.sap/KEN/80/MtE-Mus

DQ447649 RAVV/H.sap/KEN/87/KiC-810040 0.77

OP924273 DEHV/R.les/CHI/16/RI133-16 KX371887 MLAV/Rousettus/CHN/15/Sha-Bat9447-1

BR001752 TAPJ/B.atr/15/BRA MW093492 KNDV/P.flu/CHE/17/CH17 MG599980
XILV/A.str/CHN/17/Wen-XYHYS28627

MN510772 FIWIV/P.flu/CHE/17/CH17

MG599981 HUJV/T.sep/CHN/17/Wen-LQMMTII17328

OQ186623 LTBV/P.flu/CHE/17/CH17 MN510773 OBLV/P.flu/CHE/17/CH17 0.5

FIGURE 216-2 Filovirid phylogeny/evolution. Midpoint-rooted maximum-likelihood tree inferred by using filovirid large gene (L) sequences. Bootstrap values are shown at each node. The scale bar indicates nucleotide substitutions per site. Tips of branches are labeled with GenBank accession numbers followed by filovirid isolate designation. Filovirids that are known to infect humans are depicted in the same nonblack colors as in other figures. BDBV, Bundibugyo virus; BOMV, Bombali virus; DEHV, D  h  ng virus; EBOV, Ebola virus; FIWIV, Fiwi virus; HUJV, Hu  ngjiao virus; KNDV, Kander virus; LLOV, Lloviu virus; LTBV, L  tschberg virus; MARV, Marburg virus; MLAV, Me  ngl   virus; OBLV, Oberland virus; RAVV, Ravn virus; RESTV, Reston virus; SUDV, Sudan virus; TAFV, Ta   Forest virus; TAPV, Tapaj  s virus; XILV, Xi-la  ng virus. (Adapted and expanded from JH Kuhn et al: Filoviridae, in Fields Virology, Vol 1, 7th ed, PM Howley et al (eds). Philadelphia, Wolters Kluwer/Lippincott Williams & Wilkins, 2020, pp 449–503. Analysis courtesy of Nicholas Di Paola, PhD, USAMRIID, Fort Detrick, MD, USA. Figure courtesy of Jiro Wada, NIH/NIAID/DCR/IRF-Frederick, Fort Detrick, MD, USA.)

case-fatality rate are likely the result of complex interactions of the specific filovirid, the reservoir hosts (known and unknown), the susceptible human population (e.g., varying with age, unknown genetic determinants of susceptibility and disease severity, and risk behavior), and the geographic setting (e.g., local public health capacity, socioeconomic conditions, and cultural practices). As of November 13, 2024, 35,608 cases of human filovirid disease and 15,886 deaths had been recorded (Fig. 216-4). These numbers emphasize both the high case-fatality rate (number of deaths per number of sick people; 44.6%) and the overall low mortality (reflecting the impact on the healthy population) related to filovirid diseases. Of these totals, 28,652 cases and 11,325 deaths occurred during the 2013–2016 EVD outbreak in Western Africa; this was the largest of all recorded FVD outbreaks. Natural FVD outbreaks had not been considered a global threat until regional and then global spread during this outbreak challenged that tenet. Filovirids that are pathogenic in humans appear to be exclusively endemic to equatorial (Western, Middle, and Eastern)

FIGURE 216-3 Ultrastructure of filovirions. Left: Colorized scanning electron micrograph of Ebola virus particles

(green) attached to the surface of an infected grivet (*Chlorocebus aethiops* (Linnaeus, 1758)) Vero E6 producer cell (blue). Right: Colorized transmission electron micrograph of a Marburg virus particle collected from purified Vero E6 producer cell supernatant. (Figure courtesy of John G. Bernbaum and Jiro Wada, NIH/NIAID/DCR/IRF-Frederick, Fort Detrick, MD, USA.)

