

107 - 215 Arthropod-Borne and Rodent-Borne Virus Infections

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infiltration of the wound(s). With multiple or large wounds, the RIG preparation may need to be diluted in order to obtain a sufficient volume for adequate infiltration of all wound sites. If the exposure involves a mucous membrane, the entire dose should be administered IM. Rabies vaccine and RIG should never be administered at the same site or with the same syringe. Commercially available RIG in the United States is purified from the serum of hyperimmunized human donors. These human RIG preparations are much better tolerated than are the equine-derived preparations still in use in some countries (see below). Serious adverse effects of human RIG are uncommon. Local pain and low-grade fever may occur. Two purified inactivated rabies vaccines are available for rabies PEP in the United States. They are highly immunogenic and remarkably safe compared with earlier vaccines. Four 1-mL doses of rabies vaccine should be given IM in the deltoid area. (The anterolateral aspect of the thigh also is acceptable in children.) Gluteal injections, which may not always reach muscle, should not be given and have been associated with rare vaccine failures. Ideally, the first dose should be given as soon as possible after exposure; failing that, it should be given without further delay. The three additional doses should be given on days 3, 7, and 14; a fifth dose on day 28 is no longer recommended except in immunocompromised patients. Pregnancy is not a contraindication for immunization. Glucocorticoids and other immunosuppressive medications may interfere with the development of active immunity and should not be administered during PEP unless they are essential. Routine measurement of serum neutralizing antibody titers is not required, but titers should be measured 2–4 weeks after immunization in immunocompromised persons. Local reactions (pain, erythema, edema, and pruritus) and mild systemic reactions (fever, myalgias, headache, and nausea) are common; anti-inflammatory and antipyretic medications may be used, but immunization should not be discontinued. Systemic allergic reactions are uncommon, but anaphylaxis does occur rarely and can be treated with epinephrine and antihistamines. The risk of rabies development should be carefully considered before the decision is made to discontinue vaccination because of an adverse reaction. Most of the burden of rabies PEP is borne by persons with the fewest resources. In addition to the rabies vaccines discussed above, vaccines grown in either primary cell lines (hamster or dog kidney) or continuous cell lines (Vero cells) are

satisfactory and are available in many countries outside the United States. Less expensive vaccines derived from neural tissues are still used in a diminishing number of developing countries; however, these vaccines are associated with serious neuroparalytic complications, including postinfectious encephalomyelitis and Guillain-Barré syndrome. The use of these vaccines should be discontinued as soon as possible, and progress has been made in this regard. Worldwide, more than 10 million individuals receive postexposure rabies vaccine each year. If human RIG is unavailable, purified equine RIG can be used in the same manner at a dose of 40 IU/kg. The incidence of anaphylactic reactions and serum sickness has been low with recent equine RIG products. Preexposure Rabies Vaccination Preexposure rabies prophylaxis should be considered for people with an occupational or recreational risk of rabies exposures and also for certain travelers to rabies-endemic areas. The primary schedule consists of two doses of rabies vaccine given on days 0 and 7. Serum neutralizing antibody tests help determine the need for subsequent booster doses. When a previously immunized individual is exposed to rabies, two booster doses of vaccine should be administered on days 0 and 3. Wound care remains essential. As stated above, RIG should not be administered to previously vaccinated persons. **OTHER RHABDOVIRUSES** ■

■ **OTHER LYSSAVIRUSES** A growing number of lyssaviruses other than rabies virus have been discovered to infect bat populations in Europe, Africa, Asia, and Australia. Six of these viruses have produced a very small number of cases of a human disease indistinguishable from rabies, including European bat lyssaviruses 1 and 2, Australian bat lyssavirus, Irkut virus,

and Duvenhage virus. Mokola virus, a lyssavirus that has been isolated from shrews with an unknown reservoir species in Africa, may also produce human disease indistinguishable from rabies.

■ **VESICULAR STOMATITIS VIRUS** Vesicular stomatitis is a viral disease of cattle, horses, pigs, and some wild mammals. Vesicular stomatitis virus is a member of the genus *Vesiculovirus* in the family *Rhabdoviridae*. Outbreaks of vesicular stomatitis in horses and cattle occur sporadically in the southwestern United States. The animal infection is associated with severe vesiculation and ulceration of oral tissues, teats, and feet and may be clinically indistinguishable from the more dangerous foot-and-mouth disease. Epidemics are usually seasonal, typically beginning in the late spring, and are probably due to arthropod vectors. Direct animal-to-animal spread can also occur, although the virus cannot penetrate intact skin. Transmission to humans usually results from direct contact with infected animals (particularly cattle) and occasionally follows laboratory exposure. In human disease, early conjunctivitis is followed by an acute influenza-like illness with fever, chills, nausea, vomiting, headache, retrobulbar pain, myalgias, substernal pain, malaise, pharyngitis, and lymphadenitis. Small vesicular lesions may be present on the buccal mucosa or on the fingers. Encephalitis is very rare. The illness usually lasts 3–6 days, with complete recovery. Subclinical infections are common. A serologic diagnosis can be made on the basis of a rise in titer of complement-fixing or neutralizing antibodies. Therapy is symptom-based. ■

■ **FURTHER READING**
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57:1, 2008. World Health Organization: WHO Expert Consultation on Rabies: Third Report (WHO Technical Report Series No. 1012). Geneva, World Health Organization, 2018. Available at <https://iris.who.int/bitstream/handle/10665/272364/9789241210218-eng.pdf>. Accessed September 20, 2024. Jens H. Kuhn, Ian Crozier

Arthropod-Borne and

Rodent-Borne Virus

Infections This chapter summarizes the major features of selected arthropodborne and rodent-borne viruses and associated infections and/or disease. Numerous viruses of this category are spread in nature among animals without ever infecting humans. Other viruses incidentally infect humans, with few causing disease. Some viruses are regularly introduced into the human population by arthropods (specifically, insects and ticks) or by chronically infected rodents. These zoonotic viruses are taxonomically diverse and therefore differ fundamentally in virion morphology, replication strategy, genomic organization, and genome sequence. Although a virus's classification in a taxon is enlightening regarding natural maintenance strategies, sensitivity to antiviral agents, and aspects of pathogenesis, it does not

necessarily predict which clinical symptoms and signs (if any) the viral infection will cause in humans. Zoonotic viruses are evolving, and "new" zoonotic viruses are regularly discovered. The epizootiology and epidemiology of zoonotic viruses continue to change because of environmental alterations affecting vectors, reservoirs, and hosts, including wildlife, livestock, and humans. Zoonotic viruses are most numerous in the tropics but are also found in temperate and frigid climates. The distribution and seasonal activity of zoonotic viruses may vary in a manner likely to depend largely on ecologic conditions (e.g., rainfall and temperature), which can affect the density of virus vectors and reservoirs, likelihood of exposure, and development of infection.

Arthropod-borne viruses (arboviruses) infect their vectors after ingestion of blood meals from viremic, usually nonhuman vertebrates; some infections may be the result of saliva-activated transmission. Arthropod vectors develop chronic systemic infection as the viruses penetrate their guts and spread throughout their bodies to their salivary glands; such virus dissemination, referred to as extrinsic incubation, typically lasts 1–3 weeks in mosquitoes. If the salivary glands become involved, the arthropod vectors are competent to continue the chain of transmission by infecting vertebrates during subsequent blood meals. Alternatively, virus maintenance in arthropod vectors may be achieved through transovarial transmission to progeny. Generally, the arthropods are unharmed by the infections and natural vertebrate partners have only transient viremia without overt disease. Rodent-borne viruses are maintained in nature by transmission among rodents, which become chronically infected. A high degree of rodent-virus specificity may be observed, and overt disease in the reservoir hosts is rare. **ETIOLOGY** Arthropod-borne and rodent-borne zoonotic viruses belong mostly to the classes *Alsuviricetes* (family *Togaviridae*), *Bunyaviricetes* (families *Arenaviridae*, *Hantaviridae*, *Nairoviridae*, *Peribunyaviridae*, and

Phenuiviridae), *Flasuviricetes* (family *Flaviviridae*), *Insthoviricetes* (family *Orthomyxoviridae*), *Monjiviricetes* (families *Bornaviridae* and *Rhabdoviridae*), and *Resentoviricetes* (families *Sedoreoviridae* and

Spinareoviridae) (Table 215-1). An exception is Syr-Darya Valley fever virus, an ixodid tick-borne cardiovirus (Pisoniviricetes: Picornaviridae) that causes febrile disease and has been found in Central Asia. PART 5 Infectious Diseases ■ ■ALSUVIRICETES: TOGAVIRIDAE Members of the family Togaviridae have linear, positive-sense RNA genomes (≈ 9.7 – 11.8 kb) and form enveloped icosahedral virions

(≈ 60 – 70 nm in diameter) that bud from the plasma membrane of the infected cell. The togavirids discussed in this chapter are all members of the genus Alphavirus and are transmitted to vertebrates by mosquitoes. ■ ■BUNYAVIRICETES: ARENAVIRIDAE Members of the family Arenaviridae that infect humans are all assigned to the genus Mammarenavirus.

Mammarenaviruses form spherical, oval, or pleomorphic enveloped and spiked virions (≈ 50 – 300 nm in diameter) that bud from the plasma membrane of the infected cell. The particles contain two genomic single-stranded RNAs (small [S], ≈ 3.5 kb, and large [L], ≈ 7.5 kb), encoding structural proteins in an ambisense orientation. Most mammarenaviruses persist by chronically infecting rodents. Human mammarenaviruses are maintained by muroid rodents that are often continuously viremic and commonly transmit viruses vertically and horizontally. One mammarenavirus associated with human infections is maintained by shrews. Strikingly, each mammarenavirus is predominantly adapted to one particular type of rodent. Humans usually become infected through inhalation of or direct contact with infected rodent excreta or secretions (e.g., from aerosolized whole rodents in harvesting machines or aerosolized dried urine or feces when sweeping floors in barns or houses) and direct contact with rodents in traps. Person-to-person transmission of mammarenaviruses occurs but is uncommon. ■ ■BUNYAVIRICETES: HANTAVIRIDAE, NAIROVIRIDAE, PERIBUNYAVIRIDAE, AND PHENUIVIRIDAE Members of these families that infect humans form spherical to pleomorphic enveloped virions containing three genomic RNAs

(S, ≈ 1 – 2 kb; medium [M], 3.6 – 5.3 kb; and L, 6.4 – 12.3 kb) of negative-sense (hantavirids, nairovirids, and peribunyavirids) or negative-sense or ambisense polarities (phenuivirids). These bunyaviricetes mature into particles ≈ 80 – 120 nm in diameter in the Golgi complexes of infected cells and exit these cells by exocytosis. Hantavirids that infect humans are classified in the genus Orthohantavirus and are maintained by muroid rodents that chronically shed virions. As with mammarenaviruses, individual orthohantaviruses are usually specifically adapted to a particular type of rodent. However, orthohantaviruses do not cause chronic viremia in their rodent hosts and are transmitted only horizontally from rodent to rodent. Also like mammarenaviruses, orthohantaviruses infect humans primarily through inhalation of or direct contact with rodent excreta or secretions, and person-to-person transmission occurs but is not common (with the notable exception of Andes virus). Nairovirids that infect humans are classified in the genus Orthonairovirus. Orthonairoviruses are predominantly maintained by ixodid ticks, which transmit these viruses vertically (transovarially and transstadially) to progeny and horizontally through contact with viremic vertebrate hosts and subsequent transmission to healthy vertebrates. Humans are usually infected via a tick bite or during handling of infected vertebrates. Peribunyavirids of one genus (Orthobunyavirus) infect humans. Orthobunyaviruses are primarily mosquito-borne (and, in rare circumstances, transmitted by midges or sandflies) and have viremic vertebrate intermediate hosts. Many orthobunyaviruses are transmitted vertically (transovarially) to their mosquito hosts. Numerous orthobunyaviruses have been associated with human infection and disease. Phenuivirids are transmitted vertically (transovarially) in their arthropod vectors and horizontally through viremic vertebrate hosts. Human phenuivirids are found in four genera: Bandavirus,

Phlebo virus, Tanzavirus, and Uukuvirus. Bandaviruses and uukuviruses are transmitted by ticks, whereas human phleboviruses are transmitted by sandflies (the ecology of tanzaviruses is unclear).

■ ■FLASUVIRICETES: FLAVIVIRIDAE The family Flaviviridae currently includes only one genus (Orthoflavi virus) that comprises arthropod-borne human viruses. Orthoflaviviruses have single-stranded positive-sense RNA genomes (≈ 11 kb) and form spherical enveloped particles or virions (40–60 nm in diameter). The orthoflaviviruses discussed in this chapter belong to two phylogenetically and antigenically distinct groups that are transmitted among vertebrates by mosquitoes (generally, *Aedes* and *Culex* spp.) and, typically, ixodid ticks, respectively. Vectors are usually infected when they feed on viremic hosts. As in the case of most other viruses discussed in this chapter, humans are accidental hosts, typically infected by arthropod bites. Arthropods maintain orthoflavivirus infections horizontally, although vertical (transovarial) transmission has been documented. Under some circumstances, orthoflaviviruses can be transmitted by aerosol or via contaminated food products; in particular, raw milk can transmit tick-borne encephalitis virus. ■

■INSTHOVIRICETES: ORTHOMYXOVIRIDAE The family Orthomyxoviridae includes two genera of medically relevant arthropod-borne viruses: Quarantavirus and Thogotovirus. Quarantaviruses are transmitted among birds by argasid ticks, whereas thogotoviruses have a predilection for mammalian host reservoirs and can be transmitted by argasid and ixodid ticks and mosquitoes. ■

■MONJIVIRICETES: BORNAVIRIDAE

AND RHABDOVIRIDAE Bornavirids and rhabdovirids that infect humans have linear non segmented, negative-sense RNA genomes (bornavirids, ≈ 9 kb; rhabdovirids, ≈ 11 –15 kb) and form spherical (bornavirids, 90–130 nm in diameter) and bullet-shaped to pleomorphic enveloped particles (rhabdovirids, 100–430 nm long and 45–100 nm wide). The only known rodent-borne bornavirid that infects humans is a member of genus Orthobornavirus and is transmitted by squirrels. The rhabdovirid genus Tibrovirus contains several uncharacterized human pathogens

TABLE 215-1 Zoonotic Arthropod- and Rodent-Borne Viruses That Infect Humans

VIRUS (ABBREVIATION)	MAJOR NONHUMAN HOST(S) ^a	VECTOR(S)	SYNDROME ^b
Alphavirus (family Togaviridae)			
Barmah Forest virus (BFV)	Cattle, horses, marsupials?	Biting midges (<i>Culicoides</i> marksii), mosquitoes (<i>Aedes camptorhynchus</i> , <i>Ae. normanensis</i> , <i>Ae. notoscriptus</i> , <i>Ae. vigilax</i> , <i>Culex annulirostris</i>)	
Chikungunya virus (CHIKV)	Bats, nonhuman primates	Mosquitoes (predominantly <i>Aedes aegypti</i> and <i>Ae. Albopictus</i>)	
Eastern equine encephalitis virus (EEEV)	Freshwater swamp passeriform birds, but also opportunistic amphibians, other birds (emu, gallinaceous poultry, pheasants), reptiles, and mammals (goats, horses, pigs, rodents)		
Everglades virus (EVEV)	Cotton deermice (<i>Peromyscus gossypinus</i>), hispid cotton rats (<i>Sigmodon hispidus</i>)		
Madariaga virus (MADV)	Likely bats, marsupials, reptiles, rodents	Mosquitoes (<i>Culex</i> , <i>Culiseta</i> spp.)	F&M, E
Mayaro virus (MAYV)	Nonhuman primates, possums, rodents; possibly caimans, horses, sheep		
Mucambo virus (MUCV)	Nonhuman primates, rodents	Mosquitoes (<i>Culex</i> , <i>Ochlerotatus</i> spp.)	F&M, E
O'nyong-nyong virus (ONNV)	Unknown	Mosquitoes (in particular <i>Anopheles gambiae</i> , <i>A. funestus</i> , <i>Mansonia</i> spp.)	
Ross River virus (RRV)	Marsupials, rodents	Mosquitoes (<i>Aedes normanensis</i> , <i>Ae. vigilax</i> , <i>Culex annulirostris</i>)	
Semliki Forest virus (SFV)	Birds, rodents	Mosquitoes (<i>Aedes</i> , <i>Culex</i> spp.)	A&R
Sindbis virus (SINV)	Typically birds, but also frogs and rats	Typically mosquitoes (<i>Culex</i> , <i>Culiseta</i> spp.), but tick isolation has been reported	
Tonate virus (TONV)	Birds, Suriname crested oropendolas (<i>Psarocolius decumanus</i>)		
Una virus (UNAV)	Birds, horses, nonhuman primates, rodents		
Venezuelan equine encephalitis virus (VEEV)	Equids, rodents	Mosquitoes (<i>Aedes</i> , <i>Culex</i> spp., <i>Psorophora confinnis</i>)	
Western equine encephalitis virus (WEEV)	Equids,		

lagomorphs, passeriform birds, pheasants Bandavirus (family Phenuiviridae) Bhanja virusf (BHAV) Cattle, four-toed hedgehog (*Atelerix albiventris*), goats, sheep, striped ground squirrels (*Xerus erythropus*) Heartland virus (HRTV) Cattle, deer, elk, goats, raccoons, sheep? Ixodid ticks (*Amblyomma americanum*) F&M Severe fever with thrombocytopenia syndrome virusg (SFTSV) Camels, cats, cattle, chickens, dogs, goats, hedgehogs, pigs, rodents, sheep? Coltivirus (family Spinareoviridae) Colorado tick fever virus (CTFV) Predominantly golden-mantled ground squirrels (*Spermophilus lateralis*), but also bushy-tailed woodrats (*Neotoma cinerea*), Columbian ground squirrels (*Spermophilus columbianus*), eastern deermice (*Peromyscus maniculatus*), least chipmunks (*Tamias minimus*), North American porcupines (*Erethizon dorsata*), Richardson ground squirrel (*Spermophilus richardsonii*), Uinta chipmunks (*Tamias umbrinus*), yellowpine chipmunks (*Tamias amoenus*) among lesser important mammal hosts Eyach virus (EYAV) Lagomorphs, rodents Ixodid ticks (*Ixodes ricinus*, *I. ventralloi*) F&M, E Salmon River virus (SRV) Unknown Ixodid ticks (*Ixodes* spp.) F&M, E Mammarenavirus (family Arenaviridae) Chapare virus (CHAPV) Unidentified cricetid rodents None VHF Flexal virus (FLEV) Unidentified cricetid rodents None (F&M) Guanarito virus (GTOV) Predominantly short-tailed zygodonts (*Zygodontomys brevicauda*) but also Alston's cotton rats (*Sigmodon alstoni*)

A&R A&Rc Mosquitoes (*Aedes*, *Coquillettidia*, *Culex* spp., *Anopheles quadrimaculatus*, *Culiseta melanura*, *Mansonia perturbans*, *Psorophora* spp.) E Mosquitoes (*Culex cedecei*) F&M, E Mosquitoes (predominantly *Haemagogus* spp., but also *Aedes*, *Culex*, *Mansonia*, *Psorophora*, *Sabethes* spp.) A&R A&R A&R A&R CHAPTER 215 Mosquitoes (*Anopheles*, *Coquillettidia*, *Culex*, *Mansonia*, *Uranotaenia*, *Wyeomyia* spp.), sandflies (*Lutzomyia* spp.) F&M, E Mosquitoes (*Aedes*, *Anopheles*, *Coquillettidia*, *Culex*, *Ochlerotatus*, *Psorophora* spp.) F&M Arthropod-Borne and Rodent-Borne Virus Infections F&M, E Mosquitoes (*Aedes* spp., *Culex tarsalis*, *Culiseta* spp.) E Ixodid ticks (*Amblyomma*, *Dermacentor*, *Haemaphysalis*, *Hyalomma*, *Rhipicephalus* spp.) F&M, E Ixodid ticks (predominantly *Haemaphysalis longicornis*, but also *Amblyomma testudinarium*, *H. concinna*, *H. flava*, *Ixodes nipponensis*, *Rhipicephalus microplus*) F&M, VHF Ixodid ticks (*Dermacentor andersoni*, possibly *D. occidentalis*) F&M, E None VHF (Continued)