Orthoebolavirus New genus? Cuevavirus Orthomarburgvirus Dianlovirus – Tapjovirus – Striavirus
Thamnovirus – Oblavirus Loebevirus CHAPTER 216 Africa (Fig. 216-5), although this distribution may change if natural or artificial environmental alterations lead to filovirid host migration and increased contacts between nonhuman hosts and humans. Outbreaks have been contained when high-risk activities (e.g., ritual washing as part of burial practices) have been limited or been made safer with appropriate infection prevention and control. Of particular importance is accessibility to health care centers with staff trained and equipped (e.g., with PPE) for adequate infection prevention and control, to limit both community spread and nosocomial amplification. The incidence of FVD may have increased over the past two decades (Fig. 216-4 and Fig. 216-5), but debate continues as to whether this increase is due to increased filovirid activity, more frequent human interaction with filovirid hosts, or improvement in surveillance capabilities. Filovirids: Orthoebolavirus and Orthomarburgvirus Infections FVD outbreaks are associated with distinct meteorologic and geographic conditions and are probably associated with distinct hosts or reservoirs. The four orthoebolaviruses that cause disease in humans appear to be endemic in humid rainforests. EVD outbreaks in particular have often been associated with hunting in forests or contact with bushmeat (i.e., meat from apes, other nonhuman primates, duikers, or bush pigs). Ecologic studies suggest that EBOV may play a role in extensive and often-fatal epizootics among wild ape populations. However, only one orthoebolavirus, TAFV, has been isolated from nonhuman primates in the wild. Orthomarburgviruses, on the other hand, seem to infect hosts inhabiting arid woodlands, and associated outbreaks have almost always been epidemiologically linked to individuals visiting or working in natural or engineered caves or mines. The cave-dwelling Egyptian rousette (*Rousettus aegyptiacus* (Geoffroy, 1810)), a pteropodid (fruit) bat, serves as a natural and subclinically infected reservoir for both Marburg virus and Ravn virus. Although bats are suspected hosts for orthoebolaviruses as

Country (Year) BDBV COD (2012) Uganda (2007–2009) Zaire (1976) Zaire (1977) Gabon (1994–1995) Zaire (1995) Russia (1996) Gabon (1996) Gabon → South Africa (1996–1997) Gabon; COG (2001–2002) COG → Gabon (2002) COG (2002–2003) COG (2003–2004) Russia (2004) COG (2005) EBOV COD (2007) COD (2008–2009) Guinea → France, Germany, Italy, Liberia,

Mali, Netherlands, Nigeria,

Norway, Senegal, Sierra Leone,

Spain, Switzerland, UK, USA

(2013–2016, '21*) COD (2014) COD (2017) COD (2018) COD → Uganda (2018–2020, '21*,

'21*, '22*) COD (2020) COD (2022) RESTV USA (1989) Sudan (1976) PART 5 Infectious Diseases UK (1976) Sudan (1979) Uganda (2000–2001) SUDV Sudan (2004) Uganda (2011) Uganda (2012) Uganda (2012) Uganda (2022–2023) TAFV Côte d'Ivoire → Switzerland (1994) Orthoebolaviruses

total: Uganda → West Germany,

Yugoslavia (1967) Rhodesia →)