TABLE 215-1 Zoonotic Arthropod- and Rodent-Borne Viruses That Infect Humans VIRUS TAXON VIRUS (ABBREVIATION) MAJOR NONHUMAN HOST(S)^a VECTOR(S) SYNDROME^b Junín virus (JUNV) Predominantly drylands lauchas (*Calomys musculinus*) but also Azara's akodonts (*Akodon azarae*) and little lauchas (*Calomys laucha*) Lassa virus (LASV) Predominantly Natal mastomys (*Mastomys natalensis*), but also reddishwhite mastomys (*M. erythroleucus*), African hylomyscus (*Hylomyscus pamfi*), and Baoule's mice (*Mus baoulei*) Lymphocytic choriomeningitis virus (LCMV) Predominantly house mice (*Mus musculus*), but also murid long-tailed field mice (*Apodemus sylvaticus*), softfurred mice (*Praomys* spp.), and golden hamsters (*Mesocricetus auratus*) Lujo virus (LUJV) Unknown None VHF Machupo virus (MACV) Big lauchas (*Calomys callosus*) None VHF Sabiá virus (SBAV) Unidentified cricetid rodents None VHF Whitewater Arroyo virus (WWAV) White-throated woodrats (*Neotoma albigula*) Orbivirus (family Sedoreoviridae) Kemerovo virus (KEMV) Birds, rodents Ixodid ticks (*Ixodes persulcatus*) F&M, E Lebombo virus (LEBV) Unknown Mosquitoes (*Aedes*, *Mansonia* spp.) F&M Orungo virus (ORUV) Camels, cattle, goats, nonhuman primates, sheep Tribe's virus (TRBV)^m Bank voles (*Myodes glareolus*), birds, common pine voles (*Microtus subterraneus*), goats, hares PART 5 Infectious Diseases Orthobornavirus (family Bornaviridae) Variegated squirrel bornavirus 1 (VSBV1) Finlayson's squirrel (*Callosciurus*

finlaysonii), Prevost's squirrels (*Callosciurus prevostii*), Swinhoe's striped squirrel (*Tamias swinhoei*), variegated squirrels (*Sciurus variegatoides*) Orthobunyavirus (family Peribunyaviridae) Apeú virus (APEUV) Bare-tailed woolly opossums (*Caluromys philander*) and other opossums; rodents; black howlers (*Alouatta caraya*), tufted capuchins (*Cebus apella*) Bangui virus (BGIV) Unknown Unknown F&M Batai virus (BATV) Birds, camels, cattle, goats, rodents, sheep Bunyamwera virus (BUNV) Birds, cows, goats, horses, sheep Mosquitoes (*Aedes* spp.) F&M Bwamba virus (BWAV) Unknown Mosquitoes (*Aedes*, *Anopheles*, *Mansonia* spp.) Cache Valley virus (CVV) Cattle, deer, dogs, foxes, groundhogs, horses, nonhuman primates, pigs, rabbits, raccoons, rodents California encephalitis virus (CEV) Lagomorphs, rodents Mosquitoes (*Aedes*, *Culex*, *Culiseta*, *Psorophora* spp.) Caraparú virus (CARV) Rodents, tufted capuchins (*C. apella*) Mosquitoes (*Culex* spp.) F&M Catú virus (CATUV) Bats, capuchins (*Cebus* spp.), opossums, rodents Cristoli virus (/) Unknown Mosquitoes? E Fort Sherman virus (FSV) Cattle, goats, horses, sheep? Mosquitoes? F&M Gan Gan virus (GGV) Unknown Mosquitoes (*Aedes*, *Culex* spp.) A&R Germiston virus (GERV) Rodents Mosquitoes (*Culex* spp.) F&M Guamá virus (GMAV) Bats, capuchins (*Cebus* spp.), howlers (*Alouatta* spp.), marsupials, rodents Guaroa virus (GROV) Unknown Mosquitoes (*Anopheles* spp.) F&M Ilesha virus (ILEV) Unknown Mosquitoes (*Anopheles gambiae*) F&M, (VHF) Inkoo virus (INKV) Cattle, foxes, hares, moose, reindeer, rodents

(Continued) None VHF None F&M, VHF None F&M, E, (VHF) None (E) Mosquitoes (*Aedes*, *Anopheles*, *Culex* spp.) F&M, E Ixodid ticks (*Ixodes persulcatus*, *I. ricinus*) F&M None E Mosquitoes (*Aedes*, *Culex* spp.) F&M Mosquitoes (*Aedes abnormalis*, *A. curtipes*, *Anopheles barbirostris*, *A. maculipennis*, *A. phillippinensis*, *Culex gelidus*, other spp.) F&M F&M Mosquitoes (*Aedes*, *Anopheles*, *Coquillettidia*, *Culiseta*, *Psorophora* spp.) F&M, E F&M, E Mosquitoes (*Culex* spp.) F&M Mosquitoes (*Aedes*, *Culex*, *Limatus*, *Mansonia*, *Psorophora*, *Trichoprosopon* spp.) F&M Mosquitoes (*Aedes* spp.) F&M, E (Continued)

TABLE 215-1 Zoonotic Arthropod- and Rodent-Borne Viruses That Infect Humans VIRUS TAXON VIRUS (ABBREVIATION) MAJOR NONHUMAN HOST(S)^a VECTOR(S) SYNDROME^b Iquitos virus (IQTV) Unknown Unknown F&M Itaquí virus (ITQV) Capuchins (*Cebus* spp.), opossums, rodents Jamestown Canyon virus (JCV) Predominantly white-tailed deer (*Odocoileus virginianus*), but also bison, elk, and moose Keystone virus (KEYV) Rabbits, squirrels Mosquitoes (*Ochlerotatus atlanticus*) E La Crosse virus (LACV) Chipmunks, squirrels Mosquitoes (*Ochlerotatus triseriatus*) F&M, E Lumbo virus (LUMV) Unknown Mosquitoes (*Aedes pembraensis*) F&M, E Madrid virus (MADV) Capuchins (*Cebus* spp.), opossums, rodents Maguari virus (MAGV) Birds, cattle, horses, sheep, water buffalo Mosquitoes (*Aedes*, *Anopheles*, *Culex*, *Psorophora*, *Wyeomyia* spp.) Marituba virus (MTBV) Capuchins (*Cebus* spp.), opossums, rodents Murutucú virus (MURV) Capuchins (*Cebus* spp.), opossums, palethroated sloths (*Bradypus tridactylus*), rodents Nepuyo virus (NEPV) Bats (*Artibeus* spp.), rodents Mosquitoes (*Culex* spp.) F&M Ngari virus (NRIV) Cattle, goats, sheep Mosquitoes (*Aedes*, *Anopheles*, *Culex* spp.) F&M, VHF Nyando virus (NDV) Unknown Mosquitoes (*Aedes*, *Anopheles* spp.), sandflies (*Lutzomyia* spp.) Oriboca virus (ORIV) Capuchins (*Cebus* spp.), opossums, rodents Oropouche virus (OROV) Marmosets (*Callithrix* spp.), pale-throated sloths (*B. tridactylus*) Ossa virus (OSSAV) Rodents Mosquitoes (*Culex* spp.) F&M Pongola virus (PGAV) Cattle, donkeys, goats, sheep Mosquitoes (*Aedes*, *Anopheles*, *Mansonia* spp.) Restan virus (RESV) Unknown Mosquitoes (*Culex* spp.) F&M Shokwe virus (SHOV) Rodents Mosquitoes (*Aedes*, *Anopheles*, *Mansonia* spp.) Shuni virus (SHUV) Horses, livestock Mosquitoes (*Culex theileri*, *Culicoides* spp.) E Snowshoe hare virus (SSHV) Collared lemmings, snowshoe hares, squirrels,

voles Tacaiuma virus (TCMV) Nonhuman primates Mosquitoes (Anopheles, Haemagogus spp.) T^hahyn^a virus (TAHV) Boars, cattle, deer, dogs, eulipotyphla, foxes, hares, horses, pigs, rodents
 Tataguine virus (TATV) Unknown Mosquitoes (Anopheles spp.) F&M Trubanaman virus (TRUV)
 Unknown Mosquitoes (Anopheles, Culex spp.) (A&R) Wyeomyia virus (WYOV) Unknown Mosquitoes (Wyeomyia spp.) F&M Xingu virus (XINV) Unknown Unknown F&M Zungarococha virus (ZUNV)
 Unknown Unknown F&M Orthoflavivirus (family Flaviviridae) Alkhurma hemorrhagic fever virus (AHFV)
 j Livestock? Argasid ticks (Ornithodoros savignyi), ixodid ticks (Hyalomma dromedarii, H. rufipes)
 Apoi virus (APOIV) Field mice, voles Unknown E Banzi virus (BANV) Rodents? Mosquitoes (Culex rubinotus) F&M
 Bussuquara virus (BSQV) Cotton rats, monkeys, spiny-rats Mosquitoes (Culex spp.) F&M
 Cacipacoré virus (CPCV) Birds, horses, nonhuman primates, water buffalo Dakar bat virus (DBV) Bats Unknown F&M
 Dengue viruses 1-4 (DENV 1-4) Nonhuman primates Mosquitoes (predominantly Aedes aegypti, A. albopictus)
 Edge Hill virus (EHV) Bandicoots, dogs, wallabies Mosquitoes (Aedes vigilax, Culex annulirostris) Ilhéus virus (ILHV) Birds, coatis, nonhuman primates, rodents, reptiles, sloths, water buffalo

(Continued) Mosquitoes (Culex spp.) F&M Mosquitoes (Aedes, Anopheles, Coquillettia, Culiseta, Ochlerotatus spp.) F&M, E Mosquitoes (Culex spp.) F&M F&M Mosquitoes (Culex spp.) F&M
 Mosquitoes (Coquillettia, Culex spp.) F&M F&M Mosquitoes (Aedes, Culex, Mansonia, Psorophora spp.) F&M
 CHAPTER 215 Biting midges (Culicoides paraensis), mosquitoes (Coquillettia venezuelensis, Culex quinquefasciatus, Mansonia spp., Ochlerotatus serratus) F&M, E F&M
 Arthropod-Borne and Rodent-Borne Virus Infections
 F&M Mosquitoes (Aedes, Culiseta, Ochlerotatus, Simulium spp.) F&M, E F&M Mosquitoes (Aedes, Anopheles, Culex, Culiseta spp.) F&M, E VHF Mosquitoes (Aedes, Anopheles, Culex spp.) F&M F&M,
 VHF F&M Mosquitoes (Aedes, Culex, Coquillettia, Haemagogus, Ochlerotatus, Psorophora, Sabethes, Trichoprosopon spp.) E (Continued)

TABLE 215-1 Zoonotic Arthropod- and Rodent-Borne Viruses That Infect Humans VIRUS TAXON
 VIRUS (ABBREVIATION) MAJOR NONHUMAN HOST(S)^a VECTOR(S) SYNDROME^b Japanese encephalitis virus (JEV) Ardeid wading birds (in particular herons), horses, pigs Karshi virus (KSIV) Great gerbils (Rhombomys opimus) Argasid ticks (Ornithodoros capensis), ixodid ticks (Hyalomma asiaticum)
 Kédougou virus (KEDV) Unknown Mosquitoes (Culex spp.) F&M Kokobera virus (KOKV) Macropods, horses Mosquitoes (Culex spp.) A&R Koutango virus (KOUV) Gerbils Mosquitoes (Aedes spp.) F&M
 Kyasanur Forest disease virus (KFDV)^k Indomalayan vandeleurias (Vandeleuria oleracea), roof rats (Rattus rattus) Modoc virus (MODV) North American deermice (Peromyscus maniculatus)
 Murray Valley encephalitis virus (MVEV) Birds (egrets, herons) Mosquitoes (predominantly C. annulirostris)
 Ntaya virus (NTAV) Birds, domestic animals Mosquitoes (Culex spp.) F&M Omsk hemorrhagic fever virus (OHFV) Migratory birds, rodents Ixodid ticks (predominantly Dermacentor spp.)
 Powassan virus (POWV) Red squirrels (Tamiasciurus hudsonicus), white-footed deermice (Peromyscus leucopus), woodchucks (Marmota monax), other small mammals
 Rio Bravo virus (RBV) Bats Unknown F&M Rocio virus (ROCV) Rufous-collared sparrows (Zonotrichia capensis), various migratory birds, horses, water buffalo (Bubalus bubalis)
 Sepik virus (SEPV) Unknown Mosquitoes (Mansonia septempunctata) F&M PART 5 Infectious Diseases
 Spondweni virus (SPOV) Cattle, sheep Mosquitoes (Aedes, Culex, Mansonia spp.) F&M St. Louis encephalitis virus (SLEV) Columbiform and passeriform birds (finches, sparrows)
 Tick-borne encephalitis virus (TBEV) Passeriform birds, deer, eulipotyphla, goats, grouse, small mammals, rodents, sheep
 Usutu virus (USUV) Accipitriform, columbiform, passeriform, and

strigiform birds Wesselsbron virus (WESSV) Cattle, goats, rodents, sheep Mosquitoes (*Aedes* spp.) F&M West Nile virus (WNV) Passeriform birds (blackbirds, crows, finches, sparrows), small mammals, horses Yellow fever virus (YFV) Nonhuman primates (*Alouatta*, *Ateles*, *Cebus*, *Cercopithecus*, *Colobus* spp.) Zika virus (ZIKV) Nonhuman primates (*Macaca*, *Pongo* spp.) Orthohantavirus (family Hantaviridae) Amur virus (AMRV) Korean field mice (*Apodemus peninsulae*) None VHF Anajatus virus (ANJV) Forner's colilargos (*Oligoryzomys forneri*) None P Andes virus (ANDV) Long-tailed colilargos (*Oligoryzomys longicaudatus*) Araraquara virus (ARAV) Hairy-tailed akodonts (*Necromys lasiurus*) None P Araucária virus (ARAUV) Black-footed colilargos (*Oligoryzomys nigripes*) Bayou virus (BAYV) Marsh rice rats (*Oryzomys palustris*) None P Bermejo virus (BMJV) Chacoan colilargos (*Oligoryzomys chacoensis*) Black Creek Canal virus (BCCV) Hispid cotton rats (*Sigmodon hispidus*) None P Blue River virus (BRV) White-footed deermice (*Peromyscus leucopus*) Caño Delgadito virus (CADV) Alston's cotton rats (*Sigmodon alstoni*) None P

(Continued) Mosquitoes (*Culex* spp., in particular *C. tritaeniorhynchus*) E F&M, E Ixodid ticks (predominantly *Haemaphysalis spinigera*) VHF Unknown E E VHF Ixodid ticks (in particular *Ixodes cookei*, other *Ixodes* spp., *Dermacentor* spp.) E Mosquitoes (*Aedes*, *Culex*, *Psorophora* spp.) E Mosquitoes (predominantly *Culex* spp., in particular *C. nigripalpus*, *C. pipiens*, *C. quinquefasciatus*, *C. tarsalis*) E Ixodid ticks (*Ixodes gibbosus*, *I. persulcatus*, *I. ricinus*; sporadically *Dermacentor*, *Haemaphysalis*, *Hyalomma* spp.) F&M, E, (VHF) Mosquitoes (*Culex* spp., in particular *C. pipiens*, but also *Aedes* spp., *Anopheles* spp., *Ochlerotatus* spp.) (E) Mosquitoes (*Culex* spp., in particular *C. pipiens*, *C. quinquefasciatus*, *C. restuans*, *C. tarsalis*) E Mosquitoes (*Aedes* spp., in particular *Ae. aegypti*) VHF Mosquitoes (*Aedes* spp.) F&M, A&R None P None P None P None P (Continued)

TABLE 215-1 Zoonotic Arthropod- and Rodent-Borne Viruses That Infect Humans VIRUS TAXON VIRUS (ABBREVIATION) MAJOR NONHUMAN HOST(S)^a VECTOR(S) SYNDROME^b Castelo dos Sonhos virus (CASV) Brazilian colilargos (*Oligoryzomys eliurus*) None P Catacamas virus (CATV) Coues' oryzomys (*Oryzomys couesi*) None P Choclo virus (CHOV) Fulvous colilargos (*Oligoryzomys fulvescens*) Dobrava virus (DOBV) Caucasus field mice (*Apodemus ponticus*), striped field mice (*A. agrarius*), yellow-necked field mice (*A. flavicollis*) El Moro Canyon virus (ELMCV) Western harvest mice (*Reithrodontomys megalotis*) Go-u virus (GOUV) Brown rats (*Rattus norvegicus*), roof rats (*R. rattus*), Oriental house rats (*R. tanezumi*) Hantaan virus (HTNV) Striped field mice (*Apodemus agrarius*) None VHF Juquitiba virus (JUQV) Black-footed colilargos (*Oligoryzomys nigripes*) Kurkino virus (KURV) Striped field mice (*Apodemus agrarius*) None VHF Laguna Negra virus (LANV) Little lauchas (*Calomys laucha*) None P Lechiguanas virus (LECV) Flavescent colilargos (*Oligoryzomys flavescens*) Maciel virus (MCLV) Dark-furred akodonts (*Necromys obscurus*) Maripa virus (MARV) Unknown None P Monongahela virus (MGLV) Eastern deermice (*Peromyscus maniculatus*) Muju virus (MUJV) Korean red-backed voles (*Myodes regulus*) New York virus (NYV) White-footed deermice (*Peromyscus leucopus*) Orán virus (ORNV) Long-tailed colilargos (*Oligoryzomys longicaudatus*) Paranoá virus (PARV) Unknown None P Pergamino virus (PRGV) Azara's akodonts (*Akodon azarae*) None P Puumala virus (PUUV) Bank voles (*Myodes glareolus*) None P, VHF Rio Mamoré virus (RIOMV) Common bristly mice (*Neacomys spinosus*) Saaremaa virus (SAAV) Striped field mice (*Apodemus agrarius*) None VHF Seoul virus (SEOV) Brown rats (*Rattus norvegicus*), roof rats (*R. rattus*) Sin Nombre virus (SNV) Western deermice (*Peromyscus sonoriensis*) Sochi virus (SOCV) Caucasus field mice (*Apodemus ponticus*) None VHF Tula virus (TULV) Common voles (*Microtus arvalis*), East European voles (*M. levis*), field voles (*M. agrestis*) Tunari virus (TUNV)

Unknown None P Orthonaïrovirus (family Nairoviridae) Aigai virus (AIGV) Cattle, goats, tortoises
 Ixodid ticks (*Hyalomma* spp., *Rhipicephalus* spp.) Avalon virus (AVAV) European herring gulls
 (*Larus argentatus*) Ixodid ticks (*Ixodes uriae*) (Polyradiculoneuritis?) Crimean-Congo hemorrhagic
 fever virus (CCHFV) Cattle, dogs, goats, hares, hedgehogs, mice, ostriches, sheep Dugbe virus
 (DUGV) Northern giant pouched rats (*Cricetomys gambianus*), Zébu cattle (*Bos primigenius*) Erve
 virus (ERVEV) Greater white-toothed shrews (*Crocidura russula*) Issyk-kul virus (ISKV) Bats, birds
 Biting midges (*Culicoides schultzei*), horseflies (*Tabanus agrestis*), mosquitoes (*Aedes caspius*,
Anopheles hyrcanus), argasid ticks (*Argas vespertilionis*, *A. pusillus*), ixodid ticks (*Ixodes*
vespertilionis)

(Continued) None F&M, P None VHF None VHF None VHF None P None P None P None P CHAPTER
 215 None VHF None P None P Arthropod-Borne and Rodent-Borne Virus Infections
 None P None VHF None P None (P), VHF VHF Predominantly ixodid ticks (*Hyalomma* spp.) VHF
 Biting midges (*Culicoides* spp.), ixodid ticks (*Amblyomma*, *Hyalomma*, *Rhipicephalus* spp.) F&M
 Unknown (Thunderclap headache?) F&M (Continued)

TABLE 215-1 Zoonotic Arthropod- and Rodent-Borne Viruses That Infect Humans VIRUS TAXON
 VIRUS (ABBREVIATION) MAJOR NONHUMAN HOST(S)^a VECTOR(S) SYNDROME^b Nairobi sheep
 disease virus (NSDV) Sheep Ixodid ticks (*Amblyomma*, *Haemaphysalis*, *Rhipicephalus* spp.),
 mosquitoes (*Culex* spp.) Sönglïng virus (SGLV) Great gerbils (*Rhombomys opimus*) Ixodid ticks
 (*Ixodes crenulatus*, *Ixodes persulcatus*, *Haemaphysalis concinna*, and *Haemaphysalis longicornis*)
 Ta'chéng tick virus 1 (TcTV1) Sheep, tortoises Ixodid ticks (*Dermacentor marginatus*, *Hyalomma*
aegyptium) Tamdy virus (TAMV) Gerbils, other mammals (including Bactrian camels), birds
 Wetland virus (WELV) Horses, pigs, sheep, North China zokors Ixodid ticks (*Dermacentor*, *Ixodes*,
Haemaphysalis spp.) Yezo virus (YEZV) Unknown Ixodid ticks (*Ixodes persulcatus*) F&M
 Phlebovirus (family Phenuiviridae) Adria virus (ADRV) Unknown Sandflies E Alenquer virus (ALEV)
 Unknown Unknown F&M Candirú virus (CDUV) Unknown Unknown F&M Chagres virus (CHGV)
 Unknown Sandflies (*Lutzomyia* spp.) F&M Chios virus (/) Unknown Unknown E Coclé virus (CCLV)
 Unknown Sandflies F&M Echarate virus (ECHV) Unknown Unknown F&M Granada virus (GRV =
 GRAV) Unknown Sandflies F&M Maldonado virus (MLOV) Unknown Unknown F&M Morumbi virus
 (MRBV = MRMBV) Unknown Unknown F&M PART 5 Infectious Diseases Punta Toro virus (PTV)
 Unknown Sandflies (*Lutzomyia* spp.) F&M Rift Valley fever virus (RVFV) Cattle, sheep Mosquitoes
 (*Aedes*, *Anopheles*, *Coquillettidia*, *Culex*, *Eretmapodites*, *Mansonia* spp.) Sandfly fever Cyprus
 virus (SFCV) Unknown Unknown F&M Sandfly fever Ethiopia virus (SFEV) Unknown Sandflies F&M
 Sandfly fever Naples virus (SFNV) Unknown Sandflies (*Phlebotomus papatasi*, *P. perfiliewi*, *P.*
perniciosus) Sandfly fever Sicilian virus (SFSV) *Eulipotyphla*, least weasels (*Mustela nivalis*),
 rodents Sandfly fever Turkey virus (SFTV) Unknown Sandflies (*Phlebotomus* spp.) F&M Serra
 Norte virus (SRNV) Unknown Unknown F&M Toscana virus (TOSV) Migratory birds? Sandflies
 (*Phlebotomus papatasi*, *P. perfiliewi*, *Sergentomyia* spp.) Quaranjavirus (family Orthomyxoviridae)
 Quarafil virus (QRFV) Birds Argasid ticks (*Argas arboreus*) F&M Seadornavirus (family
 Sedoreoviridae) Banna virus (BAV) Cattle, pigs Biting midges (*Culicoides* spp.), mosquitoes (*Aedes*,
Anopheles, *Culiseta* spp.), ticks Tanzavirus (family Phenuviridae) Dar es Salaam virus (DeSV)
 Unknown Unknown F&M Tibrovirus (family Rhabdoviridae) Bas-Congo virus (BASV) Artiodactyls?
 Biting midges? (VHF) Ekpoma virus 1 (EKV1) Artiodactyls? Biting midges? F&M Ekpoma virus 2
 (EKV2) Artiodactyls? Biting midges? F&M Mundri virus (MUNV) Artiodactyls? Biting midges? E (New
 onset nodding syndrome) Thogotovirus (family Orthomyxoviridae) Bourbon virus (BRBV) Raccoons

(*Procyon lotor*), white-tailed deer (*Odocoileus virginianus*)? Dhori virus (DHOV) p Bats, camels, horses Mosquitoes (*Aedes*, *Anopheles*, *Culex* spp.), argasid ticks (*Ornithodoros* spp.), ixodid ticks (*Dermacentor*, *Hyalomma* spp.) Thogoto virus (THOV) Camels, cattle Ixodid ticks (*Amblyomma*, *Hyalomma*, *Rhipicephalus* spp.)

(Continued) F&M F&M F&M Ixodid ticks (*Dermacentor*, *Hyalomma* spp.) F&M F&M F&M, E, VHF F&M Sandflies (predominantly *Phlebotomus papatasi*) F&M F&M, E E Ixodid ticks (*Amblyomma americanum*) F&M F&M, E F&M, E (Continued)

TABLE 215-1 Zoonotic Arthropod- and Rodent-Borne Viruses That Infect Humans VIRUS TAXON VIRUS (ABBREVIATION) MAJOR NONHUMAN HOST(S)^a VECTOR(S) SYNDROME^b Uukuvirus (family Phenuiviridae) Ta'chéng tick virus 2 (TcTV2) Unknown Ixodid ticks (*Dermacentor marginatus*, *Dermacentor nuttalli*, *Dermacentor silvarum*, *Hyalomma asiaticum*) Uukuniemi virus (UUKV) Birds, cattle, rodents Ixodid ticks (*Ixodes* spp.) F&M Vesiculovirus (family Rhabdoviridae) Chandipura virus (CHPV) Hedgehogs Mosquitoes (*Aedes aegypti*), sandflies (*Phlebotomus*, *Sergentomyia* spp.) Isfahan virus (ISFV) Great gerbils (*Rhombomys opimus*) Sandflies (*Phlebotomus papatasi*) F&M Piry virus (PIRYV) Gray four-eyed opossums (*Philander opossum*) Vesicular stomatitis Indiana virus (VSIV) Cattle, horses, pigs Sandflies (*Lutzomyia* spp.) F&M Vesicular stomatitis New Jersey virus (VSNJV) Cattle, horses, pigs Biting midges (*Culicoides* spp.), chloropid flies, mosquitoes (*Culex*, *Mansonia* spp.), muscoid flies (*Musca* spp.), simuliid flies ^aMammalian names as listed in Wilson & Reeder's Mammal Species of the World, 3rd edition

(<https://www.departments.bucknell.edu/biology/resources/msw3/>). ^bAbbreviations refer to the syndromes most associated with the viruses: A&R, arthritis and rash; E, encephalitis; F&M, fever and myalgia; P, pulmonary; VHF, viral hemorrhagic fever. Abbreviations are placed in parentheses when cases are controversial. ^cIn the older literature, chikungunya virus often is also listed as a causative agent of VHF. However, later studies revealed that, in most cases, people with "chikungunya hemorrhagic fever" were co-infected with one or more dengue viruses, an observation suggesting that the VHF was severe dengue. ^dAlso known as Igbo-Ora virus. ^eAlso known as Ockelbo virus (OCKV), Pogosta virus, and Karelian fever virus (KfV). ^fAlso known as Palma virus (PALV). ^gAlternatives used in the literature are Huáiyángsha - n virus (HYSV) and Hénán fever virus (HNFV). ^hAlso known as Alfuy virus (ALFV). ⁱAlso includes Kunjin virus (KUNV). ^jAlso spelled Alkhumra hemorrhagic fever virus (AHFV) and known as Alkhurma/Alkhumra virus (ALKV). ^kAlso known as Nánjiànyí(n) virus. ^lWhitewater Arroyo virus is often listed as a causative agent of VHF in the literature, but convincing data associating this virus with VHF have not been published. ^mAlso known as Brezová virus, Cvilín virus, Kharagys virus, Koliba virus, or Lipovnik virus. ⁿAlso known as Čalovo virus (CVOV) or Chittoor virus (CHITV). ^oAlso known as Ganjam virus (GV). ^pAlso known as Astra virus and Batken virus (BKNV). that cause fever and myalgia (F&M) syndrome and possibly viral hemorrhagic fever, whereas the genus Vesiculovirus includes confirmed human arthropod-borne viruses, all of which are transmitted by insects (biting midges, mosquitoes, and sandflies). The general properties of rhabdovirids are discussed in more detail in Chap. 214. ■ ■ RESENTOVIRICETES: SEDOREOVIRIDAE

AND SPINAREOVIRIDAE The families Sedoreoviridae and Spinareoviridae are established for viruses with linear, multisegmented, double-stranded RNA genomes (≈16–29 kb in total). These viruses produce particles that have icosahedral symmetry and are 60–80 nm in diameter. In contrast to all other virions discussed in this chapter, resentovirions are not enveloped and thus are

insensitive to detergent inactivation. Human arthropod-borne viruses are found within the genera Coltivirus (family Spinareoviridae), Orbivirus, and Seadornavirus (both in family Sedoreoviridae). Arthropod-borne coltiviruses possess 12 genome segments and are transmitted by numerous tick types transstadially but not transovarially. Therefore, maintenance of the transmission cycle involves viremic mammalian hosts infected by tick bites. Arthropod-borne orbiviruses have 10 genome segments and are transmitted by mosquitoes or ixodid ticks, whereas relevant seadornaviruses have 12 genome segments and are transmitted exclusively by mosquitoes.

EPIDEMIOLOGY Arthropod-borne and rodent-borne viruses are generally confined to the areas inhabited by their reservoir hosts and/or vectors. Consequently, a patient's geographic origin or travel history can provide important clues in the differential diagnosis. Table 215-2 lists the approximate geographic distribution of most arthropod-borne and rodent-borne infections. Many of these diseases can be acquired in rural or urban settings. However, diseases commonly associated with urban outbreaks include yellow fever (YF), dengue without/with warning signs (previously called dengue fever), severe dengue (previously called dengue hemorrhagic fever and dengue shock syndrome), chikungunya virus disease, hemorrhagic fever with renal syndrome (HFRS) caused by Seoul virus, sandfly fever caused by sandfly fever Naples and Sicilian viruses, and Oropouche virus disease.

DIAGNOSIS In patients with suspected viral infection, a history of mosquito bite(s) has little diagnostic significance, but a history of tick bite(s) is more useful. Patients infected with hantaviruses or orthohantaviruses

(Continued) (E) F&M, E Mosquitoes (*Aedes*, *Culex*, *Toxorhynchites* spp.) F&M F&M sometimes report exposure to rodents. Although clinical signs and epidemiologic clues may enable presumptive etiologic diagnosis in epidemic settings, laboratory diagnosis is required in all cases. For most arthropod-borne and rodent-borne virus diseases, acute-phase serum samples (collected within 3 or 4 days of onset) have yielded isolates. Paired serum samples have been used to show rising antibody titers. Intensive efforts to develop rapid tests for viral hemorrhagic fevers (VHFs) have resulted in reliable antigen-detection enzyme-linked immunosorbent assays (ELISAs), IgM-capture ELISAs, and multiplex polymerase chain reaction (PCR) assays. These tests can provide a diagnosis based on a single serum sample within a few hours and are particularly useful for assessment of patients with severe disease. More sensitive reverse transcriptase PCR (RT-PCR) assays may yield diagnoses based on samples without detectable antigen and may also provide useful truly quantifiable genetic information about the etiologic agent.

CHAPTER 215 Arthropod-Borne and Rodent-Borne Virus Infections

At diagnosis, patients with encephalitides generally are no longer viremic or antigenemic and usually do not have virions in cerebrospinal fluid (CSF). In this situation, either serologic detection of IgM or RT-PCR detection of viral nucleic acid may enable diagnosis. Increasingly, IgM-capture ELISAs are used for the simultaneous testing of serum and CSF. IgG ELISA or classic serology is useful in the evaluation of past exposure to viruses, many of which circulate in areas with minimal medical infrastructures and sometimes cause only mild or subclinical infections (and are not recognized).

CLINICAL DISEASE SYNDROMES There is a wide spectrum of possible human responses to infection with arthropod-borne or rodent-borne viruses, and knowledge of the outcome of most of these infections is limited. People infected with these viruses may not develop or recognize symptoms or signs of illness. If viral disease is recognized, it can usually be grouped into one of five broad syndromic categories: F&M, arthritis and rash (A&R), encephalitis, pulmonary disease, or VHF (Table 215-3). Although a useful clinical heuristic, it should be acknowledged that these categories often overlap in the complex spectra of disease caused by arthropod-borne and

rodent-borne viruses. Furthermore, illness caused by many of these viruses is often best known by the most severe disease phenotypes, which typically do not result in the most common disease manifestations. For example, infections with West Nile virus (WNV) and Venezuelan equine encephalitis virus (VEEV) are discussed in this chapter as encephalitides, but during epidemics, many patients present with much milder F&M. Similarly, Rift Valley fever virus (RVFV)

TABLE 215-2 Geographic Distribution of Zoonotic Arthropod-Borne or Rodent-Borne Viral Diseases

BUNYAVIRICETES (Arenaviridae, Hantaviridae, Nairoviridae, Peribunyaviridae, Phenuiviridae)

FLASUVIRICETES (Flaviviridae) AREAa Africa Aigai, Bangui, Batai, Bhanja, Bunyamwera, and Bwamba virus infections, Crimean-Congo hemorrhagic fever, Dar es Salaam, Dugbe, Germiston, Ilesha virus infections, Lassa fever, Lujo virus, Nairobi sheep disease virus infection, Ngari, Nyando, and Pongola virus infections, Rift Valley fever, sandfly fever, Shokwe, Shuni, Tataguine virus infections Alkhurma hemorrhagic fever, Banzi virus infection, Dakar bat, dengue without/with warning signs/severe dengue, Kédougou, Koutango, Ntaya, Spondweni, Usutu, Wesselsbron, West Nile virus infections, yellow fever, Zika virus disease Central Asia Bhanja, Issyk-kul virus infections, Far Eastern tick-borne encephalitis, Karshi, Powassan, West Nile virus infections Crimean-Congo hemorrhagic fever, sandfly fever, Tʼahynʼ a, Tamdy virus infections Eastern Asia Crimean-Congo hemorrhagic fever, hemorrhagic fever with renal syndrome, sandfly fever, severe fever with thrombocytopenia syndrome, Taʼchéng tick virus 1 (and 2) and Tʼahynʼ a, Tamdy, So Apoi virus infection, dengue without/ with warning signs/ severe dengue, Far Eastern tickborne encephalitis, Japanese encephalitis, Karshi virus infection, Kyasanur Forest disease –ngliʼng, wetland, and Yezo virus infections PART 5 Infectious Diseases Southern Asia Batai, Bhanja virus infections, Crimean-Congo hemorrhagic fever, hemorrhagic fever with renal syndrome, Nairobi sheep disease virus infection, sandfly fever Dengue without/with warning signs/severe dengue, Japanese encephalitis, Kyasanur Forest disease, West Nile virus infection, Zika virus disease SouthEastern Asia Batai virus infection, hemorrhagic fever with renal syndrome Dengue without/with warning signs/severe dengue, Japanese encephalitis, West Nile virus infection, Zika virus disease Western Asia Aigai, Batai, Bhanja virus infections, Crimean-Congo hemorrhagic fever, hemorrhagic fever with renal syndrome, sandfly fever, Taʼchéng tick virus 1, Tamdy virus infections Alkhurma hemorrhagic fever, Central European tickborne encephalitis, dengue without/with warning signs/severe dengue, West Nile virus infection Latin/ Central America and the Caribbean Alenquer, Apeú virus infections, Argentinian hemorrhagic fever, Bolivian hemorrhagic fever, “Brazilian hemorrhagic fever”, Bunyamwera, Candirú, Caraparú, Catú, Chagres, Chapare, Coclé, Echarate, (Flexal,) Fort Sherman, Guamá, Guaroa virus infections, hantavirus pulmonary syndrome, Iquitos, Itaquí, Juquitiba virus infections, lymphocytic choriomeningitis, Madrid, Maguari, Maldonado, Marituba, Mayaro, Morumbi, Murutucú, Nepuyo, Oriboca virus infections, Oropouche virus disease, Ossa, Punta Toro, Restan, Serra Norte, Tacaiuma, Trinidad virus infections, Venezuelan hemorrhagic fever, Wyeomyia, Xingu, Zungarococha virus infections Bussuquara, Cacipacoré virus infections, dengue without/with warning signs/severe dengue, Ilhéus, Rio Bravo virus infections, Rocio viral encephalitis, Spondweni, St Louis encephalitis, yellow fever, Zika virus disease

TYPE OF DISEASEb RESENTOVIRICETES (Sedoreoviridae, Spinareoviridae) MONJIVIRICETES (Bornaviridae, Rhabdoviridae) INSTHOVIRICETES (Orthomyxoviridae) ALSUVIRICETES (Togaviridae) Dhori, Quaranfil, Thogoto virus infections Lebombo, Orungo, Tribecʼ virus infections (Bas-Congo virus infection,) Ekpoma virus 1, Ekpoma virus 2, Mundri virus infections Chikungunya virus disease, oʼnyongnyong fever, Semliki Forest, Sindbis virus infections Dhori virus infections —

Isfahan virus infection Sindbis virus infection — Banna virus infection — — Dhori, Quarantilla, Thogoto virus infections — Chandipura, Isfahan virus infections, variegated squirrel bornavirus 1? Chikungunya virus disease — — — Chikungunya virus disease Dhori, Quarantilla virus infections — — Chikungunya virus disease — — Piry fever, vesicular stomatitis fever Chikungunya virus disease, Madariaga, Mayaro, Mucambo, Tonate, Una virus infections, Venezuelan equine encephalitis (Continued)

TABLE 215-2 Geographic Distribution of Zoonotic Arthropod-Borne or Rodent-Borne Viral Diseases

BUNYAVIRICETES (Arenaviridae, Hantaviridae, Nairoviridae, Peribunyaviridae, Phenuiviridae)

FLASUVIRICETES (Flaviviridae) **AREAa** Northern America (Avalon,) Cache Valley virus infections, California encephalitis, hantavirus pulmonary syndrome, Heartland and Keystone virus infections, lymphocytic choriomeningitis, Nepuyo, snowshoe hare, (Whitewater Arroyo virus) infections

Dengue without/with warning signs/severe dengue, Modoc virus infection, Powassan virus disease, Rio Bravo virus infection, St Louis encephalitis, West Nile virus infection, Zika virus disease

Europe Adria, Aigai, (Avalon,) Batai, Bhanja, Cristoli virus infections, California encephalitis, CrimeanCongo hemorrhagic fever, (Erve virus infection), hemorrhagic fever with renal syndrome, Inkoo, Issykkul virus infections, lymphocytic choriomeningitis, sandfly fever, snowshoe hare, T`ahyn` a, Uukuniemi virus infections

Central European tick-borne encephalitis, dengue without/with warning signs/severe dengue, Ntaya virus infection, Omsk hemorrhagic fever, Powassan, Usutu, West Nile virus infections

Oceania Batai, Gan Gan, (Trubanaman) virus infections Dengue without/ with warning signs/ severe dengue, Edge Hill virus infection, Japanese encephalitis, Kokobera virus infection, Murray Valley encephalitis, Sepik virus, West Nile virus infections, Zika virus disease

aGeographic names here and throughout the chapter are as recommended by the UN geoscheme (<https://unstats.un.org/unsd/methodology/m49/>). **b**Disease names according to the World Health Organization's International Classification of Diseases 11th revision (ICD-11; <https://icd.who.int/browse11/l-m/en>). Quotation marks indicate common usage in the absence of ICD-11 recognition. Diseases not acknowledged by the ICD-11 are designated as "virus infection(s)." is best known as a cause of VHF, but the prevalence of milder F&M syndrome is far higher after infection, with encephalitis and ocular disease also occurring occasionally. Lymphocytic choriomeningitis virus (LCMV) is classified in this chapter as a cause of F&M syndrome because it is the most common disease manifestation. Even when central nervous system (CNS) disease evolves during infection with this virus, neurologic manifestations are usually mild and preceded by F&M. However, this virus may also cause fetal microcephaly. Overlap between syndromic categories is further complicated by evolving nomenclature around their classification. For example, infection with any dengue virus (DENV-1-4) is considered as a cause of F&M syndrome because this disease presentation, historically called "dengue fever," is by far the most common manifestation. However, severe manifestations of DENV infection have a complicated pathogenesis: the historical classification of disease as "dengue hemorrhagic fever" included a subset of patients with "dengue shock syndrome," which is of tremendous consequence for pediatric populations in particular areas of the world. Further complicating this overlap, a relatively recent World Health Organization (WHO) revision of disease classification recommended a less descriptive but more pragmatic use of "dengue without warning signs," "dengue with warning signs," and "severe dengue" to describe the same spectrum and enhance clinical management and case reporting. Unfortunately, most of the known arthropod-borne and rodentborne viral diseases have not been studied in detail with modern medical approaches. Thus, available data may be incomplete, at relatively low resolution, or biased toward severe disease. Data on

geographic distribution are often difficult to interpret. Frequently, the literature is not clear as to whether the data pertain to the distribution of a particular virus or to the areas where human disease has been observed. In