(a cirf A h t u o S Kenya (1980) USSR (1988) USSR (1990) COD (1998–2000) Angola (2004–2005) Uganda (2007) MARV Uganda → Netherlands (2008) Uganda → USA (2008) Uganda (2012) Uganda (2014) Uganda (2017) Guinea (2021) Tanzania (2023) Ghana (2022) Equatorial Guinea (2023) Rwanda (2024) Kenya (1987) COD (1998–2000) RAVV Uganda (2007) Orthommarburgviruses total: Filovirids total: FIGURE 216-4 Characteristics of outbreaks of human filovirid disease. Seven of 17 classified filovirids have caused disease in humans. Left column: Outbreaks considered to be caused by independent zoonotic spillover are listed by virus in chronological order in the left column. Outbreaks considered to be related to reignition from a persistently infected survivor of a prior outbreak are included with the initial outbreak (denoted by asterisk). Laboratory infections are in gray italicized text. International case exportations are indicated with arrows. Right column: Numbers of fatal cases and total cases are summarized. Middle column: The case-fatality rate (colored dots) for each outbreak is plotted on a 0–100% scale along with 99% confidence intervals (gray horizontal bars). The overall case-fatality rate for disease caused by a particular virus is delineated by vertical colored lines, with vertical colored dashed lines indicating the corresponding 99% confidence intervals. The overall case-fatality rates for all Orthoebolavirus, all Orthommarburgvirus, and all filovirid disease outbreaks are shown by (underlaid) vertical gray bars. BDBV, Bundibugyo virus; COD, Democratic Republic of the Congo (formerly Zaire); COG, Republic of the Congo; EBOV, Ebola virus; MARV, Marburg virus; RAVV, Ravn virus; RESTV, Reston virus; SUDV, Sudan virus; TAFV, Taï Forest virus; UK, United Kingdom; USSR, Union of Soviet Socialist Republics (today Russia). (Adapted and expanded from JH Kuhn et al: Evaluation of perceived threat differences posed by filovirus variants. Biosecur Bioterror 9:361, 2011. Figure courtesy of Jiro Wada, NIH/NIAID/DCR/IRF-Frederick, Fort Detrick, MD, USA.)

Total cases Deceased Lethality (%)

11,337 28,675

2,303 3,494

14,887 33,838

15,439 35,008

15,886 35,608

Switzerland Senegal Mali USA Guinea '13–'16,'21* Nigeria Sierra Leone '21 '22 '94 Liberia Ghana Côte d'Ivoire USA and three European countries Equatorial Guinea Kenya USA and five European countries Gabon BDBV EBOV SUDV TAFV MARV RAVV '94–'95 '01–'02 '96 Gabon '02–'03 '03–'04 FIGURE 216-5 Geographic distribution of human filovirid disease outbreaks and years of occurrence. Arrows indicate international case exportations. BDBV, Bundibugyo virus; COD, Democratic Republic of the Congo (formerly Zaire); COG, Republic of the Congo; EBOV, Ebola virus; MARV, Marburg virus; RAVV, Ravn virus; SUDV, Sudan virus; TAFV, Taï Forest virus. (Figure courtesy of Jiro Wada, NIH/NIAID/DCR/IRF-Frederick, Fort Detrick, MD, USA.) well, definitive proof is

lacking. To date, the nonpathogenic Bombali virus is the only orthoebolavirus for which coding-complete genome nucleic acid has been detected in bats. EBOV and Reston virus have been loosely connected to frugivorous and insectivorous bats by means of antibody or genome fragment detection, whereas the hosts of BDBV, SUDV, and TAFV are enigmatic. ■ ■PATHOGENESIS Human infections typically occur through direct exposure of skin lesions or mucosal surfaces to contaminated body fluids or material or by parenteral inoculation (e.g., via accidental needlesticks or reuse of needles in poorly equipped hospitals). Numerous studies, both in vitro and in vivo (in several animal models of human disease), have