(Continued) TYPE OF DISEASEb RESENTOVIRICETES (Sedoreoviridae, Spinareoviridae)
MONJIVIRICETES (Bornaviridae, Rhabdoviridae) INSTHOVIRICETES (Orthomyxoviridae)
ALSUVIRICETES (Togaviridae) Bourbon virus infection Colorado tick fever, Salmon River virus infection Vesicular stomatitis fever Eastern equine encephalitis, Everglades virus infection, western equine encephalitis Dhorì, Thogoto virus infections Eyach, Kemerovo, Tribec³ virus infections — Chikungunya virus disease, Sindbis virus infection — — — Barmah Forest virus infection, Ross River disease, Sindbis virus infection CHAPTER 215 Arthropod-Borne and Rodent-Borne Virus Infections addition, the designations for viruses and viral diseases have changed multiple times over decades. In this chapter, virus and taxon names are in line with the latest reports of the International Committee on Taxonomy of Viruses, and disease names are in accordance with the WHO's International Classification of Diseases 11th revision (ICD-11). When needed for clarity or historical reference, alternative nomenclature is used. Considering this syndromic approach, it should be noted that the variable clinical manifestations of particular viruses may be captured over a number of sections. ■ ■ FEVER AND MYALGIA (F&M) F&M is by far the most common clinical syndrome and has the most favorable outcomes after arthropod-borne and rodent-borne infections. However, it is also a common prodrome en route to more invasive syndromes associated with these infections. In logical sequence, therefore, F&M will be discussed initially but should not be considered in isolation. Indeed, clinicians evaluating patients with F&M should pay careful attention for symptoms and signs that suggest the A&R, neuroinvasive, pulmonary, or VHF syndromes that are subsequently discussed in this chapter. Although many of the viruses listed in Table 215-1 probably cause F&M, only some of these viruses have prominent associations with the syndrome that are considered biomedically important. F&M syndrome typically begins with the abrupt onset of fever, chills, intense myalgia, and malaise. Patients may also report joint pain, but true arthritis is not found. Anorexia is characteristic and may be accompanied by nausea or vomiting. Headache is common and may be severe, with photophobia and retroorbital pain. Physical findings are minimal and usually confined to conjunctival injection, pharyngeal erythema/exudate, muscle tenderness, abdominal tenderness,

PART 5 Infectious Diseases TABLE 215-3 Clinical Syndromes Caused by Zoonotic Arthropod-Borne or Rodent-Borne Viruses SYNDROME VIRUS Fever and myalgia (F&M) Arenaviridae: (Flexal,) Lassa and lymphocytic choriomeningitis viruses Flaviviridae: Bussuquara, Banzi, Cacipacoré, Dakar bat, dengue 1-4, Edge Hill, Karshi, Kédougou, Koutango, Ntaya virus, Rio Bravo, Sepik, Spondweni, tick-borne encephalitis, Wesselsbron, and Zika viruses Hantaviridae: Choclo virus Nairoviridae: Dugbe, Issyk-kul, Nairobi sheep disease, So³-ngl³ng viruses, Ta³chéng tick virus 1, Tamdy, wetland, Yezo virus Orthomyxoviridae: Bourbon, Dhorì, and Thogoto viruses Peribunyaviridae: Apeú, Bangui, Batai, Bunyamwera, Bwamba, Cache Valley, California encephalitis, Caraparú, Catú, Fort Sherman, Germiston, Guamá, Guaroa, Ilesha, Inkoo, Iquitos, Itaquí, Jamestown Canyon, La Crosse, Lumbo, Madrid, Maguari, Marituba, Nepuyo, Ngari, Nyando, Oriboca, Oropouche, Ossa, Pongola, Restan, Shokwe, snowshoe hare, Tacaiuma, T³ahyn³a, Tataguine, Wyeomyia, Xingu, and Zungarococha viruses Phenuiviridae: Alenquer, Bhanja, Candirú, Chagres, Dar es Salaam, Echarate, Heartland, Maldonado, Morumbi, Punta Toro, Rift Valley fever, sandfly fever Cyprus, sandfly fever Ethiopia, sandfly fever Naples, sandfly fever Sicilian, sandfly fever Turkey, Serra Norte, severe fever with

thrombocytopenia syndrome, Toscana, and Uukuniemi viruses Sedoreoviridae: Kemerovo, Lebombo, Orungo, and Tribec[✓] viruses Spinareoviridae: Colorado tick fever, Eyach, and Salmon River viruses Rhabdoviridae: Ekpoma virus 1, Ekpoma virus 2, Chandipura, Isfahan, Piry, vesicular stomatitis Indiana, and vesicular stomatitis New Jersey viruses Togaviridae: Everglades, Madariaga, Mucambo, Tonate, Una, and Venezuelan equine encephalitis viruses Arthritis and rash (A&R) Flaviviridae: Kokobera and Zika viruses Peribunyaviridae: Gan Gan virus, (Trubanaman virus) Togaviridae: Barmah Forest, chikungunya, Mayaro, o'nyong-nyong, Ross River, Semliki Forest, and Sindbis viruses Encephalitis Arenaviridae: lymphocytic choriomeningitis virus, (Whitewater Arroyo virus) Flaviviridae: Apoi, Ilhéus, Japanese encephalitis, Karshi, Modoc, Murray Valley encephalitis, Powassan, Rocio, St. Louis encephalitis, tick-borne encephalitis, Usutu, and West Nile viruses Orthomyxoviridae: Dhori and Thogoto viruses Bornaviridae: variegated squirrel bornavirus 1 Peribunyaviridae: Cache Valley, California encephalitis, Cristoli, Inkoo, Jamestown Canyon, Keystone, La Crosse, Lumbo, Oropouche, snowshoe hare, Shuni, and T[✓]ahyn[✓] a viruses Phenuiviridae: Adria, Bhanja, Chios, Rift Valley fever, (Ta[✓]chéng tick virus 2), and Toscana viruses Sedoreoviridae: Banna, Kemerovo, and Orungo viruses Spinareoviridae: Colorado tick fever, Eyach, and Salmon River viruses Rhabdoviridae: Chandipura, Mundri viruses Togaviridae: eastern equine encephalitis, Everglades, Madariaga, Mucambo, Tonate, Venezuelan equine encephalitis, and western equine encephalitis viruses Pulmonary disease Hantaviridae: Anajatuba, Andes, Araucária, bayou, Bermejo, Black Creek Canal, Blue River, Caño Delgadito, Castelo dos Sonhos, Catacamas, Choclo, Juquitiba, Laguna Negra, Lechiguana, Maciel, Monongahela, New York, Orán, Paranoá, Pergamino, Puumala, Rio Mamoré, Sin Nombre, (Tula,) and Tunari viruses Viral hemorrhagic fever (VHF) Arenaviridae: Chapare, Guanarito, Junín, Lassa, Lujo, (lymphocytic choriomeningitis,) Machupo, and Sabiá viruses Hantaviridae: Amur, Dobrava, El Moro Canyon, go - u, Hantaan, Kurkino, Muju, Puumala, Saaremaa, Seoul, Sochi, and Tula viruses Nairoviridae: Crimean-Congo hemorrhagic fever virus Peribunyaviridae: (Ilesha virus,) Ngari viruses Phenuiviridae: Rift Valley fever and severe fever with thrombocytopenia syndrome viruses Flaviviridae: Alkhurma hemorrhagic fever, dengue 1–4, Kyasanur Forest disease, Omsk hemorrhagic fever, (tick-borne encephalitis,) and yellow fever viruses Rhabdoviridae: (Bas-Congo virus) Viruses are placed in parentheses if cases were controversial. and possibly the presence of a nonpruritic maculopapular rash that may have a petechial component. The spectrum of disease varies from subclinical to temporarily incapacitating. When present, the evolution and duration of symptoms/signs are quite variable (generally 2–5 days) and may be biphasic after some viral infections. Less-common findings include epistaxis (not necessarily indicating a bleeding diathesis) and signs of aseptic meningitis. Even in the presence of headache, photo phobia, and meningismus, challenges in obtaining and examining the CSF in remote areas makes diagnosis difficult. Although upper and lower respiratory symptoms/signs and radiographic evidence of pulmonary infiltrates are noted in some patients, the agents causing this syndrome are not primary respiratory pathogens. F&M syndrome is the most nonspecific of the disease syndromes caused by arboviral infections. The early stages of other syndromes discussed in this chapter begin similarly and are encompassed in a broad differential diagnosis that also includes community-acquired parasitic infections (e.g., malaria), bacterial infections (e.g., anicteric leptospirosis and rickettsial diseases), and other viral infections. F&M syndrome is often described as “influenza-like,” but the usual absence of cough and coryza makes influenza an unlikely confounder except at the earliest stages. Treatment is supportive, but acetylsalicylic acid is generally avoided because of the potential for exacerbated bleeding or Reye syndrome. Complete recovery is the expected outcome for symptomatic patients, although prolonged asthenia and nonspecific symptoms have been described, particularly after

infection with LCMV or DENV-1-4. Nonetheless, it must be reemphasized that this non specific syndrome may be the prodrome for arthritic, neuroinvasive, pulmonary, or VHF syndromes with less favorable outcomes. Efforts to prevent viral infections causing this syndrome are best targeted to vector control, which, however, may be expensive or impossible. Destruction of mosquito breeding sites is generally the most economically and environmentally sound approach. Emerging containment technologies include the release of genetically modified mosquitoes and the spread of Wolbachia bacteria to limit mosquito

multiplication rates. Depending on the vector and its habits, other possible strategies include the use of window screens on dwellings or other barriers (e.g., permethrin-impregnated bed nets), judicious application of arthropod repellents (e.g., N,N-diethyltoluamide [DEET]) to the skin, use of long-sleeved (ideally permethrin-impregnated) clothing, and avoidance of vector habitats, particularly at peak feeding times. Bunyaviricetes F&M syndrome is caused by numerous bunyaviricetes, many of which cause isolated individual infections and usually do not cause epidemics. These viruses include arenavirids (mammarenaviruses), hantavirids (orthohantaviruses), nairovirids (orthonairoviruses), peribunyavirids (orthobunyaviruses), and phenuivirids (bandaviruses and phleboviruses). ARENAVIRIDS Infection with LCMV is the only human mammarenavirus infection resulting predominantly in F&M syndrome. LCMV is transmitted to humans from the common house mouse (*Mus musculus*) by aerosols of excreta or secretions. The virus is maintained in the mouse mainly by vertical transmission from infected dams. Infected mice remain viremic and shed virus for life, with high concentrations of virus in all tissues. Mouse-acquired infections of colonies of pet hamsters also can serve as a link for human acquisition. Patients may have a history of residence in rodent-infested housing or other exposure to rodents. An antibody prevalence of $\approx 5\text{--}10\%$ has been reported among urban adults from Argentina, Germany, and the United States. In addition, laboratory infections among scientists and animal care takers can occur because the virus is widely used in immunology laboratories to study T-lymphocyte function and can silently infect cell cultures and passaged tumor lines. Transmission has occurred via organ transplantation. Lymphocytic choriomeningitis (LCM) differs from the general F&M syndrome in a characteristic gradual onset of the otherwise typical illness. Orchitis, transient alopecia, arthritis, pharyngitis, cough, and maculopapular rash are associated with LCM. An estimated one fourth (or less) of patients experience an initial febrile phase of 3-6 days. After a brief remission, many develop recurrent fever accompanied by meningeal (severe headache, photophobia, nausea and vomiting, and neck stiffness) and/or less common encephalitic signs (altered mental status or level of consciousness, sensorimotor deficits) as part of a ≈ 1 -week CNS phase. Patients with neuroinvasive disease, including patients with clear-cut signs of encephalitis, almost always recover fully. Rarely, disease is complicated by transient hydrocephalus (that may require shunting) and myelitis. During the initial febrile phase, leukopenia and thrombocytopenia are common, and virus can usually be isolated from blood. During the CNS phase, the virus may be found in the CSF, and antibodies are detected in the blood. The pathogenesis of LCM is thought to resemble manifestations resulting from direct intracranial inoculation of the virus into adult mice. The onset of the immune response leads to T-cell-mediated immunopathologic meningitis. During the meningeal phase, CSF monocyte counts range from the hundreds to the low thousands per microliter, and, unusually for a viral meningitis, hypoglycorrhachia is found in one-third of patients. IgM-capture ELISA, immunochemistry, and RT-PCR are used in the diagnosis of lymphocytic choriomeningitis. IgM-capture ELISA of serum and CSF usually yields positive results; RT-PCR assays have been developed for CSF detection. Particular diagnostic challenges arise in

immunosuppressed patients with fulminant infections transmitted by recent organ transplantation: in the absence of typical immune responses, molecular diagnosis via RT-PCR or immunohistochemistry may be required. Infection should be suspected in acutely ill febrile patients with marked leukopenia and thrombocytopenia and meningitis syndromes. In patients with aseptic meningitis, a diagnosis of LCM is suggested by the following: a well-marked febrile prodrome, adult age, occurrence in the autumn, low CSF glucose levels, or CSF monocyte counts of $>1,000/\mu\text{L}$. Throughout a pregnancy, maternal-to-fetal transmission may occur, leading to fetal death (in the first trimester) or to consequent congenital hydrocephalus, microcephaly, and/or chorioretinitis (in the second or third trimesters). Because a mild maternal infection may be unrecognized or unrecalled, specific

antibodies to the virus should be sought in both mother and fetus under suspicious circumstances, particularly in neonatal hydrocephalus testing negative for toxoplasmosis, rubella, cytomegalovirus, herpes simplex, and HIV-1/HIV-2 (TORCH) pathogens.

PERIBUNYAVIRIDS Apeú, Caraparú, Itaquí, Madrid, Marituba, Muru tucú, Nepuyo, Oriboca, Ossa, Restan, and Zungarococha viruses are among the most common causes of arboviral infection in humans entering South American jungles. These viruses cause acute febrile disease and are transmitted by mosquitoes in neotropical forests. Oropouche virus is transmitted in urban settings in Central and South America by biting midges (*Culicoides paraensis*), which often breed to high density in cacao husks and other vegetable detritus found in towns and cities. Explosive epidemics involving thousands of patients with Oropouche virus disease have been reported in Brazil and Peru, with smaller outbreaks in Panama and French Guiana and most recent outbreaks in Cuba and Haiti. Direct human-to-human transmission does not occur. Sloths and nonhuman primates may play a role as vertebrate hosts during maintenance sylvatic cycles. After a 3- to 10-day incubation period, most patients develop typical F&M syndrome with a biphasic evolution (recurrence of symptoms in the second week of illness) and, uncommonly, hemorrhagic manifestations. However, a small percentage of patients develop severe illness with neurologic (meningoencephalitis, Guillain-Barré) or hemorrhagic syndromes that have been associated with fatal outcome. Recently, infection of pregnant women has been associated with spontaneous miscarriage, intrauterine fetal death, and congenital anomalies. Oropouche virus has been detected in umbilical cord blood and fetal tissues in these clinical settings. Serologic detection (IgM or a rise in antibody titer on paired samples) or PCR confirms the diagnosis of acute F&M syndrome; IgM and viral nucleic acid have been detected in the CSF in rare cases of neuroinvasive disease. Postacute sequelae have not been described, though some patients have prolonged asthenia after the acute syndrome. Specific therapeutics or vaccines are not available. **CHAPTER 215** Iquitos virus, a recently discovered reassortant and close relative of Oropouche virus, causes disease that is easily mistaken for Oropouche virus disease; its overall epidemiologic significance remains to be determined.

Arthropod-Borne and Rodent-Borne Virus Infections

PHENUIVIRIDS The genus *Phlebovirus* includes numerous viruses that may cause human infection. Sandfly fever Cyprus virus, sandfly fever Ethiopia virus, sandfly fever Sicilian virus, and sandfly fever Turkey virus (and the encephalitis-causing Chios virus) are genetically and antigenically very closely related. In contrast, sandfly fever Naples virus (SFNV) is only genetically and antigenically distantly related to these viruses. SFNV has not been detected in sandflies, humans, or nonhuman vertebrates since the 1980s and therefore may be extinct, but closely related viruses, such as Granada virus and Toscana virus, continue to circulate. Toscana virus is thus far the only

Phlebovirus transmitted by sandflies that is known to cause central and peripheral nervous system disease, such as encephalitis, meningitis, or polymyelo radiculopathy. Phlebotomus sandflies transmit the virus, probably by biting small mammals and humans. Female sandflies may be infected orally during blood meals and may transmit the virus to progeny when they lay their eggs. This prominent transovarial transmission confounds virus control. Sandfly fever is found in the circum-Mediterranean area, extending to the east through the Balkans into parts of China as well as into Western Asia. Sandflies are found in both rural and urban settings and are known for their short flight ranges and small sizes; the latter enables them to penetrate standard mosquito screens and netting. Epidemics have been described in the wake of natural disasters and wars. After World War II, extensive spraying in parts of Europe to control malaria greatly reduced sandfly populations and transmission of SFNV; the incidence of sandfly fever continues to be low. A common pattern of disease in endemic areas consists of high attack rates among visitors (including military personnel) but little or no disease in the local population, having developed protective immunity after childhood infection. Toscana virus infection is common during the summer among rural residents and vacationers, particularly in

Italy, Spain, and Portugal; several cases have been identified in travelers returning to Germany and Scandinavia. Clinical presentation is typical for F&M syndrome, with onset 3–6 days after a sandfly bite (a papule at the bite site may be observed). Notably, outbreaks of aseptic meningitis (virus can be isolated from the CSF) or meningoencephalitis have been associated with Toscana virus infection.

Coclé and Punta Toro viruses are not directly related to sandfly fever viruses but, like them, are transmitted by sandflies and cause a sandflyfever-like disease. These two viruses are maintained in Latin American and Caribbean tropical forests, respectively, where the vectors rest on tree buttresses. Epidemics have not been reported, but antibody prevalence among inhabitants of villages in endemic areas indicates a cumulative lifetime exposure rate of >50% in the case of Punta Toro virus. Heartland virus is notable as an emerging virus in the eastern, mid western, and southern United States (>60 cases since its first description in 2012), where it causes often-fatal infection among males >50 years of age with comorbidities. Flavivirids The most clinically significant orthoflaviviruses that cause F&M syndrome are DENV-1–4 and Zika virus (ZIKV). In fact, dengue without or with warning signs (“dengue,” historically called “dengue fever”—to be distinguished from severe dengue) is probably the most prevalent arthropod-borne viral disease worldwide, with ≈400 million infections occurring per year, of which ≈100 million (25%) cause clinical illness. Dengue is endemic in >100 countries worldwide, including those in Africa, the Americas, the eastern Mediterranean, Southeastern Asia, and the western Pacific. More than half of the world’s population is considered at risk, although Asia bears 70% of the global burden, with alarming increases over the past decade including, for example, >400,000 cases in 2019 in the Philippines. Year-round transmission of DENV-1–4 occurs between latitudes 25°N and 25°S, but seasonal forays of the viruses into the United States and Europe have been documented. The principal vectors for all four viruses are YF mosquitoes (*Aedes aegypti*). Through increasing spread of mosquitoes throughout the tropics and subtropics and international travel by infected humans, large areas of the world have become vulnerable to the introduction of DENV-1–4. Thus, dengue and severe dengue (see “Viral Hemorrhagic Fever,”) are becoming increasingly common. For instance, conditions favorable to DENV-1–4 transmission via YF mosquitoes exist in Hawaii and the southern United States. The range of a lesser vector of DENV-1–4, the Asian tiger mosquito (*Aedes*

albopictus), now extends from Asia to the continental United States, the Indian Ocean, parts of Europe, and Hawaii. Also anthropophilic, YF mosquitoes typically breed near human habitation, using relatively fresh water in locations such as jars, vases, discarded containers, coconut husks, and old tires. These mosquitoes usually bite during the day. Bursts of dengue and severe dengue cases are to be expected in the southern United States, particularly along the Mexican border, where containers of water may be infested with YF mosquitoes. Airconditioned buildings with screened vents may inhibit transmission of many arboviruses, including DENV-1–4. PART 5 Infectious Diseases Most primary DENV infections are subclinical. After an incubation period of ≈ 4 –7 days, symptomatic patients present with three evolving phases: febrile, critical, and recovery. Although most patients presenting with F&M syndrome do not go through a critical phase, early recognition of the critical phase consistent with severe dengue must be considered in all patients. In most patients, dengue begins with the typical sudden onset of high-grade fever, frontal headache, retroorbital pain, back pain, and severe myalgia. These symptoms and signs gave rise to the colloquial designation of dengue as “break-bone fever.” A transient macular rash is often present at illness onset, and conjunctival redness, pharyngeal erythema, lymphadenopathy, and hepatomegaly may be noted on physical examination. The illness may last a week and include additional symptoms and signs (anorexia, nausea or vomiting, and marked cutaneous hypersensitivity). Near the time of defervescence (days 3–5), a maculopapular rash begins on the trunk and spreads to the extremities and the face. Epistaxis and scattered petechiae are often noted in uncomplicated dengue (without/ with warning signs), and preexisting gastrointestinal lesions may bleed

during the acute illness. A positive tourniquet test—i.e., the detection of 10 or more new petechiae in one square inch of the upper arm after a 5-min blood pressure cuff inflation to midway between systolic and diastolic pressure—may demonstrate microvascular damage, but this finding is more likely to be associated with severe dengue. After defervescence and a brief remission, a subset of patients has recurrence of fever and other signs in a “saddle-back” pattern. Regardless, most patients recover from acute illness by 7–10 days, though convalescence can be prolonged. Laboratory findings of dengue (without/with warning signs) include leukopenia, thrombocytopenia, and, in many cases, modest elevations of serum aspartate aminotransferase (AST) activity without hepatic synthetic dysfunction. The diagnosis is made by antigen-detection ELISA or RT-PCR during the acute phase or by IgM ELISA or paired serology during recovery. Virus is readily isolated from blood in the acute phase if mosquito inoculation or mosquito cell culture is used. Further clinical management and vaccine prevention are discussed in reference to severe dengue. ZIKV is an emerging pathogen that is transmitted to nonhuman primates and humans by *Aedes* mosquitoes. The virus was discovered 1947 in a sentinel rhesus monkey (*Macaca mulatta*) and *Aedes africanus* mosquitoes in the Zika Forest in what was then the British Protectorate of Uganda. Human ZIKV infection was first documented during a YF outbreak in 1954 in Nigeria. Later, ZIKV infections were recognized in Southeastern Asia and Southern Asia. Prior to 2007, only 14 clinically identified cases of Zika virus disease had been reported. In recent years, the number of reported ZIKV infections has increased steadily and rapidly, with large but generally mild disease outbreaks on Yap Island and Micronesia (2007) and in Cambodia (2010), the Philippines (2012), and French Polynesia (2013–2014). ZIKV disease in the Americas was first reported on Easter Island, Chile (2014), and in Brazil (2015). By the end of 2015, an estimated 440,000 to 1.3 million cases had occurred in Brazil. At the end of May 2017, ZIKV infections had been recorded on five continents in 85 countries, including Mexico and the United States. Beginning in 2018, the global activity of ZIKV declined

rather rapidly for unknown reasons. Phylogenetic analysis of all available African ZIKV isolates revealed two geographically overlapping clades (Eastern and Western Africa). A descendant Asian lineage, represented by viruses collected from mosquitoes trapped in homes in Malaysia, was first reported in 1969. All ZIKV isolates causing human cases outside of Africa trace back to this Asian lineage. Human infections are usually asymptomatic or benign and self-resolving and are most commonly misdiagnosed as dengue without/ with warning signs or influenza. Typically, ZIKV disease is characterized by low-grade fever, an itchy maculopapular rash, arthralgia/ myalgia, nonpurulent conjunctivitis, headache, and malaise. Other clinical manifestations include involvement of the gastrointestinal (nausea, vomiting, abdominal pain, and/or diarrhea), genitourinary (hematospermia), and, less commonly, cardiac (myocarditis and/or pericarditis), ocular (uveitis), and auditory (hearing loss) systems. The most concerning complications of ZIKV infection are neurologic syndromes, such as, Guillain-Barré syndrome and congenital fetal microcephaly, which may be associated either with fetal death or serious developmental delay in newborn infants. Other neurologic complications include encephalitis, meningoencephalitis, transverse myelitis, demyelinating polyneuropathies, cerebrovascular ischemia, retinopathies, and neurologic birth defects. Although most human ZIKV infections are acquired after bites by infected female mosquitoes, transmission may also occur perinatally or via breast-feeding, sexual contact with an infected person, transfusion of blood products, or organ transplantation. Infectious ZIKV or ZIKV RNA has been documented in the semen of male patients for up to 69 and 188 days after illness onset, respectively; sexual transmission associated with persistence has been documented up to 41 days after illness onset. Antiviral treatments (curative or preventive) and licensed vaccines against ZIKV are not yet available. Of note, some evidence suggests that prior exposure to ZIKV infection may increase the risk of severe disease syndrome and poor outcomes from DENV infection.

Orthomyxovirids Bourbon virus is emerging as a rare cause of F&M in humans in at least 14 states of the United States (≈ 60 cases since discovery in 2015). Onset is typical, but severe disease progression occurs among older individuals with comorbidities, including multisystem organ (kidney, respiratory, and/or hemodynamic) failure that has been fatal. Sedoreovirids Several orbiviruses (Lebombo, Kemerovo, Orungo, and Tribeč viruses) can cause F&M in humans. Lebombo and Orungo viruses are transmitted by mosquitoes, whereas Kemerovo and Tribeč viruses are transmitted by ticks. Spinareovirids Several coltiviruses (Colorado tick fever, Eyach, and Salmon River viruses) can cause F&M in humans. All are transmitted by ticks. The most significant spinareovirid arthropod-borne disease is Colorado tick fever. Several hundred patients with this disease are reported annually in the United States and Canada. The infection is acquired between March and November through the bite of Rocky Mountain wood ticks (*Dermacentor andersoni*) in mountainous western regions at altitudes of 1200–3000 m. Small mammals serve as amplifying hosts. After a tick exposure (reported by almost all patients) and a mean incubation period of 1–14 days, the most common presentation is F&M, often with headache; rash develops in a minority of patients. Meningoencephalitis is not uncommon, especially in children, and disseminated intravascular coagulation (DIC) with hemorrhagic manifestations, pericarditis, myocarditis, orchitis, and pulmonary disease have also been reported. Leukopenia and thrombocytopenia are noted. The disease usually lasts 7–10 days and is often biphasic. Historically, the most important differential diagnostic considerations have been Rocky Mountain spotted fever (although Colorado tick fever is much more common in Colorado) and tularemia. Notably, seropositivity may be delayed for 10–14 days, limiting the utility of typical serologic testing early in the disease course; molecular RT-PCR

testing may be used in this setting. Also, Colorado tick fever virus replicates for several weeks in erythropoietic cells and can be found in erythrocytes. This feature, detected in erythroid smears stained by immunofluorescence, can be diagnostically helpful and is important during screening of blood donors. ■ ■

ARTHRITIS AND RASH (A&R)

Arthritides are common clinical presentations (or manifestations) of several viral diseases, such as hepatitis B, hepatitis C, parvovirus B19 infection, and rubella, and occasionally accompany infection due to adenovirids, enteroviruses, herpesvirids, mumps virus, or HIV-1/ HIV-2. Arthropod-borne alphaviruses are also common causes of arthritides—usually acute febrile syndromes with joint involvement often accompanied by a maculopapular rash. Rheumatic involvement includes arthralgia with or without typical inflammatory signs, including periarticular redness, swelling (less commonly, joint effusions), and immobility. Most alphavirus infections are less severe and have fewer articular manifestations in children than in adults. In temperate climates, these ailments are summer diseases. The most significant alphavirus causes of arthritides are chikungunya virus disease, Ross River disease, Barmah Forest virus infection, and Sindbis virus infection. ZIKV infections may also be associated with joint manifestations. Less significant but historically notable are viruses that caused isolated cases or epidemics. A large (>2 million cases), albeit isolated, epidemic was caused by o'nyong-nyong virus from 1959 to 1962 (o'nyong-nyong fever). Mayaro virus, Semliki Forest virus, and Una virus caused isolated cases or limited and infrequent outbreaks (30 to several hundred cases per year). Symptoms and signs of infections with these viruses often are similar to those observed with chikungunya virus disease. Two orthobunyaviruses—Gan Gan virus and Trubanaman virus—and the orthoflavivirus Kokobera virus have been associated with single cases of polyarthritic disease. Except for a vaccine to prevent chikungunya virus disease, no specific therapies or licensed vaccines exist. Chikungunya Virus Disease Historically, chikungunya virus (CHIKV) was considered endemic in rural areas of Africa, with intermittent outbreaks occurring in towns and cities of both Africa and Asia.

In 2004, a large epidemic began in the Indian Ocean region (specifically on the islands of Réunion and Mauritius) and was most likely spread by travelers. YF mosquitoes and Asian tiger mosquitoes are the major CHIKV vectors. All regions with established populations of these two vectors have now documented local mosquito-borne transmission, and the virus has now been identified across Africa, Asia, Europe, and the Americas, including in the continental United States, where suitable vector mosquitoes are present in southern states and local transmission has been documented. From December 2013 to June 2023, >3.6 million cases were reported from 50 countries or territories in the Americas.

The disease is more common in adults. After an incubation period of 2–10 days, the abrupt onset of fever (often severe, with a saddle back pattern) and severe arthralgia are accompanied by constitutional symptoms and signs, including chills, abdominal pain, anorexia, conjunctival injection, headache, nausea, and photophobia. Migratory polyarthritis mainly affects the small joints of the ankles, feet, hands, and wrists, but the larger joints may be involved. Rash may appear at the outset or several days into the illness; its development often coincides with defervescence around day 2 or 3 of clinical illness. The rash is most intense on the trunk and limbs and may desquamate. In hospitalized patients with severe acute disease, uncommon but reported manifestations include cardiorespiratory, neurologic, renal, neurologic, and ocular complications; deaths have been reported, typically in the context of large outbreaks. Young children develop less prominent symptoms and signs and are therefore less frequently hospitalized. Children also often

develop a bullous rather than a maculopapular/ petechial rash. Although pregnant women are not at risk of more severe disease, there is a high risk of maternal-fetal transmission, particularly during the intrapartum period, that, in some cases, has led to fetal death. Recovery may require weeks, and a significant portion of middle-aged to older patients develop chronic arthritis or arthralgia syndromes (typically involving the same joints) that may be disabling. The risk of chronic musculoskeletal syndromes is increased in patients with preexisting osteoarthritis or severe acute disease who test positive for the human leukocyte antigen B27 subtype (HLA-B27) and may be associated with cryoglobulins. Although petechiae and epistaxis are occasionally seen, CHIKV should not be considered as a cause of VHF. Laboratory abnormalities may include transient lymphopenia and mild thrombocytopenia, as well as elevated activities of AST and concentrations of C-reactive protein (CRP). Treatment of chikungunya virus disease relies on acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs). For patients with refractory arthritis, glucocorticoids or disease-modifying antirheumatic drugs (DMARDs) may be considered. A live-attenuated vaccine to prevent chikungunya virus disease has been approved by the U.S. Food and Drug Administration (FDA) and is undergoing postmarketing evaluation. Other vaccine and therapeutic candidates in preclinical development may benefit from the designation of CHIKV as the representative pathogen for arthritic alphaviruses. CHAPTER 215 Arthropod-Borne and Rodent-Borne Virus Infections

Ross River Disease and Barmah Forest Virus Infection Ross River virus (RRV) and Barmah Forest virus (BFV) cause diseases that are clinically indistinguishable (hence the previously common disease designation of “epidemic polyarthritides” for both infections). RRV has caused epidemics in Australia, Papua New Guinea, and the South Pacific since the beginning of the 20th century. In 1979 and 1980, the virus swept through the Pacific Islands, causing >500,000 infections. From 1991 to 2011, the virus caused 92,559 infections in rural and suburban areas of Australia. From 2014 to 2015, >10,000 cases were recorded in Australia. RRV is predominantly transmitted by *Aedes nor manensis*, *Aedes vigilax*, and *Culex annulirostris* mosquitoes. Marsupials (e.g., kangaroos, wallabies, and koalas) and rodents are probably the main vertebrate hosts, but infection also occurs in horses and other livestock. BFV infections have been increasingly documented since the early 1990s. For instance, from 1991 to 2011, 21,815 cases were recorded in Australia, and new data indicate that the disease also occurs in Papua New Guinea. BFV is transmitted by both *Aedes* and *Culex* mosquitoes and has been isolated from biting midges. The vertebrate hosts remain to be determined, but serologic studies implicate horses and possums.

Of the human RRV and BFV infections surveyed, 55–75% were asymptomatic; however, clinical illness can be debilitating when it occurs. After a typical incubation period of 3–9 days, patients develop the sudden onset of symmetric joint pain predominantly involving the peripheral extremities. Generally, a nonitchy, diffuse, maculopapular rash (more common in BFV infection) develops coincidentally or follows shortly; but, in some patients, rash can precede joint pain by several days. Constitutional symptoms (e.g., low-grade fever, asthenia, headache, myalgia, and nausea) are not prominent or are absent in many cases. Most patients are incapacitated for considerable periods (6 months or more) by joint involvement that interferes with grasping, sleeping, and walking. Ankle, interphalangeal, knee, metacarpophalangeal, and wrist joints are most often involved, although elbows, shoulders, and toes may also be affected. Periarticular swelling and tenosynovitis are common, and one third of patients have true arthritis (more common in Ross River disease). Myalgia and nuchal stiffness may accompany joint pain. Only half of all patients with arthritis can resume normal activities within 4 weeks, and 10% continue to limit

their activities after 3 months. Occasionally, patients are symptomatic for >1 year but without progressive arthropathy.

In the diagnosis of either infection, clinical laboratory values are normal or variable. Tests for rheumatoid factor and antinuclear anti bodies are negative, and the erythrocyte sedimentation rate is acutely elevated. Joint fluid contains 1000–60,000 monocytes per microliter, and viral antigen can usually be detected in macrophages. Serologic demonstration of rising antibody titers is the cornerstone of diagnosis, though it should be noted that virus-specific IgM antibodies may persist for month to years. Isolation of the virus from blood after mosquito inoculation or growth of the virus in cell culture is possible early in the illness. Because of the great economic impact of annual epidemics in Australia, an inactivated RRV vaccine has been under advanced development; phase 3 trials were completed in 2015 with promising results, but the candidate vaccine has not yet been developed for the market. Analgesics or NSAIDs are used for symptomatic treatment.

PART 5 Infectious Diseases Sindbis Virus Infection Sindbis virus is typically transmitted to birds primarily by infected *Culex* and *Culiseta* mosquitoes that also vector human transmission over a range that includes Africa, Asia, Europe, and Australia. Infections with northern European or southern African variants are particularly likely in rural environments. Although infections may be subclinical, rash and arthralgia typically develop after an incubation period of <1 week. Constitutional clinical signs are not marked, and fever is modest or absent. The rash, which lasts $\approx$ 1 week, begins on the trunk, spreads to the extremities, and evolves from macules to papules that often vesiculate. The arthritis is polyarticular, migratory, and incapacitating, with resolution of the acute phase in a few days. The ankles, elbows, knees, phalangeal joints, wrists, and—to a much lesser extent—proximal and axial joints are involved. Persistence of joint pain and occasionally arthritis may continue for months or even years despite lack of deformities. ■ ■

ENCEPHALITIS The major encephalitis viruses are found in the families Flaviviridae, Peribunyaviridae, Rhabdoviridae, and Togaviridae. However, individual agents of other families, including Dhori virus and Thogoto virus (Orthomyxoviridae) and Banna virus (Sedoreoviridae), have caused isolated cases of encephalitis. Arboviral encephalitides are seasonal diseases, commonly occurring in the warmer months. Their incidence varies markedly with time and place, depending on ecologic factors that determine vector activity and human exposure. The causative viruses differ substantially in terms of the ratio of clinical to subclinical infections, case-fatality rate (CFR), and postacute sequelae. Humans are not considered important amplifiers of these viruses. All the viral encephalitides discussed in this section share a similar pathogenesis. An infected arthropod ingests blood from a human and, through this contact, initiates infection. Initial viremia, thought to originate from the lymphoid system, leads to multifocal entry into the CNS, presumably via infection of olfactory neuroepithelium and subsequent passage through the cribriform plate via infected macrophages

or infection of brain capillary endothelial cells. During the viremic phase, there may be little or no recognizable disease except in tickborne orthoflavivirus encephalitides, which have clearly delineated phases of fever and systemic illness. CNS dysfunction or damage and associated clinical symptoms/signs arise partly from direct neuronal infection and subsequent damage and partly from edema, inflammation, and other indirect effects of the host response. The usual pathologic features of arboviral encephalitides are focal necroses of neurons, inflammatory glial nodules, and perivascular lymphoid cuffing. Involved areas display the “luxury perfusion” phenomenon, with normal or increased total blood flow and low oxygen extraction. The typical patient presents with a prodrome of nonspecific constitutional symptoms and signs, including fever, abdominal pain, sore

throat, and respiratory signs. Headache, meningeal signs, photophobia, and vomiting quickly follow. The severity of human infection widely varies from an absence of symptoms/signs to febrile headache, aseptic meningitis, and full-blown encephalitis. The proportions and severity of these manifestations vary with the infecting virus and with known (e.g., age) and mostly unknown host immunogenetic determinants. Encephalitic involvement of deeper brain structures may be signaled by lethargy, somnolence, and cognitive deficit detected by mental status examination. More severely affected patients are obviously disoriented and may become comatose. Tremors, loss of abdominal reflexes, cranial nerve palsies, hemiparesis, monoparesis, difficulty swallowing, limb-girdle syndrome, and frontal lobe signs are common. Spinal and motor neuron diseases have been documented after WNV and Japanese encephalitis virus infections. Seizures and focal signs may be evident early or may appear during the disease. Some patients present with an abrupt onset of fever, convulsions, and other signs of CNS involvement. Encephalitis usually lasts a few days to several weeks and may be fatal, or recovery may be slow (with weeks or months before the return of maximal recoverable function) or incomplete (with persisting long-term deficits). Difficulty concentrating, fatigability, tremors, and personality changes are common during recovery. The diagnosis of arboviral encephalitides depends on careful history-taking (travel/exposures), physical examination (in particular, of a febrile patient with signs of CNS dysfunction), and virus-specific or serology-specific laboratory testing. Clinicians should (1) consider empirical acyclovir treatment for herpesvirus meningoencephalitis and antibiotic treatment for bacterial meningitis until test results are received; (2) exclude intoxication and metabolic or oncologic causes, including paraneoplastic syndromes, hyperammonemia, liver failure, and anti-N-methyl-D-aspartate (NMDA) receptor encephalitis; and

(3) rule out a brain abscess or a cerebrovascular event. Leptospirosis, neurosyphilis, Lyme disease, cat-scratch disease, opportunistic infections in immunocompromised patients, and more recently described viral encephalitides (e.g., Nipah virus infection), among others, should be considered in the differential diagnosis if epidemiologically relevant. CSF examination usually shows a modest increase in white blood cell (WBC) counts—in the tens or hundreds or perhaps a few thousand. In early phases of disease, a significant proportion of CSF WBCs may be polymorphonuclear leukocytes (PMNs), but monocytes later predominate. CSF glucose concentrations are generally normal. There are exceptions to this pattern of findings. In eastern equine encephalitis, for example, PMNs may predominate during the first 72 h of disease, and hypoglycorrhachia may be detected. In lymphocytic choriomeningitis, lymphocyte counts may be in the thousands, and glucose concentrations may be diminished. A humoral immune response is usually detectable at or near the onset of disease. Both serum (sampled in the acute or convalescent phase) and CSF should be examined for IgM antibodies, and plaque-reduction neutralization testing and/or RT-PCR should be conducted to detect viruses. Viruses generally can not be isolated from blood or CSF, although Japanese encephalitis virus has been recovered from CSF of patients with severe disease. RT-PCR analysis of CSF may yield positive results but cannot exclude diagnoses. Metagenomic/high-throughput sequencing of CSF may support diagnosis of arboviral encephalitides. Viral antigen is present in brain tissue, although its distribution may be focal. Electroencephalography usually shows diffuse abnormalities and thus is not directly helpful.