South Sudan (Sudan) '04 '76,'79 '76 '98–'00 '77 '17 Uganda '12 '76 '23 '80 '98–'00 '14 '20 '87 '96–'97 COD (Zaire) '22 '18 '23 '24 COG '07 Tanzania Rwanda '95 '08–'09 '04–'05 Angola CHAPTER 216 '75 Zimbabwe (Rhodesia) Filovirids: Orthoebolavirus and Orthomarburgvirus Infections South Africa South Africa '00–'01 COD (Zaire) Uganda COG '00–'01 '17 Netherlands West Germany and Yugoslavia '12 '11 '07–'09 '11,'12 '18–'20, '21*,'21*, '22*' '14 '02 '22–'23 '07 '67 '07 '08 '00–'01 '05 '12 illuminated aspects of FVD pathogenesis (Fig. 216-6). The GP1,2 spikes on the surface of filovirions determine their cell and tissue tropism by engaging cell-surface molecules and the intracellular filovirid receptor NPC intracellular cholesterol transporter 1 (NPC1). One of the hallmarks of filovirid pathogenesis is a pronounced modulation and dysregulation of immune responses. The first targets of filovirions are local macrophages, monocytes, and dendritic cells. Several structural proteins of filovirions (i.e., VP35, VP40, and/or VP24) then suppress intrinsic and innate immune responses by, for example, inhibiting the type I interferon antiviral pathways. This immunomodulation ultimately enables a productive filovirid infection, resulting in very high viral titers (>10⁶ PFU/mL of serum in humans) with dissemination to most tissues. In tissues, filovirions infect additional

Onset of signs and symptoms Incubation Early phase Peak phase Recovery Nonspecific prodrome: fever, fatigue, anorexia, myalgia, and headache Gastrointestinal symptoms: nausea, vomiting, diarrhea, and abdominal pain Rash Hemorrhagic manifestations Hemodynamic instability, Shock Renal dysfunction/failure Respiratory dysfunction/failure Neurologic manifestations Cardiac dysfunction (myocarditis and pericarditis) ↓WBCs, ↓PLTs ↑WBCs (↑PMNs), ↓Hb, ↓HCT ↑PLTs Hepatic injury: ↑AST, ↑ALT Hypoglycemia Renal dysfunction: ↑BUN, ↑creatinine Abnormal electrolytes: ↓Na⁺, ↑or↓K⁺, ↓Ca²⁺, ↓Mg²⁺ Metabolic acidosis: ↑lactate, ↓HCO₃⁻ ↑CPK, myoglobinuria PART 5 Infectious Diseases Hypoalbuminemia Coagulopathy: ↑PT, ↑PTT, ↑D-dimer Inflammation: ↑CRP Magnitude Days since disease onset

–10 to –7 FIGURE 216-6 Ebola virus disease course. ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CPK, creatine phosphokinase; CRP, C-reactive protein; Hb, hemoglobin; HCT, hematocrit; PLTs, platelets; PMNs, polymorphonuclear leukocytes; PT, prothrombin time; PTT, partial thromboplastin time; WBCs, white blood cells. (Adapted and expanded from JH Kuhn et al: Filoviridae, in Fields Virology, 7th ed, Vol. 1. Howley PM et al (eds). Philadelphia, Wolters Kluwer/Lippincott Williams & Wilkins, 2020, pp 449–503. Figure courtesy of Jiro Wada, NIH/NIAID/DCR/IRF-Frederick, Fort Detrick, MD, USA.) phagocytic cells, including other macrophages (alveolar, peritoneal, and pleural macrophages; Kupffer cells in the liver; and microglia in the CNS), epithelial cells (e.g., adrenal cortical cells and hepatocytes), stromal cells (fibroblasts), and endothelial cells. Infection is cytolytic in some—but not all—infected cells; e.g., hepatocyte necrosis likely contributes to elevated aminotransferase activities, and hepatic

synthetic dysfunction contributes to coagulopathy. Infection leads to the secretion of soluble signaling molecules (varying with the cell type) that likely contribute to forward dysregulation of immune responses and ultimately to multiorgan dysfunction syndromes. For instance, infected macrophages secrete proinflammatory cytokines, leading to further recruitment of monocyte-derived macrophages to the site of infection. In contrast, infected dendritic cells are not activated to secrete cytokines, and the expression of major histocompatibility class II antigens is partially suppressed, with consequently deficient antigen presentation. Immunosuppression also occurs in part by massive lymphoid depletion in lymph nodes, spleen, and thymus in the absence of effective humoral and cell-mediated immune responses, especially in severe or fatal disease. Results from animal studies suggest that depletion is

Uveitis Clinical presentation Innate immune response Laboratory findings Viremia (nonsurvivor) Viremia (survivor) IgM Cellular immune response Humoral immune response (IgG) a direct consequence of considerable lymphocyte death; this explanation would also account for the severe lymphopenia that develops in patients. In addition to potential florid filovirid dissemination, another consequence of lymphocyte depletion may be susceptibility to secondary bacterial and fungal infections. Other pathogenic hallmarks of filovirid infections include coagulopathy and endothelial dysfunction. Along with hepatic synthetic dysfunction, disseminated intravascular coagulation may contribute though this remains controversial. Thrombocytopenia, increased concentrations of tissue factor, consumption of clotting factors, increased concentrations of fibrin degradation products (D-dimers), and declining concentrations of protein C are typical features of severe disease. Consequently, fibrin deposition and microthrombotic small-vessel occlusion and necrotic/hypoxic infarction may occur in some tissues, particularly in the gonads and, less often, in the kidneys and spleen. In addition, petechiae, ecchymoses, extensive visceral effusions, and other hemorrhagic signs are observed in internal organs, mucous membranes, and skin. However, actual severe blood loss is a rare event (although it frequently occurs during or after childbirth). Most likely,

aberrance in cytokines or other factors, such as nitric oxide, and direct infection and activation of endothelial cells are responsible for upregulated permeability of blood-vessel endothelia. This upregulation leads to fluid redistribution and interstitial tissue edema and hypovolemic or septic shock are common features of severe disease. Despite this long list of pathogenetic hallmarks, increasing evidence from clinical settings suggests that effective filovirid-specific adaptive immune responses do develop, coinciding with control and clearance of viremia and subsequent clinical improvement in surviving patients. However, depending on the severity of illness (including organ dysfunction and late complications), clinical illness may be protracted and recovery incomplete. ■
■CLINICAL MANIFESTATIONS Diseases caused by orthoebolaviruses and orthomarlburgviruses present very similar clinical phenotypes that cannot be distinguished at the bedside and, for all practical purposes, may be considered the same disease; this approach may change as higher-resolution characterization of human FVD accrues. The prevalence and character of clinical signs do not differ significantly in disease caused by disparate filovirids (except for the possibly apathogenic Reston virus), although, with the exception of the 2013–2016 EVD outbreak, the numbers of deeply characterized clinical observations are very low. The incubation period is 2–25 days (most commonly 7–10 days), after which infected people develop a nonspecific influenza-like syndrome 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

symptoms/signs. A subsequent second phase ($\approx$ 5–7 days after disease onset and thereafter) involves the gastrointestinal (nausea and vomiting and/or diarrhea, sometimes with abdominal pain), respiratory (chest pain, cough, and/or dyspnea), cardiovascular (hypotension and/or edema), and central nervous (confusion, head ache, and/or coma) systems. Common hemorrhagic manifestations include subconjunctival injection, petechial rash, gingival bleeding, and bleeding at injection sites; epistaxis, hematemesis, hematuria, and melena occur but are less common. Patients usually succumb to acute disease 4–14 days after infection, often with severe multiorgan dysfunction that commonly includes shock and acute renal or respiratory failure. Typical laboratory findings are leukopenia (with cell counts as low as 1000/ μ L) with a left shift prior to leukocytosis, thrombocytopenia (with counts as low as 50,000/ μ L), increased activities of liver enzymes (aspartate aminotransferase > alanine aminotransferase, γ -glutamyltransferase), increased creatinine and urea concentrations with proteinuria, electrolyte derangement (hypokalemia or hyperkalemia, hyponatremia, and/or hypocalcemia), hypoglycemia, hypoalbuminemia, prolonged prothrombin and partial thromboplastin times, and elevated creatine phosphokinase activities. Nonspecific markers of systemic inflammation (e.g., C-reactive protein concentrations) may be markedly elevated in severely ill patients. ■ ■DIAGNOSIS Filovirid disease cannot be diagnosed based on clinical presentation alone. Numerous diseases common in equatorial Africa need to be considered in the differential diagnosis of a febrile patient. Almost all of these occur at a much higher incidence than FVD and are much more likely diagnoses in non-outbreak settings; however, during outbreaks and in peri-outbreak periods, timely and accurate laboratory diagnosis to rule in or rule out filovirid infection is critical. The most important infectious disease mimics of FVD 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 other high-consequence viral infections (in particular, Lassa fever and yellow fever). Rarer noninfectious possibilities, including venomous snakebites, warfarin intoxication, and the many causes of acquired or inherited