Experience with medical imaging is still evolving but is generally nonspecific, as most patients do not present with pathognomonic abnormalities; however, imaging may be useful to rule out other suspected causes of disease. Both computed tomography (CT) and magnetic resonance imaging

(MRI) scans may show normal results except for evidence of preexisting conditions or occasional diffuse edema. Notably, images acquired early may be normal and imaging abnormalities may only be detected later as the disease evolves. Although not pathognomonic, characteristic imaging abnormalities for some arboviral encephalitides have been reported, such as with eastern equine encephalitis (focal abnormalities) and severe Japanese encephalitis (hemorrhagic bilateral thalamic abnormalities). Supportive care for severely ill patients may require management of elevated intracranial pressure, the syndrome of inappropriate secretion of antidiuretic hormone, respiratory failure, or seizures. Specific therapies for these viral encephalitides are not available. The only practical preventive measures are vector management and personal protective measures against the arthropod transmitting the virus. Direct human-to-human transmission has not been confirmed. For Japanese or Central European/Far Eastern tick-borne encephalitides, vaccination should be considered in specific circumstances (see relevant sections that follow). Flavivirids The most significant orthoflavivirus encephalitides are Central European/Far Eastern tick-borne encephalitides, Japanese encephalitis, St. Louis encephalitis, and WNV infection. Murray Valley encephalitis and Rocio virus infection resemble Japanese encephalitis but are documented only occasionally in Australia and Brazil. Powassan virus has caused ≈ 400 cases of often-severe disease (CFR $\approx 8\%$), frequently occurring among children in eastern Canada and the United States. Usutu virus causes sporadic human infections (e.g., 105 cases from 2012 to 2021 in Europe), but such infections may be underdiagnosed. Central European/Far Eastern tick-borne encephalitides Tick-borne encephalitis virus (TBEV) is currently subdivided into four groups: the western/European subtype (previously called Central European encephalitis virus), the (Ural-)Siberian subtype (previously called Russian spring-summer encephalitis virus), the Far Eastern subtype, and the louping ill subtype (previously called louping ill virus, or, in Japan, Negishi virus). Small mammals, grouse, deer, and sheep are the vertebrate amplifiers for these viruses, which are transmitted by ticks. The risk of infection varies by geographic area and can be highly localized. Human infections usually follow outdoor activities during which tick bites occur or consumption of raw (unpasteurized) milk or cheese from infected goats or, less commonly, infected cows or sheep. Milk seems to represent the main transmission route for louping ill subtype viruses, which cause disease very rarely. Several thousand infections with TBEV are recorded each year among people of all ages. Tick-borne encephalitis occurs between April and October, with a peak in June and July. Western/European viruses classically caused bimodal disease. After an incubation period of 7–14 days, the illness begins with an influenzalike febrile prodrome (fever, arthralgia/myalgia, headaches, and nausea and/or vomiting) that lasts for 2–4 days and is thought to correlate with viremia. A subsequent remission for several days is followed by the recurrence of fever and the onset of neurologic signs. The neuroinvasive phase (7–10 days before onset of improvement) varies from mild aseptic meningitis (more common among younger patients) to severe (meningo)encephalitis with coma, seizures, tremors, and motor signs. Spinal and medullary involvement can lead to typical limb-girdle paralysis and respiratory paralysis. Most patients with western/European virus infections recover (CFR $\approx 1\text{--}2\%$), and only a minority of patients have significant residual deficits. However, patients with (Ural-)Siberian virus infections have worse outcomes (CFR $\approx 7\text{--}8\%$) and are more likely to experience prolonged infections and develop chronic disability. Infections with Far Eastern viruses generally run a more abrupt and severe course. The encephalitic syndrome caused by these viruses

sometimes begins without a remission from the fever-myalgia phase and has more severe manifestations than the western/European syndrome. CFR is high ($\approx 20\text{--}40\%$), and major

sequelae—most notably, lower motor neuron paralyses of the proximal muscles of the extremities, trunk, and neck—are common, developing in approximately half of patients. Thrombocytopenia may occur during the initial febrile illness, resembling the early hemorrhagic phase of some other tick-borne orthoflavivirus infections, such as Kyasanur Forest disease. In the early stage of the illness, virus may be detected by PCR or isolated from the blood; however, after the onset of CNS manifestations, virus cannot typically be detected in or isolated from the CSF, and diagnosis requires detection of IgM antibodies in serum and/or CSF.

Diagnosis of Central European/Far Eastern tick-borne encephalitis primarily relies on serology and detection of viral genomes by RT-PCR. There is no specific therapy for infection. However, effective alum-adjuvanted, formalin-inactivated virus vaccines (FSMEIMMUN and Encepur) are produced in Austria, Germany, and Russia in chicken embryo cells. Two doses of the Austrian vaccine separated by an interval of 1–3 months appear to be effective in the field, though antibody responses are similar when vaccine doses are given 2 weeks apart. Because rare cases of postvaccination Guillain-Barré syndrome have been reported, vaccination should be reserved for people likely to experience rural exposure in an endemic area during the season of transmission. Cross-neutralization for the western/European and Far Eastern variants has been established, but there are no published field studies on cross-protection among formalin-inactivated vaccines. Because up to 4% of ticks in endemic areas may be infected, the use of immunoglobulin prophylaxis of Central European/Far Eastern tickborne encephalitis has increased in some regions. Prompt administration of high-titer-specific immunoglobulin is routine in some areas (e.g., Russia) but has been discontinued in many European countries because of concerns for antibody-mediated enhancement of infections and/or disease.

CHAPTER 215 JAPANESE ENCEPHALITIS

Japanese encephalitis is the most significant viral encephalitis in Asia. Each year, ≈68,000 cases and ≈13,600–20,400 deaths are reported. Japanese encephalitis virus is found throughout Asia—including in the Russian Far East, Japan, China, India, Pakistan, and Southeastern Asia—and causes occasional epidemics on western Pacific Islands. The virus has previously been considered endemic in Australia's Torres Strait Islands; from 2021 to 2022, 45 cases causing seven deaths were identified across a broad region of eastern and southern Australia. The virus is particularly common in areas where irrigated rice fields attract the natural avian vertebrate hosts and provide abundant breeding sites for *Culex tritaeniorhynchus* mosquitoes, which transmit the virus to humans. Amplification by pigs, which subsequently abort pregnancies, and horses, which develop encephalitis, may be significant, as well. Vaccination of domestic pigs and horses may reduce the transmission of the virus. After an incubation period of 5–15 days, clinical signs of Japanese encephalitis range from nonspecific febrile illness (nausea, vomiting, diarrhea, and/or cough) to aseptic meningitis, meningoencephalitis, acute flaccid paralysis, and severe encephalitis. Common findings are cerebellar signs, cranial nerve palsies, and cognitive and speech impairments. A Parkinsonian presentation and seizures are typical in severe cases. Patients may present with neuropsychiatric manifestations, including abnormal behavior and acute psychosis. MRI detection of thalamic abnormalities is specific but insensitive. CFR in hospitalized patients is high (≈20–30%) and long-term neurologic dysfunction and disability are common in survivors. However, most long-term residents of endemic areas eventually seroconvert after natural environmental exposures and develop protective immunity. Effective vaccines are available and indicated for naïve individuals who are relocating or traveling frequently or over extended periods to endemic rural areas. Usually, two intramuscular doses of the vaccine are given 28 days apart, with the second dose administered at least 1 week prior to travel.

Arthropod-Borne and Rodent-Borne Virus

Infections

ST. LOUIS ENCEPHALITIS St. Louis encephalitis virus is transmitted among birds by mosquitoes. This virus causes a low-level endemic infection among rural residents of the central and western United States,

where *Culex tarsalis* mosquitoes serve as vectors. Urban mosquitoes (*Culex pipiens* and *Culex quinquefasciatus*) have been responsible for epidemics, resulting in hundreds or even thousands of cases in cities of the central and eastern United States. Most cases occur in June through October in the United States, but sporadic cases of the disease have been noted throughout the year in Latin/Central America and the Caribbean. The urban mosquitoes breed in accumulations of stagnant water and sewage with high organic content. The elimination of open sewers and trash-filled drainage systems is expensive and may not be possible. However, installation of screens on windows and vents of houses and implementation of personal protective measures may be effective in preventing infection. Mosquitoes are most active outdoors at dusk; bites can be avoided by modifying activities and using repellents.

Most St. Louis encephalitis virus infections are subclinical; susceptibility to severe disease increases with age. Infections that result in aseptic meningitis or mild encephalitis are concentrated among children and young adults, whereas severe and/or fatal cases primarily affect the elderly. Infection rates are similar in all age groups; a pathophysiologic explanation for higher risk of severe disease in older individuals is unclear. After an incubation period of 4–21 days, patients typically present with a nonspecific prodrome (fever, malaise, myalgia, and/or headache), followed by rapid-onset CNS manifestations with neurologic abnormalities that commonly include nuchal rigidity, hypotonia, hyperreflexia, myoclonus, and tremors. Severe cases can include cranial nerve palsies, hemiparesis, and seizures. Of interest, during and after the prodrome, patients often report dysuria and may have viral antigenuria and pyuria. Overall CFR is $\approx 7\%$ but may be increased up to $\approx 20\%$ among patients >60 years of age. Recovery is slow, and emotional lability, difficulty concentrating, memory issues, asthenia, and tremors are commonly prolonged in older convalescent patients. The CSF of patients with St. Louis encephalitis usually contains tens to hundreds of WBCs, with a lymphocytic predominance and a left shift. The CSF glucose concentration is normal in these patients.

PART 5 Infectious Diseases WEST NILE VIRUS INFECTION

WNV is now the primary cause of arboviral encephalitis in the United States. From 1999 to 2022, 28,684 cases of neuroinvasive disease (e.g., meningitis, encephalitis, and acute flaccid paralysis), with 2641 deaths, and 26,891 cases of nonneuroinvasive infection, with 135 deaths, were reported. WNV was initially described as being transmitted among wild birds by *Culex* mosquitoes in Africa, Asia, and southern Europe. In addition, the virus has been implicated in severe and fatal hepatic necrosis in Africa. WNV was introduced into New York City via diseased birds in 1999 and subsequently spread to other areas of the northeastern United States, causing die-offs among crows, exotic zoo birds, and other birds. The virus has continued to spread and is now found in all states (of the United States) as well as in Canada, Mexico, South America, and the Caribbean islands. *C. pipiens* mosquitoes remain the major vectors in the northeastern United States, but mosquitoes of several other *Culex* species and Asian tiger mosquitoes are also involved. Jays compete with crows and other corvids as amplifiers elsewhere in the United States. The majority of WNV infections are subclinical. After an incubation period of 3–14 days, 20% of those infected develop typical F&M syndrome (without CNS involvement); $<1\%$ develop aseptic meningitis and severe encephalitis, particularly among the elderly. The febrile syndrome associated with WNV

infection is notable for the frequent—rather than occasional—appearance of a maculopapular rash concentrated on the trunk (especially in children) and the development of lymphadenopathy. Back pain, fatigue, headache, myalgia, retroorbital pain, sore throat, nausea and vomiting, and arthralgia (but not arthritis) are common symptoms. Most patients fully recover, though asthenia may persist for several weeks. Patients who develop neuroinvasive disease typically have meningitis, encephalitis, or acute flaccid paralysis syndromes, often with some overlap. The risk of encephalitis, neurologic sequelae, and death is increased in male, elderly, diabetic, and hypertensive patients and in patients with previous CNS disease, but the pathophysiologic determinants of such a wide spectrum of disease phenotype and severity have otherwise been unexplained.

Host genetic risk factors for neuroinvasive disease and death may include chemokine receptor CCR5 deficiency. Recent identification of a high prevalence ($\approx 35\%$) of preexisting autoantibodies against type I interferons in patients with encephalitis (vs patients with subclinical WNV infection, in whom the prevalence approximated the general population) suggests this predisposition may underlie 40% of cases of WNV encephalitis. In addition to the more severe motor and cognitive sequelae, milder neurologic findings may include cranial nerve palsies, tremor, slight abnormalities in motor skills, and loss of executive functions. Given the burden of disease, intense clinical interest, and widely available diagnostics, more unusual features are increasingly described (including chorioretinitis, myocarditis, myositis and rhabdomyolysis, orchitis, flaccid paralysis with histologic lesions resembling poliomyelitis, and initial presentation with fever and focal neurologic deficits in the absence of diffuse encephalitis). Immunosuppressed patients may have fulminant courses or may develop persistent CNS infection. Postacute neurologic sequelae are common, especially in patients with severe neuroinvasive disease syndromes, and thus far have persisted in some patients for >5 years. Virus transmission through both transplantation and blood transfusion has necessitated screening of blood and organ donors by nucleic acid-based tests. A low but non-zero risk of maternal-to-fetal/neonatal transmission has been reported. Diagnosis rests upon detection of IgM antibodies in serum or CSF. In patients with potential prior exposures to serocross-reactive flaviviruses, plaque-reduction neutralization testing for specific neutralizing antibodies or molecular testing (PCR) may aid in specific diagnosis. Treatment is supportive only, and ventilatory support may be required for severe neuroinvasive disease. Although an equine vaccine is available, prevention of WNV infection in humans relies on avoidance of mosquito bites, vector control, and safe handling of potentially infected carcasses.

Peribunyavirids • CALIFORNIA ENCEPHALITIS California encephalitis virus has been implicated in only a very few cases of encephalitis (California encephalitis *sensu stricto*), whereas its close relative, La Crosse virus (LACV), is the major cause of this disease (historically ≈ 80 – 100 cases per year in the United States, although prevalence has been lower in recent years). La Crosse encephalitis is most reported in the upper midwestern United States but is also found in other areas of the central and southeastern parts of the country, such as West Virginia, Tennessee, North Carolina, and Georgia. Inkoo, Jamestown Canyon, Lumbo, snowshoe hare, and *Ťahyňa* viruses are close relatives of LACV that also cause human disease (California encephalitis *sensu lato*, including La Crosse encephalitis). Transovarial infection is a strong component of transmission of these viruses in *Aedes* and *Ochlerotatus* mosquitoes. The vector of LACV is the *Ochlerotatus triseriatus* mosquito. These mosquitoes are infected by transovarial transmission, venereal transmission, and feeding on viremic chipmunks and other mammals. *O. triseriatus* mosquitoes breed in standing water in locations such as tree holes and abandoned tires; they bite during daylight hours. Risk factors for

human cases include recreation in forested areas, residence at a forest's edge, and nearby standing water. Intensive environmental modification based on these findings has reduced the incidence of disease in a highly endemic area in the midwestern United States. Most humans are infected from July through September. Asian tiger mosquitoes efficiently transmit LACV to mice and have transmitted it transovarially in the laboratory. This aggressive anthropophilic mosquito has the capacity to urbanize, and its possible transmission of virus to humans is of concern. The prevalence of antibody to LACV in humans is 20% or higher in endemic areas, indicating that infection is common but most often asymptomatic or subclinical. Neuroinvasive disease after LACV infection varies from aseptic meningitis accompanied by confusion to severe and occasionally fatal encephalitis (CFR <0.5%). CNS disease has been recognized primarily in children <15 years of age. After an incubation period of $\approx 3\text{--}7$ days, a usual nonspecific febrile prodrome is followed by the sudden onset of CNS manifestations, including headache and lethargy, often with nausea, vomiting, convulsions (in half of patients), and coma (in

one-third of patients). Focal seizures, hemiparesis, tremor, aphasia, chorea, Babinski signs, and other evidence of significant neurologic dysfunction are common during acute neuroinvasive disease. Most patients recover completely, but $\approx 10\%$ develop postacute sequelae, including recurrent seizures, focal neurologic deficits, and cognitive and behavioral problems that may affect learning abilities. The WBC count is commonly elevated and left-shifted in patients with LACV infection, sometimes reaching $20,000/\mu\text{L}$. CSF leukocyte counts are typically $30\text{--}500/\mu\text{L}$, usually with a monocyte predominance (although 25–90% of cells are PMNs in some patients). The blood protein concentration is normal or slightly increased, and the glucose concentration is normal. Specific virologic diagnosis based on IgM capture assays of serum and CSF is efficient. The only human anatomic site from which virus has been isolated is the brain. Treatment is supportive over a 1- to 2-week acute phase and focused on the prevention and management of status epilepticus, cerebral edema, and the syndrome of inappropriate secretion of antidiuretic hormone. A phase 2B clinical trial of IV ribavirin in children with LACV infection was discontinued during dose escalation because of adverse effects. Jamestown Canyon virus has been implicated in several cases of encephalitis in adults ($\approx 10\text{--}40$ cases per year since 2011), usually with a significant respiratory illness at onset. Human infection with this virus has been documented in Northern America (in the United States in at least 10 states and in Canada), where the vector mosquito (*Aedes stimulans*) feeds on its main host, the white-tailed deer (*Odocoileus virginianus*). Tšahyňa virus can be found in Africa, China, Central Europe, and Russia. The virus is a prominent cause of undifferentiated febrile disease but can also cause pharyngitis, pulmonary syndromes, aseptic meningitis, or meningoencephalitis.

Rhabdovirids • CHANDIPURA VIRUS INFECTION Chandipura virus is an emerging and increasingly significant human virus in India, where it is transmitted among hedgehogs by mosquitoes and sandflies. In humans, the disease begins as a rapid-onset influenza-like illness, with fever, headache, abdominal pain, nausea, and vomiting. These manifestations are followed by infection-related or autoimmune-mediated encephalitis that may cause altered mental status and seizures. Notably, neither the virus nor abnormal cells are detected in CSF; the brain has not been examined histopathologically, but limited cerebral imaging data query whether CNS disease is more likely related to cerebrovascular events (vasospasm/vasculitis) than to infectious encephalitis. Several hundred cases of Chandipura virus infection are recorded in India every year in children, with a CFR $\approx 45\text{--}80\%$. Infections with other arthropod-borne rhabdovirids (Isfahan, Piry, vesicular stomatitis Indiana, and vesicular stomatitis New Jersey viruses) may imitate the early febrile stage of Chandipura virus infection.

Togavirids • EASTERN EQUINE ENCEPHALITIS This

disease is encountered primarily in swampy foci along the east coast and, more recently and specifically, the southeastern coast of the United States, with a few inland foci as far removed from the coastlines as Michigan, Wisconsin, Arkansas, and Montana ($\approx 4\text{--}40$ cases/year). Humans are mostly infected from June through October. During this period, *Culiseta* mosquitoes infect birds and virus spills over into other vectors, such as *Aedes sollicitans* or *Aedes vexans* mosquitoes, which are more likely to feed on mammals. Especially with spread to the southeastern coast, there is concern over the amplifying role of introduced Asian tiger mosquitoes, which have been found to be infected with eastern equine encephalitis virus and are an effective experimental vector in the laboratory. Horses are a common target for the virus. Contact with unvaccinated horses may be associated with human disease, but horses probably do not play a significant role in amplification of the virus. Most infections are subclinical. After an incubation period of $\approx 5\text{--}10$ days, symptomatic individuals develop a nonspecific febrile prodrome, after which a small proportion (2% of adults, 6% of children) develop sudden and rapidly progressive neuroinvasive disease with (meningo)encephalitis syndromes associated with focal neurological deficits, seizures, profoundly altered mental status, and coma.

Neuroinvasive disease is highly fatal (CFR $\geq 30\text{--}50\%$) and $>50\%$ survivors have residual postacute sequelae. Acute PMN CSF pleocytosis, often occurring during the first 1–3 days of disease, is another indication of severity, and it parallels peripheral leukocytosis with a left shift. Extensive necrotic lesions and PMN infiltrates are found at post mortem examination of the brain. Specific treatment is not available, although the therapeutic role of IV immunoglobulin (IVIG) remains under query. A formalin-inactivated vaccine has been used to protect laboratory workers but is not generally available or applicable.