coagulopathy, also must be considered in the bleeding patient. An exposure history—including exposure to caves or mines; direct contact with bats, nonhuman primates, or “bushmeat”; direct contact with severely ill local residents; or admission to rural hospitals with patient-to-patient or patient-to-health-care-worker clusters of illness—should raise the index of suspicion.

If FVD is suspected based on epidemiologic and/or clinical manifestations, infectious disease specialists and the proper public health authorities should be notified immediately. Laboratory diagnosis of FVD is relatively straightforward but ideally requires the capacity for maximum containment, which usually is not available in filovirid endemic countries. Increasingly, laboratory diagnosis is performed with patient samples inactivated in mobile field “glove boxes” by on-site personnel trained in the safe use of diagnostic assays adapted for field use in lower-containment settings. Consequently, diagnostic samples should be collected and processed with great caution and with the use of appropriate PPE and strict barrier techniques. With adherence to established biosafety precautionary measures, samples should be sent in suitable transport media to national or international reference laboratories. Acute-phase blood/serum is the preferred diagnostic specimen because it usually contains high titers of filovirions. The current assay of choice for the diagnosis of filovirid infection is reverse-transcription polymerase chain reaction (RT-PCR) targeting one or more filovirid genes; a typical detection limit is 1000–5000 PFU/mL of serum, depending

on the assay. When available, safe, rapid-turnaround, and standardized in-field PCR-based approaches (e.g., the Cepheid GeneXpert platform) are now standardly deployed during outbreaks. Antigen-capture enzyme-linked immunosorbent assays (ELISAs) or immunochromatographic assays for the detection of filovirion proteins are in development and may be useful as point-of-care rapid diagnostic tests (RDTs) in the future; sensitivity limitations of EBOV-specific antigen-based RDTs restrict current use to diagnosis of postmortem samples only. Direct immunoglobulin M (IgM) capture, direct IgG capture, or IgM-capture ELISAs (including multiplex approaches) are used for the detection of filovirion-targeting antibodies from patients in the later stages of disease (i.e., those who have been able to mount a detectable antibody response), including survivors. All of these assays can be conducted on samples treated with guanidinium isothiocyanate (for RT-PCR), cobalt-60 irradiation (for ELISA), or other effective measures (heat or irradiation treatment) that render filovirids noninfectious. Virus isolation in cell culture and plaque assays for quantification or diagnostic confirmation are relatively simple but must be performed in maximum-containment laboratories. If available, electron microscopic examination of inactivated samples or cultures for the unique filamentous structures of filovirions can further support diagnosis (Fig. 216-3). Formalin-fixed skin biopsy samples and possibly skin swabs can be useful for safe postmortem diagnoses. In-field (or near in-field) rapid genome sequencing was first deployed to inform classic epidemiology in Western Africa during the 2013–2016 EVD outbreak and has become a mainstay of outbreak control and response, even in endemic settings.