VENEZUELAN EQUINE ENCEPHALITIS VEEV is separated into epizootic viruses (subtypes IA/B and IC) and enzootic viruses (subtypes ID, IE, and IF). Closely related enzootic viruses are Everglades virus, Mucambo virus, and Tonate virus. Enzootic viruses are found primarily in humid tropical-forest habitats and are maintained between culicoid mosquitoes and rodents. These viruses cause acute febrile syndromes in humans but are not pathogenic for horses and do not cause epizootics. Everglades virus has caused sporadic cases of encephalitis in humans in Florida. Extrapolation from the rate of genetic change suggests that Everglades virus may have been introduced into Florida <200 years ago. Everglades virus is most closely related to the ID-subtype viruses that appear to have given evolutionary rise to the epizootic variants active in South America. Epizootic viruses have an unknown natural cycle but periodically cause extensive epizootics/epidemics in equids and humans in the Americas. These epizootics/epidemics are the result of high-level viremia in horses and mules, which transmit the infection to several types of mosquitoes, which in turn infect humans. Humans also have high-level viremia, but their role in virus transmission is unclear. Relatively restricted epizootics of Venezuelan equine encephalitis (VEE) occurred repeatedly in South America in <10 -year intervals from the 1930s until 1969, when a massive epizootic, including tens of thousands of equine and human infections, spread throughout Central America and Mexico, reaching southern Texas in 1971. Genetic sequencing suggested that the virus from that outbreak originated from residual “un-inactivated” IA/B-subtype virus in veterinary vaccines. The outbreak was terminated in Texas with a live-attenuated vaccine (TC-83), originally developed for human use by the U.S. Army; the epizootic virus was then used for further production of inactivated veterinary vaccines. No further major outbreaks occurred until 1995 and 1996, when large epizootics of VEE occurred in Colombia/Venezuela and Mexico, respectively. Of the $>85,000$

clinical cases, 4% (more children than adults) had neurologic symptoms/signs, resulting in 300 deaths. The viruses involved in these epizootics, as well as previously epizootic IC viruses, are close phylogenetic relatives of known enzootic ID viruses. This finding suggests that active virus evolution and selection of epizootic viruses are underway in South America. CHAPTER 215

Arthropod-Borne and Rodent-Borne Virus Infections

During epizootics, extensive human infection is typical, with clinical disease occurring in 10–60% of infected individuals. Most infections result in notable acute febrile syndromes, whereas relatively few (5–15%) result in neurologic disease. A low rate of CNS invasion is supported by the absence of encephalitis after the many infections (from exposure to aerosols) that have occurred in the laboratory setting. Small-molecule and monoclonal antibody-based antiviral therapeutics are in preclinical development but not yet approved. These (and vaccine; see below) efforts may benefit from the designation of VEEV as a representative pathogen for the encephalitic alphaviruses. The prevention of epizootic VEE depends on vaccination of horses with the attenuated TC-83 vaccine or with an inactivated vaccine prepared from that variant. Enzootic viruses are genetically and antigenically different from epizootic viruses, and protection against the former with vaccines prepared from the latter is relatively ineffective. Humans can be protected by immunization with similar vaccines prepared from Everglades virus, Mucambo virus, and VEEV, but the use of the vaccines is restricted to laboratory personnel because of reactogenicity, possible fetal pathogenicity, and limited availability. WESTERN EQUINE ENCEPHALITIS The primary maintenance cycle of western equine encephalitis virus in the western United States and Canada involves *Aedes*, *C. tarsalis*, and *Culiseta* mosquitoes and

birds (principally sparrows and finches). Equids and humans become infected, and both suffer encephalitis without amplifying the virus. St. Louis encephalitis virus is transmitted via a similar cycle in the same regions harboring western equine encephalitis virus; disease caused by the former occurs about a month earlier than that caused by the latter (July through October). Large epidemics of western equine encephalitis occurred in the western and central United States and Canada from the 1930s through the 1950s but have been uncommon since then. From 1964 through 2010, only 640 cases were reported in the United States. This decline in incidence may reflect, in part, the integrated approach to mosquito management employed in irrigation projects and, in part, the increasing use of agricultural pesticides. The decreased incidence of western equine encephalitis almost certainly reflects the increased tendency for humans to be indoors behind closed or screened windows at dusk—the peak biting period of the major vector.

Most infections are subclinical or mild. After an incubation period of $\approx$ 5–10 days, most symptomatic patients develop a nonspecific febrile prodrome with spontaneous recovery. The small minority of patients who develop neuroinvasive disease present with a typical viral meningoencephalitis syndrome (headache, vomiting, neck and back stiffness, and/or altered mental status). The frequency and morbidity of severe neurologic disease are increased among infants and very young children; in addition, CFR is high in this and in very elderly populations (3–7% overall). One-third of individuals who have convulsions during the acute illness have subsequent seizure activity. Infants <1 year of age—particularly those in the first months of life—are at serious risk of persistent motor and cognitive deficits. Of those 5–9 years of age, twice as many males as females develop clinical encephalitis; the contribution of biological versus behavioral factors (increased outdoor exposure to the vector) to incidence differences is uncertain. Specific treatment is not available. A formalin-inactivated vaccine has been used to protect laboratory workers but is not generally available.

PART 5 Infectious Diseases ■ ■ PULMONARY DISEASE Hantavirus pulmonary syndrome (HPS) was first described in 1993, but retrospective identification of cases by immunohistochemistry (1978) and serology (1959) supports the idea that HPS is a recently discovered disease rather than a truly new one. The causative agents are orthohantaviruses of a distinct phylogenetic lineage that is associated with the cricetid rodent subfamily Sigmodontinae. Sin Nombre virus, which chronically infects western deermice (*Peromyscus sonoriensis*), is the most important agent of HPS in the United States. Several other related viruses (Anajatuba, Andes, Araraquara, Araucária, bayou, Bermejo, Black Creek Canal, Blue River, Caño Delgadito, Castelo dos Sonhos, Catacamas, Choclo, Juquitiba, Laguna Negra, Lechiguanas, Maciel, Maripa, Monongahela, New York, Orán, Paranoá, Pergamino, Rio Mamoré, and Tunari viruses) cause the disease in Northern and South America. Andes virus is unusual in that it has been implicated in human-to-human transmission. HPS particularly affects rural residents living in dwellings permeable to rodent entry or workers in occupations that risk rodent exposure. Each type of rodent has particular habits; in the case of deermice, these behaviors include living in and around human habitation. After a typical incubation period of 2–3 weeks, HPS begins with a nonspecific prodrome of ≈ 3 –4 days (range 1–11 days) comprising fever, malaise, myalgia, and—in many cases—gastrointestinal disturbances (e.g., abdominal pain, nausea, and vomiting). Dizziness is common, and vertigo is occasional. Severe prodromal symptoms/signs may bring some patients to medical attention, but most cases are recognized as the pulmonary phase begins, with typical signs of slightly lowered blood pressure, tachycardia, tachypnea, mild hypoxemia, thrombocytopenia, and early radiographic signs of pulmonary edema. Physical findings in the chest are often surprisingly scant. The conjunctival and cutaneous signs of vascular involvement seen in orthohantavirus VHFs (see “Viral Hemorrhagic Fever,” below) are uncommon but may be more frequent with HPS outside Northern America. Early recognition and triage of patients at this stage are critical because, shortly after onset, hypotension and noncardiogenic edema progress rapidly to hypoxemic respiratory failure.

The differential diagnosis of HPS includes undifferentiated sepsis syndromes and severe acute respiratory infections and should be informed by local epidemiology. Considerations include severe atypical pneumonia (*Legionella*, *Mycoplasma*, and Q fever), influenza, rickettsial disease, meningococcemia, septicemic plague, tularemia, leptospirosis, dengue, and YF. Fever with severe abdominal pain and tenderness merits consideration of the causes of a “surgical” abdomen and pyelonephritis. A specific diagnosis is best made when antigen-specific IgM, present in most symptomatic patients, is detected in acute-phase serum. Sin Nombre virus antigen testing detects antibodies to the related HPS-causing orthohantaviruses. Occasionally, heterotypic viruses will cross-react (only to the IgG ELISA), but the very low seroprevalence of these viruses in normal populations queries this laboratory finding. Orthohantaviral RNA is cleared quickly, although RT-PCR may be useful to detect virus in tissue biopsies, thrombus, or at autopsy. RT-PCR and DNA sequencing may be needed in specifically identifying the infecting virus in areas outside the home range of deermice, in atypical cases, and for molecular epidemiology. During the prodrome, differentiating HPS from other causes is difficult, but diagnostically helpful features emerge at or soon after initial presentation. A new dry cough, usually absent at disease onset, may signal the pulmonary phase. Early in disease, interstitial edema may be evident radiographically; with progression, bilateral alveolar infiltrates in a central pattern and with a normal-sized heart signal the development of noncardiogenic edema. Pleural effusions are often seen. Coincident thrombocytopenia, circulating atypical lymphocytes (lymphoblasts), and a left shift (often with marked leukocytosis) are considered almost diagnostic in experienced centers. Hemoconcentration

tration, hypoalbuminemia, and proteinuria also aid in diagnosis. Although thrombocytopenia and partial thromboplastin time (PTT) prolongation are usually found, clinical evidence of coagulopathy or laboratory indications of DIC are found in only a minority of severely ill patients. Patients with severe illness also have acidosis and elevated serum lactate concentrations. Oliguria and mildly increased values in serum creatinine concentrations are common, but patients with severe HPS often have markedly decreased glomerular filtration. Some American orthohantaviruses other than Sin Nombre virus (e.g., Andes virus) have been associated with more severe renal dysfunction, but few such cases have been studied. After recognition, early triage-based monitoring and management of hemodynamic, respiratory, and renal dysfunction during the first few hours are critical to improved outcomes. During this period, hypotension and hemoconcentration suggest intravascular volume depletion; however, aggressive IV fluid therapy is not advised in the setting of widespread capillary leak, frequently depressed cardiac output, and oliguria. Mild hypoxemia may be managed by oxygen administration alone, but mechanical ventilatory support of respiratory failure and shock is often needed. Pulmonary artery catheterization enables pulmonary capillary wedge pressure-guided inotropic and vasopressor support and cautious intravascular volume replacement. The most critically ill patients with a low cardiac index or refractory hypoxemia despite this support may benefit from extracorporeal membrane oxygenation, ideally before the onset of shock. CFR is high ($\approx 30\text{--}40\%$), even with appropriate management, but most patients surviving the first 48 h of hospitalization are extubated and discharged within a few days with no apparent long-term sequelae. Although ribavirin inhibits orthohantaviruses in vitro and has been effectively used in patients with HFRS due to Hantaan virus, an underpowered randomized clinical trial of ribavirin for HPS failed to show efficacy. Preclinical development of novel small-molecule- and monoclonal antibody-based therapeutics for HPS is ongoing. ■ ■ VIRAL

HEMORRHAGIC FEVER VHF syndrome encompasses a small number of acute viral infections that cause severe disease and multisystem organ dysfunction sharing a mutual pathophysiologic disruption to vascular function, stability, and integrity. In practice, viral infections classified as VHFs vary widely across a spectrum of clinical phenotypes and severity; indeed, hemorrhagic manifestations are typically not the most prominent nor severe

features of disease. Nonetheless, the VHF designation largely captures a useful common theme: hemorrhagic manifestations are a sign of widespread vascular dysfunction or damage that plays a central role in local, organ-specific, and systemic expression of disease. Direct or indirect damage to the microvasculature leads to increased permeability and (particularly when platelet function is decreased) to actual disruption and local hemorrhage most evident in the skin and mucous membranes. Cutaneous flushing and conjunctival suffusion are examples of common observable abnormalities due to dysfunction of local circulation. Similarly, affected microvasculature may be fragile to trauma and external forces, such as the application of a blood pressure cuff causing a positive tourniquet sign. Although overt hemorrhage occurs infrequently, subtle local hemorrhagic signs (e.g., bleeding of the gums or at IV catheter sites) are often present on careful examination. Circulatory dysfunction may also contribute to specific organ dysfunction or damage that may be particularly prominent in some VHF cases; for instance, the kidneys are primary targets in HFRS, and the liver is a primary target in YF. Regarding severe systemic manifestations, hypotension and shock are not usually a direct result of life-threatening blood loss but rather an indication of generalized circulatory dysfunction contributing to hemodynamic instability. Despite this common theme, the pathogenesis of VHF is poorly understood and varies among the viruses regularly implicated in the syndrome. In some viral infections, direct damage to the vascular system or even

to parenchymal cells of target organs is an important factor; in other viral infections, soluble mediators are thought to play a major role in the development of hemorrhage or hemodynamic derangement. Symptom initiation in the acute phase in most VHF syndromes is associated with ongoing virus replication and viremia, typically with nonspecific fever and arthralgia/myalgia, usually of abrupt onset (mammarenavirus infections are exceptions, as they often develop gradually). Within a few days, patients present for medical attention with severe fatigue and prostration that is often accompanied by anorexia, severe headache, sore throat, chest pain, gastrointestinal symptoms (abdominal pain, nausea, vomiting, and/or diarrhea), dizziness, hyperesthesia, and photophobia. Initial examination often reveals only an acutely ill febrile patient with asthenia, conjunctival suffusion, tenderness to palpation of muscles or abdomen, and borderline hypotension or postural hypotension (perhaps with tachycardia). Petechiae (often best visualized in the axillae), flushing of the head and thorax, periorbital edema, and proteinuria are common. AST activities are usually elevated at presentation or within a day or two thereafter. Hemoconcentration from vascular leakage is usually evident and is most marked in HFRS and in severe dengue. Seriously ill patients develop more severe clinical signs, including initial organ dysfunction typical of the causative virus; continued high viral loads coupled with ineffective and dysregulated immune responses lead to progressive multiorgan dysfunction characterized by shock, acute kidney injury, CNS injury (encephalopathy, coma, seizures), severe hemorrhagic manifestations, and death. One of the major diagnostic clues is travel to an endemic or active outbreak area within the incubation period for a given syndrome. Except in infections with Seoul virus, DENV-1-4, and yellow fever virus (YFV), which have urban hosts/vectors, rural travel exposures are more commonly associated with a VHF. In addition, several travel-associated diseases—falciparum malaria, shigellosis, typhoid fever, leptospirosis, relapsing fever, and rickettsial diseases—should also be considered in the differential diagnosis, as they are treatable despite being potentially fatal. Early recognition of VHF is crucial for timely initiation of appropriate supportive clinical care and virus-specific therapy (if available). Key components of clinical care include prompt isolation and hospitalization even in absence of clinical signs; rapid triage and ongoing monitoring of vital signs; the prevention and management of dehydration, hypovolemia, and hemodynamic instability (with closely monitored IV fluids and vasopressors); the prevention and management of acute kidney injury and electrolyte abnormalities; empiric or specific treatment of common concurrent or secondary bacterial or parasitic infections; replacement of blood products (packed red blood cells, clotting factors,

and platelets as indicated); and the usual precautionary measures used in the treatment of patients with hemorrhagic diatheses. DIC should be treated only with clear laboratory evidence and if laboratory monitoring of therapy is feasible; there is no proven benefit of such therapy. Of note, VHF patients are commonly hypovolemic from insensible fluid and gastrointestinal losses and require intravascular fluids to maintain blood pressure and glomerular filtration; however, VHF patients may also have decreased cardiac output, capillary leak syndromes, and oliguria that require judicious fluid management and inotropic/vasopressor support. Specific therapy is available for several of the VHFs. Strict barrier nursing and other precautions against infection of medical staff and visitors are indicated when VHFs are encountered, except when the illness is due to DENV-1-4, orthohantaviruses, RVFV, or YFV.

Novel VHF-causing agents are still being discovered. Some of these viruses have recently emerged and continue to cause disease (e.g., severe fever with thrombocytopenia syndrome virus [SFTSV]).

Others have caused isolated VHF-like cases without recurrence, including viruses for whom Koch's postulates are yet to be fulfilled (e.g., Bas-Congo virus). Bunyaviricetes The most significant VHF-causing bunyaviricetes are arenavirids (Junín, Lassa, and Machupo viruses), hantavirids, and reovirids (Crimean-Congo hemorrhagic fever virus), and phenuivirids (RVFV and SFTSV). Other bunyaviricetes—e.g., the Garissa variant of Ngari virus and Ilesha virus (both orthobunyaviruses) or Chapare, Guanarito, Lujo, and Sabiá viruses (all mammarenaviruses)—have caused sporadic VHF outbreaks. ARGENTINIAN AND BOLIVIAN HEMORRHAGIC FEVERS These severe diseases (with CFR reaching >50% in individual outbreaks) are caused by Junín virus and Machupo virus, respectively. Clinical presentations of both diseases are similar, but epidemiology differs because of the distribution and behavior of the distinct rodent reservoirs. Argentinian hemorrhagic fever has been recorded only in rural areas of Argentina, whereas Bolivian hemorrhagic fever seems to be confined to rural Bolivia. Unusually for arboviruses, infection with the causative agents almost always results in disease, and all ages and both sexes are affected. Person-to-person or nosocomial transmission is rare but has occurred. The transmission of Junín virus from male survivors to their partners suggests the need to avoid intimate contact in early convalescence (and counseling in this regard for all patients with mammarenavirus hemorrhagic fevers). In contrast to LF (see below), thrombocytopenia—often marked—is the rule, mucosal hemorrhage is common, and CNS dysfunction (e.g., marked confusion, tremors of the upper extremities and tongue, and cerebellar signs) is much more common in disease caused by Junín virus and Machupo virus (20–30%). Some cases follow a predominantly neurologic course, with a poor prognosis. Convalescence is protracted and frequently associated with sequelae such as hearing loss. CHAPTER 215 Arthropod-Borne and Rodent-Borne Virus Infections

Typical clinical laboratory findings (thrombocytopenia, leukopenia, and proteinuria) support the diagnosis. Argentinian and Bolivian hemorrhagic fevers are readily treated with convalescent plasma given within the first 8 days of illness; however, the use of convalescent plasma may be associated with neurologic sequelae. In the absence of passive antibody therapy, (off-label) IV ribavirin in the dose recommended for LF is likely to be effective in all South American VHFs caused by mammarenaviruses. A safe, effective, live-attenuated vaccine exists for Argentinian hemorrhagic fever. After vaccination of >250,000 high-risk people in the endemic area, the incidence of this VHF decreased markedly. In experimental animals, this vaccine is cross-protective against Bolivian hemorrhagic fever. Other mammarenaviruses have caused isolated or sporadic VHF in South America, including Guanarito virus (Venezuelan hemorrhagic fever) and Chapare and Sabiá viruses. Multivalent vaccine approaches against all five VHF-causing mammarenaviruses in this region are in preclinical development. LASSA FEVER Lassa virus (LASV) is known to cause endemic and epidemic disease in Nigeria, Sierra Leone, Guinea, and Liberia, although it is probably more widely distributed in Western Africa. In Western Africa alone, probably tens to hundreds of thousands of LASV

infections occur annually, and ≈20% of these develop LF, which can be a prominent cause of febrile disease. For example, in one hospital in Sierra Leone, laboratory-confirmed LF is consistently responsible for one-fifth of admissions to the medical wards. LASV can be transmitted by close person-to-person contact. Nosocomial spread has occurred but is uncommon if appropriate infection prevention and control practices are followed. All ages and both sexes are affected; the incidence of disease is highest in the dry season, but transmission occurs year-round.

The majority of LASV infections are subclinical or mild. After a highly variable incubation period of 1–3 weeks, symptomatic patients have the gradual onset of a nonspecific febrile prodrome (among the VHF agents, only mammarenaviruses are typically associated with a gradual onset of illness). Progression in the second week of illness includes sore throat, cough, retrosternal chest and back pain, and gastrointestinal symptoms (abdominal pain, vomiting, and/or diarrhea). A maculopapular rash may be noted in light-skinned patients. Further disease progression includes conjunctival infection, head and neck edema, and respiratory (pneumonia and/or pleural effusions) and cardiac (pericarditis and/or pericardial effusions) manifestations. In late stages, multisystem organ dysfunction occurs with acute kidney injury, CNS manifestations (encephalopathy, coma, and/or seizures), shock, and hemorrhage (seen in only $\approx 15\text{--}30\%$ of LF patients overall). Laboratory abnormalities may include leukocytosis, thrombocytopenia, elevated serum creatinine levels, hyperkalemia, hypoalbuminemia, elevated AST and ALT activities, and proteinuria. Viral load, age, pregnancy status, clinical signs (CNS features, face and neck swelling, hypotension, hemorrhage, and/or jaundice), and laboratory abnormalities (high serum creatinine levels, AST activity, leukocytosis, and/or thrombocytopenia) have been associated with fatal outcome. Pregnancy is associated with higher case fatality, especially during the last trimester, when fetal death is 90%. Interruption of pregnancy via medical abortion may increase survival rates, but data on LF and pregnancy outcomes remain sparse. In survivors, a high rate ($\approx 30\%$) of sensorineural deafness (onset during the acute illness or in convalescence, usually bilateral) occurs; other postacute sequelae of LF are poorly defined but include neurologic and mental health issues. The virus is detected in the urine during convalescence and has been detected in seminal fluid early in recovery. Reinfection may occur but has not been associated with severe disease.

PART 5

Infectious Diseases Aggressive supportive and critical care, including renal replacement therapy when available, is required to improve outcomes. Regarding LASV-specific therapy, observational studies in the 1980s informed the current practice of treating patients with (off-label) ribavirin (IV route preferred). Historically, ribavirin appeared to be partially effective in reducing fatality from that documented among retrospective controls. However, possible side effects, such as reversible anemia (which usually does not require transfusion), dependent hemolytic anemia, and bone marrow suppression, need to be kept in mind. When used, ribavirin should be given by slow IV infusion in a dose of 32 mg/kg; this dose should be followed by 16 mg/kg every 6 h for 4 days and then by 8 mg/kg every 8 h for 6 days. Small-molecule and monoclonal antibody therapeutics are in advanced preclinical development, and research networks in Western Africa are preparing for randomized clinical trials that will be critical to inform best specific therapeutic approaches. Inactivated LASV vaccines failed in preclinical studies, but several promising vaccine platforms are under experimental evaluation.

HEMORRHAGIC FEVER WITH RENAL SYNDROME HFRS is the most significant VHF today, with $>100,000$ cases of severe disease in Asia annually and thousands of mild infections in Europe. The disease is widely distributed in Eurasia. The major causative viruses are Puumala virus (Europe), Dobrava virus (the Balkans), and Hantaan virus (Eastern Asia). Amur, gōu, Kurkino, Muju, Saaremaa, Sochi, and Tula viruses also cause HFRS but much less frequently and in more geographically confined areas that are determined by the distribution of reservoir hosts. Seoul virus is an exception; because it is associated with brown rats (*Rattus norvegicus*), which migrate on ships, the virus has a worldwide distribution. Despite the wide distribution of Seoul virus,

only mild or moderate HFRS occurs in Asia; human disease has been difficult to identify in many areas of the world, although an outbreak in North America has been described. Most cases of HFRS

occur in rural residents or vacationers; again, the exception is Seoul virus infection, which may be acquired in an urban, rural, or laboratory setting. Classic Hantaan virus infection in Korea and in rural China is most common in the spring and fall and is related to rodent density and agricultural practices. Human infection is acquired primarily through aerosols of rodent urine, although virus is also present in rodent saliva and feces. Patients with HFRS are not infectious. Most patients with hantavirus infections do not develop severe disease. Classic features of HFRS include fever, hypotension, hemorrhage, and acute kidney injury, with severe disease expressed in four identifiable stages after a typical 1- to 2-week incubation period:

1. The febrile stage lasts 3 or 4 days and is identified by the abrupt onset of fever, headache, severe myalgia, thirst, anorexia, and often nausea and vomiting. Photophobia, retroorbital pain, and pain on ocular movement are common, and the vision may become blurred with ciliary body inflammation. Flushing over the face, the anterior neck, and back is characteristic, as are pharyngeal injection, periorbital edema, and conjunctival suffusion. Petechiae often develop in areas of pressure, the conjunctivae, and the axillae. Back pain and tenderness to percussion at the costovertebral angle reflect massive retroperitoneal edema. Thrombocytopenia and mild to moderate DIC is present, and hemorrhagic manifestations may occur. Other early laboratory findings include proteinuria and an active urinary sediment.
2. During the hypotensive stage (lasting from a few hours to 48 h), the blood pressure falls (sometimes with shock) with a compensatory tachycardia (vs the relative bradycardia typical of the febrile phase). Kinin activation and capillary leak are marked, leading to hemoconcentration. Leukocytosis with a left shift develops, and thrombocytopenia persists. Atypical lymphocytes—which, in fact, are activated CD8+ and, to a lesser extent, CD4+ T cells—circulate. Renal perfusion is compromised from local and systemic circulatory changes resulting in necrosis of tubules, particularly at the corticomedullary junction, and oliguria. Consequent inability to concentrate the urine develops, and the urine's specific gravity falls to 1.010. Proteinuria is marked. Diffuse hemorrhage may appear, including hematemesis, hemoptysis, and melena.
3. During the oliguric stage, hemorrhagic tendencies continue, probably in large part because of uremic bleeding defects. Oliguria persists for 3–10 days before the return of renal function marks the onset of the polyuric stage.
4. During the polyuric stage (diuresis with hyposthenuria), the inability to concentrate the urine may lead to volume depletion and electrolyte abnormalities. Mild cases of HFRS may be much less stereotypical, presenting only with fever, gastrointestinal abnormalities, and transient oliguria followed by hyposthenuria. Infections with Puumala virus, the most common cause of HFRS in Europe (“nephropathia epidemica”), result in a similar general but much-attenuated presentation. Bleeding manifestations are found in only 10% of patients, hypotension rather than shock is usually documented, and oliguria is present in only about half of patients. The dominant features may be fever, abdominal pain, proteinuria, mild oliguria, and sometimes blurred vision or glaucoma, followed by polyuria and hyposthenuria in recovery. CFR is <1%. HFRS should be suspected in patients with exposure in an endemic (typically rural) area. Prompt recognition of the disease permits rapid hospitalization and expectant management of shock and renal failure. Clinical laboratory parameters include leukocytosis (which may be leukemoid and with a left shift), thrombocytopenia, elevated serum creatinine level, proteinuria, and

hematuria. HFRS is readily diagnosed by an IgM-capture ELISA that is positive at admission or within 24–48 h thereafter. The isolation of orthohantaviruses is difficult, but RT-PCR of renal biopsy, thrombus (collected early in the clinical course), or postmortem tissues may yield molecular diagnosis and should be used if definitive identification of the infecting virus is required.

Mainstays of therapy are management of shock with vasopressor support and modest crystalloid infusion, IV human serum albumin administration, timely renal replacement therapy to prevent volume overload that may result in pulmonary edema, and control of hypertension to prevent intracranial hemorrhage. Use of IV ribavirin has reduced CFR and morbidity in severe cases, provided treatment is begun within the first 4 days of illness. CFR approaches 15% but should be lower than 5% with adequate supportive and critical care. Generally, surviving patients make a full recovery, even of glomerular function, and postacute sequelae have not been identified. CRIMEAN-CONGO HEMORRHAGIC FEVER (CCHF) CCHFV causes severe VHF over a wide endemic area (Africa, Asia, and Europe), determined primarily by the distribution of ixodid *Hyalomma* ticks. Incidence has been increasing in known endemic areas (particularly in Western Asia), and recent autochthonous infections in nonendemic areas, such as Spain, suggest that the at-risk geography is expanding. Because of the propensity of CCHFV-transmitting ticks to feed on domestic livestock and some wild mammals, veterinary serosurveys are the most effective mechanism for the monitoring of virus circulation. Human infections are acquired via tick bites, during the crushing of infected ticks, and contact with blood or body fluids of infected animals or humans (including nosocomial and vertical transmission). Domestic animals do not become ill but do develop viremia. Thus, risk of acquiring CCHFV occurs during sheep shearing, animal slaughter, or contact with infected hides or carcasses from recently slaughtered infected animals. Nosocomial outbreaks are common and are usually related to extensive blood exposure or needlesticks. The majority of infections are subclinical. After an incubation period that varies by exposure to a tick bite (1–3 days) or blood or body fluids (3–7 days, perhaps shorter after nosocomial exposures to highly viremic patients), patients develop a sudden-onset nonspecific febrile prodrome typical to VHF. Severe illness is also typical, with the possible exceptions of a profound and dysregulated inflammatory component, more severe hemorrhagic manifestations (including extended ecchymoses and/or retinal and pulmonary hemorrhage), and more severe liver injury, resulting in jaundice in some patients. Recovery (for most patients; sequelae are not identified) or rapid progression to fatal disease occurs in the second week of illness with multiorgan (renal and respiratory) dysfunction, shock, and profound coagulopathy leading to massive bleeding. Clinical laboratory findings indicate coagulopathy as well as markers of liver (elevations in activities of AST/ALT and bilirubin concentrations) and muscle (elevations in creatine phosphokinase levels) injury. Predictors of fatal outcome include clinical features (hematemesis, melena, and/or altered mental status), laboratory biomarkers (viral load, thrombocytopenia, elevated AST/ALT levels, and/or obvious DIC), and delayed CCHFV-specific IgM and IgG responses. The mainstay of treatment is supportive and critical care, including extracorporeal support of organ dysfunction. The pathophysiology argues for combined virus-specific and diseasemodifying immunomodulatory approaches. The benefit of IV ribavirin, suggested in observational studies that were likely confounded, has not been borne out in randomized trials. Small-molecule antivirals (favipiravir and molnupiravir), monoclonal antibodies, and the use of convalescent plasma are in preclinical evaluation, but clinical studies are needed. The routine use of steroids and/or IVIG is not currently recommended. No human or veterinary vaccines are recommended. RIFT VALLEY FEVER The natural range of RVFV was previously con

fined to sub-Saharan Africa, with circulation of the virus markedly enhanced by substantial rainfall. The El Niño Southern Oscillation phenomenon of 1997 facilitated subsequent spread of Rift Valley fever (RVF) to the Arabian Peninsula, with epidemic disease in 2000. The virus has also been found in Madagascar and Egypt, where it caused major epidemics in 1977–1979, 1993, and thereafter. RVFV is maintained by transovarial transmission in floodwater Aedes mosquitoes and presumably also via a vertebrate amplifier. Increased transmission during particularly heavy rains leads to epizootics characterized by high-level viremia in cattle, goats, or sheep. Numerous

types of mosquitoes feed on these animals and become infected, thereby increasing the possibility of human infections. Remote sensing via satellite can detect the ecologic changes associated with high rainfall that predict the likelihood of RVFV transmission. High-resolution satellites can also detect the special depressions in floodwaters from which the mosquitoes emerge. The virus can be transmitted to humans by mosquitoes but most commonly by contact with blood or aerosols from domestic animals. Therefore, transmission risk is high during birthing, and both abortuses and placentas need to be handled with caution. Risk is also high during animal slaughter but decreases thereafter as anaerobic glycolysis in postmortem tissues results in an acidic environment that rapidly inactivates bunyaviruses in carcasses. Neither person-to-person nor nosocomial transmission of RVFV has been documented.

RVFV is unusual in that it causes several clinical syndromes. Most infections are either subclinical or produce a typical F&M syndrome after an incubation period of 2–6 days. A much smaller proportion (<1%) of patients develop typical VHF notable for prominent liver involvement (jaundice) and an extremely rapid course with high case fatality (50%, within 3–6 days), often with renal failure and DIC/

hemorrhagic manifestations. Further, <1% of patients develop a late onset (1–4 weeks) meningoencephalitis syndrome that is not usually fatal but does lead to severe neurologic sequelae. Perhaps 10% of otherwise mild infections develop a late-onset (1–3 weeks) retinal vasculitis causing blurred or loss of vision. Funduscopic examination reveals edema, hemorrhages, and infarction of the retina as well as optic nerve degeneration. In a small proportion of patients (<1 in 200), retinal vasculitis is followed by viral encephalitis. Of interest, the late onset of both retinal disease and meningoencephalitis—after serum neutralizing antibody has developed—suggests (so far, undefined) immunopathology. CHAPTER 215 No proven therapy exists for RVF. Epidemic disease is best prevented by vaccination of livestock. The ability of this virus to propagate after introduction into Egypt suggests that other potentially receptive areas, including the United States, should develop response plans. RVF, like VEE, is likely to be controlled only with adequate stocks of an effective live-attenuated vaccine, but global stocks are unavailable. A formalin-inactivated vaccine confers immunity in humans; however, quantities are limited, and three injections are required. This vaccine is recommended for potentially exposed laboratory workers and for veterinarians working in sub-Saharan Africa. A new live-attenuated vaccine, MP-12, is being tested in humans (phase 2 trials have been completed). The vaccine is safe and licensed for use in sheep and cattle. A modified replication-incompetent chimpanzee adenovirus (ChAdOx1) vectored vaccine has recently been shown to be safe and immunogenic in phase 1 trials. In addition, several vaccines are being developed specifically for use in animals. Arthropod-Borne and Rodent-Borne Virus Infections

SEVERE FEVER WITH THROMBOCYTOPENIA SYNDROME This tickborne disease is caused by SFTSV.

The primary tick vector, the Asian long-horned tick (*Haemaphysalis longicornis*), is endemic in areas of southeast Asia and Oceania, and geographic distribution has been increasing, likely via migratory birds (in Asia) or by importation of pets or livestock (in the United States, where the vector is now widespread and considered invasive). Numerous human infections have been reported during the past few years from China, and cases have also been detected in Japan, the Republic of Korea, Vietnam, and Thailand. Seroprevalence in endemic areas of China approaches 5%. The clinical presentation ranges from mild nonspecific febrile syndromes to severe VHF with high CFR (>12%) particularly in older individuals. After a 1- to 2-week incubation period, patients develop a nonspecific febrile prodrome that may include abdominal pain, vomiting, and diarrhea. Common laboratory abnormalities include prominent thrombocytopenia, leukopenia (often with atypical lymphocytes), markers of hepatocyte injury, and elevated ferritin levels. Most patients recover spontaneously; however, in the second week of illness, some patients develop severe disease with multiorgan dysfunction that can include acute renal injury, myocarditis, meningoencephalitis, DIC with hemorrhage, and hemophagocytic lymphohistiocytosis. Diagnosis requires RT-PCR, as serologic tests are not available. No vaccines or approved

therapeutics are available (though ribavirin and favipiravir have been used in patients) and treatment relies on supportive care.

Flasuviricetes The most significant orthoflaviviruses that cause VHF are the mosquito-borne DENV-1-4 and YFV. These viruses are widely distributed and cause tens to hundreds of thousands of infections each year. Alkhurma hemorrhagic fever virus (>600 cases since discovery in 1995), Kyasanur Forest disease virus (≈10,000 cases over 60 years), and Omsk hemorrhagic fever virus (isolated infections every year with intermittent larger outbreaks) are geographically very restricted but prevalent tick-borne orthoflaviviruses that cause VHF, sometimes with subsequent viral encephalitis. Tick-borne encephalitis virus has caused VHF in a few patients. There is currently no therapy for infection with these VHFs, but an inactivated vaccine has been used in India to prevent Kyasanur Forest disease (and there is a vaccine to prevent tick-borne encephalitis; see above).

SEVERE DENGUE Although most individuals infected with DENV1-4 have either subclinical infection or F&M syndrome (the febrile phase), some of these patients enter a critical (or plasma leakage) phase—often as fever declines—and develop the criteria for severe dengue: a definite or presumptive diagnosis of dengue infection plus either (1) plasma leakage severe enough to cause shock or respiratory distress, or (2) severe bleeding, or (3) severe organ dysfunction. Early recognition and action long before this critical period are crucial to initiate appropriate supportive care. Indeed, all patients with a presumptive diagnosis of dengue (of any severity) should be initially assessed for designated warning signs (dengue with warning signs, directing inpatient management) as well as for the criteria for severe dengue (i.e., a provisional diagnosis of severe dengue should be made clinically).

PART 5 Infectious Diseases The complex determinants of risk for this progression to severe dengue include host and viral factors but center most notably around the potential for immune-mediated enhancement of disease. Several weeks after convalescence from infection with DENV-1-4, the transient protection conferred by that infection against reinfection with a heterotypic DENV usually wanes. Heterotypic reinfection may result in classic dengue without/warning signs or, less commonly, in severe dengue. In the past 20 years, YF mosquitoes have progressively reinvaded Latin America and other areas, and frequent travel by infected individuals has introduced multiple variants of DENV-1-4 from many geographic areas. Thus, the pattern of hyperendemic transmission of multiple DENV serotypes established in the

Americas and the Caribbean has led to the emergence of severe dengue as a major problem. Among the millions of DENV-1–4 infections, $\approx 500,000$ cases of severe dengue occur annually, with a CFR of $\approx 2.5\%$. The induction of vascular permeability and shock depends on multiple factors, such as the presence or absence of enhancing and nonneutralizing antibodies, age (susceptibility to severe dengue drops considerably after 12 years of age), sex (females are more often affected than males), race (white people are more often affected than black people), nutritional status, and the timing and sequence of infections (e.g., DENV-1 infection followed by DENV-2 infection seems to be more severe than DENV-4 infection followed by DENV-2 infection). The presence of neutralizing antibodies is associated with decreased viremia on subsequent infection. In addition, considerable heterogeneity exists among variants in each DENV population. For instance, Southeastern Asian DENV-2 variants have more potential to cause severe dengue than do other variants. Recent evidence points to a key role for the DENV NS1 protein in the vascular leak phenomenon associated with severe dengue. In milder cases of severe dengue, restlessness, lethargy, thrombocytopenia ($<100,000/\mu\text{L}$), and hemoconcentration are detected 2–5 days after the onset of typical dengue, usually at the time of defervescence. The maculopapular rash that often develops in dengue (without/ with warning signs) may also appear in severe dengue. However, severe dengue is most notoriously identified as the consequence of a vascular leak syndrome leading to intravascular volume depletion, hypoalbuminemia, serosal effusions (pleural, ascitic), and, in severe cases, circulatory collapse (i.e., shock, typically lasting 2–3 days), often with an accompanying narrowed pulse pressure, hepatomegaly, and cyanosis. Bleeding tendencies (evidenced by a positive tourniquet test

and petechiae) or overt bleeding in the absence of underlying causes (e.g., preexisting gastrointestinal lesions) may be detected but are less common in children. Organ involvement may include mild hepatic injury, CNS abnormalities (e.g., altered mental status, seizures), cardiac abnormalities (e.g., arrhythmias), renal disturbances (e.g., acute kidney injury), and ocular dysfunction. A virologic diagnosis of severe dengue can be made by the usual means (nucleic acid amplification or antigen detection) in the first 5 days of infection, after which diagnosis relies on serologic testing. Combination testing—point-of-care rapid tests for NS1 antigen and IgM antibody assays—is increasingly used in the clinical setting. The early detection of IgG (starting at 4 days after illness onset, rapidly rising) suggests a secondary rather than primary infection, in which IgG is detected later and at much lower titers. However, serologic crossreactivity after infection with (or vaccination for) antigenically similar orthoflaviviruses (e.g., YFV, ZIKV, and Japanese encephalitis virus) confounds diagnosis. As above, patients with severe dengue should be hospitalized and rapidly triaged (and then closely monitored) for hemodynamic instability and bleeding. In general, appropriate IV fluids should be administered as early as possible, preferably before shock develops. Based on clinical parameters (vital signs, urine output, hematocrit, bleeding, and signs of volume overload), algorithmic approaches have been developed to standardize appropriate fluid management (crystalloid vs colloid vs blood rate) and monitoring of patients with and without shock and/or bleeding. CFR varies greatly depending on early recognition and quality of treatment. However, most patients with severe dengue respond well to supportive therapy, and the overall CFR at experienced clinical centers in the tropics is probably as low as 1%. When patients enter the convalescent phase, significant fluid reabsorption (of extra vascular fluid and effusions) occurs as the plasma leak resolves, blood pressure improves, and diuresis occurs. Notably, a patchy erythematous pruritic rash may develop and desquamate during recovery. Significant postacute sequelae include prolonged fatigue and depression. The key to control of both dengue (without/with warning signs) and severe dengue is the control of YF mosquitoes, which also reduces

the risk of urban YF and CHIKV circulation. Control efforts have been handicapped by the presence of nondegradable tires and long-lived plastic containers in trash repositories—creating perfect mosquito breeding grounds upon filling with water during rainfall—and by insecticide resistance. Urban poverty and an inability of the public health community to mobilize the human population to respond to the need to eliminate mosquito breeding sites are also factors in lack of mosquito control. New approaches that may be considered in the future of vector control include the release of *Aedes* mosquitoes infected with *Wolbachia* or carrying dominant lethal genetic mutations that will be passed on to offspring. A tetravalent live-attenuated dengue vaccine based on the attenuated YFV 17D platform (CYD-TDV, or Dengvaxia) was licensed in 2015 and registered in 20 countries for individuals 9–45 years of age. However, retrospective analysis of phase 3 trials in Latin America and Asia suggested protection from severe dengue only in previously seropositive individuals; indeed, the risk of severe dengue was actually increased in seronegative vaccine recipients over that in nonvaccinated seronegative individuals, suggesting that a “first serologic hit” from the vaccine predisposes naïve recipients to more severe primary dengue infection. Strategic revision to avoid vaccine-enhanced disease pivoted to include prevaccination serologic screening aimed to avoid vaccination of seropositive individuals; however, the requirement for prevaccine testing and decision-making is challenging. Recently, live-attenuated candidate vaccines based on modified recombinant DENVs have been or are being evaluated, with these learnings in mind. Qdenga (TAK-3), given in two doses 3 months apart, has shown overall efficacy against infection and hospitalization in seropositive and seronegative children, although not against DENV-3 (in fact, a very small signal of potentially increased risk of hospitalization after DENV-3 infection was observed), and the trial did not include DENV-4 infections. This vaccine has been approved for use in several European countries. Recommendations globally are currently for introduction in settings with high transmission intensity for maximal

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