CHAPTER 216 Filovirids: Orthoebolavirus and Orthomarburgvirus Infections

TREATMENT Filovirid Disease Clinical management of patients with suspected or confirmed filovirid disease should be conducted by health care workers who have been well-trained in the complex care of FVD patients and who are using appropriate PPE in care environments with appropriate infection prevention and control measures (see “Control and Prevention,” below). Historically, management of FVD had been entirely supportive (and even that limited by resource constraints) because the efficacy and safety of specific antiviral countermeasures had not been rigorously studied outside of animal models of disease. The 2013–2016 EVD outbreak in Western Africa highlighted the need to conduct rigorous, feasible, and ethical clinical research during outbreaks. Building on challenges and lessons learned in that setting, the first-of-its-kind Pamoja Tulinde

Maisha (PALM) randomized clinical trial was conducted during the 2018–2020/2021 EVD outbreak in the Democratic Republic of the Congo and identified two therapeutics based on mAbs specific to EBOV to improve survival rates. mAb114 (ansuvimab-zykl) and REG-EB3 (atoltivimab, maftivimab, and odesivimab-ebgn) were subsequently approved for the treatment of EVD in PCR-confirmed adults (including pregnant women) and children. Both are administered via carefully monitored single-dose infusions initiated as soon as possible after diagnosis. In addition, efforts during this outbreak demonstrated the will and capacity to deliver more advanced supportive and critical care accompanying specific therapeutics in the African outbreak setting. Although evidence is lacking, consensus treatment strategies include those generally recommended for severe septicemia/sepsis/shock (Chap. 315) and should be applied with an emphasis on standard approaches—i.e., monitoring and response to respiratory dysfunction (e.g., oxygen), circulatory dysfunction (e.g., intravascular fluid repletion and vasopressor support), and CNS dysfunction (e.g., ruling out of reversible causes, notably hypoglycemia)—as well as the detection and management of acute kidney injury, hemorrhage, electrolyte derangements, and nutritional status and the prevention and treatment of secondary or co-infections. Pain management and administration of antipyretics, antiemetics, and antidiarrheal agents may be considered. Crucial

strategies to improve outcomes in the most severely ill FVD patients include preventing organ dysfunction and providing safe and effective temporary organ support (e.g., mechanical ventilation and renal replacement) to expand the window for administration of medical countermeasures and development of effective endogenous immune responses.

PART 5 Infectious Diseases ■ ■ COMPLICATIONS Even in patients who have initial virologic or clinical improvement, complications in the second or third week of illness may include secondary infections; persistent renal dysfunction and electrolyte abnormalities; respiratory insufficiency; neurologic compromise (e.g., EBOV-related meningoencephalitis, cerebrovascular events, and seizures); cardiac dysfunction (e.g., myocarditis and pericarditis); and venous thrombosis. Pregnancy and labor are historically associated with severe complications and poor outcomes in filovirid disease due to clotting factor consumption, fetal loss, and/or severe blood loss during birth; in the era of EBOV-specific therapeutics and optimized supportive care, maternal and fetal outcomes are improved. A number of sequelae have been self-reported or historically described in survivors of FVD, including prolonged and sometimes incapacitating arthralgia and myalgia, asthenia, alopecia, visual problems (including uveitis), hearing loss, memory loss and neurocognitive dysfunction, mental health conditions (anxiety, depression, and post traumatic stress disorder), and reproductive problems. Well-controlled observational studies of EVD survivors were first conducted in the aftermath of the 2013–2016 Western Africa EVD outbreak. Compared with their close-contact controls, Liberian EVD survivors had an increased incidence of headache, arthralgia and myalgia, memory loss, fatigue, and urinary frequency as well as abnormal results in abdominal, chest, neurologic, musculoskeletal, and ocular exams. Of individual and public health significance is the potential for persistence of filovirids in immune-privileged tissue compartments (and their associated fluids) in FVD survivors, most commonly in the semen of male survivors (with the rare but documented potential for sexual transmission) and rarely in the CNS (causing recrudescent meningoencephalitis), the eye (causing recrudescent uveitis), and the placenta (causing transmission or placental insufficiency). True relapses that resemble the course of primary FVD are extremely rare but have been described. The risk of the remote reignition of outbreaks from persistently infected FVD survivors is apparently rare but obviously consequential. Notably, these events have only been detected after the two largest EVD outbreaks, suggesting a likely limitation, with the caveat that available samples and genomic tools to determine outbreak relatedness have historically not been available. EVD outbreaks in the

Democratic Republic of the Congo in 2021 were genomically linked to the previous 2018–2020 outbreak. After a 5- to 7-year interim, an EVD outbreak in Guinea in 2021 was genomically linked to the 2013–2016 Western African outbreak; this event remains enigmatic as corroborating epidemiologic links have not been found. ■ ■ **PROGNOSIS** Among the most severe of acute viral diseases in humans, FVD generally has a poor prognosis, although with much greater heterogeneity than was historically assumed; i.e., the 70–90% case-fatality rate ascribed for many decades to EVD has required revision. With an incomplete evidence base, the outcome probably depends on factors that include the particular filovirid causing the infection (Fig. 216-4), host factors (age, immune status, coinfections, and unknown host genetic factors), virus exposure route and dose, viral load, the presence and severity of organ dysfunction, and—critically—the availability of filovirid-specific countermeasures and requisite supportive care. Despite the receipt of effective EBOV-specific therapeutics, outcomes in severe EVD patients with high viral loads and complex organ dysfunction remain suboptimal and will require future research to evaluate and advance virus-targeted (e.g., combination therapeutic), disease-targeted (e.g., immunomodulatory), and

optimized supportive care strategies. After resolution of acute disease, the long-term health and survival outcomes for FVD survivors are unknown. It is uncertain how increased access to filovirid-specific therapeutics and life-saving support will impact filovirid persistence in survivors; short- and long-term surveillance will be necessary to avoid individual consequences (e.g., relapse and/or recrudescent inflammatory syndromes) and public health consequences (e.g., reignition of outbreak transmission chains in the peri-outbreak or post-outbreak period). Although remarkable progress in understanding and improving outcomes in EVD has occurred in recent years, the same cannot yet be said for disease caused by filovirids other than EBOV, either in acute disease or in convalescence. ■ ■

CONTROL AND PREVENTION

Prevention of viral exposure in nature is challenged by an incomplete understanding of filovirid ecology. To prevent orthomarbuvirus infection, people entering or living in areas where Egyptian rousettes can be found should avoid direct or indirect contact with these animals. Prevention in nature is more difficult in the case of pathogenic orthoebolaviruses, largely because ecologic reservoirs have not yet definitively been identified. EVD outbreaks have been associated with hunting or consumption of nonhuman primates more than exposure to bats. Indeed, the mechanism of introduction of orthoebolaviruses into nonhuman primate populations, if it occurs at all, is unclear. (Only one pathogenic orthoebolavirus, TAFV, has unequivocally been detected in wild nonhuman primates.) Therefore, to prevent orthoebolavirus infection, the only evidenced advice that can be offered to travelers and locals is to avoid contact with “bushmeat,” nonhuman primates, and bats. In any setting, the local involvement of medical anthropologists and careful community engagement is strongly advised to ensure preventive risk communication is not received as threatening or patronizing. Biomedical prevention strategies have historically been limited to tried-and-true pillars of outbreak control, centering on the identification and isolation of cases, contact tracing, ensuring that health care workers and other response personnel have appropriate training and capacity in infection prevention and control, and preventing high-risk transmission events. Measures aimed at preventing and controlling infection, including relatively simple barrier nursing techniques, vigilant use of appropriate PPE, quarantine, and contact tracing, usually effectively terminate or at least contain FVD outbreaks. Isolation of infected people and their contacts and avoidance of direct person-to-person contact without appropriate PPE usually prevent further spread, as the virions are not transmitted through droplets or aerosols under natural conditions. Typical protective gear sufficient to prevent filovirid infections consists of disposable gloves, gowns, and shoe

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