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(mosquitoes, ticks, others), or from infectious excreta of ro- dents and other small mammals, and rarely person to person. Many are transmitted from infected arthropod vector females to the next generation by transovarial transmission, thereby surviving adverse environmental conditions and leading to marked seasonal distribu- tion of disease. There are few vaccines or drugs available to protect against infection. Prevention is by avoidance of exposure to poten- tially infected arthropod and small mammal vectors. Clinical features Bunyaviridae cause a variety of clinical illnesses, ranging from self- limited febrile disease to severe, life-threatening haemorrhagic fever, acute respiratory distress, or encephalitis. The most important human diseases include those caused by: La Crosse virus—the most common cause of 'California encephal- itis', most cases of which are relatively mild and with good prognosis; treatment is supportive. Oropouche fever—causes epidemics of febrile illness, sometimes with meningitis, throughout the Amazon Basin and elsewhere in tropical America; prognosis is good; treatment is supportive. Haemorrhagic fever with renal syndrome—caused by four distinct viruses (Hantaan, Dobrava, Puumala, Seoul); Hantaan and Dobrava cause the most severe disease, characterized sequentially by (1) fe- brile phase with features including headache, myalgias, petechiae and conjunctival haemorrhage, (2) hypotensive phase with shock, (3) oliguric phase, when one-third of cases have severe haem- orrhage, (4) diuretic phase, (5) convalescent phase, which may be prolonged; ribavirin is effective if started early in disease. Inactivated vaccines against hantaviruses are available for use in Asia. Hantavirus pulmonary syndrome—most commonly reported from the western United States, Canada, Central and South America; symptoms are primarily those of acute unexplained adult respiratory distress syndrome; treatment is supportive; mortality is 20–40%. Other diseases caused by Bunyaviridae—these include sandfly fever, Rift Valley fever, severe fever with thrombocytopenia syndrome, and Crimean–Congo haemorrhagic fever. Some viruses of the family (e.g. Rift Valley fever virus and Nairobi sheep disease virus), are important pathogens of domestic animals. Viral taxonomy and vectors Based on the 9th ICTV report of 2011, the family Bunyaviridae currently contains around 350 viruses, and is divided into five genera (Table 8.5.16.1). The family name, and that of the genus Orthobunyavirus, is derived from the type species Bunyamwera virus, which was isolated in Uganda from Aedes mosquitoes. The other genera are Hantavirus named after Hantaan virus (the cause of Korean haemorrhagic fever), Nairovirus after Nairobi sheep dis- ease virus, Phlebovirus after phlebotomus or sandfly fever virus, and Tospovirus after tomato spotted wilt virus. All members of the family share structural, biochemical, and genetic properties,

 such as a spherical enveloped virion 80–120 nm in diameter (Fig. 8.5.16.1) and a genome of single-stranded negative-sense RNA divided into three segments (L, M, S). Members of dif- ferent genera vary substantially in their biological and bio- chemical properties and in their mechanisms of replication. Orthobunyaviruses, nairoviruses, and phleboviruses, which to- gether make up most of the family, are all arthropod-borne animal viruses (arboviruses). These circulate in a wide variety of dif- ferent vertebrate hosts and are transmitted between vertebrates, including humans, by the bites of blood-sucking arthropods, principally mosquitoes for orthobunyaviruses, sandflies and ticks for phleboviruses, and ticks for nairoviruses. Hantaviruses are zoonotic agents infecting rodents and other small mammals. They may spread to humans who are in close contact with infected small mammal excreta. Tospoviruses are arthropod-transmitted plant viruses of no known medical importance. Viruses within the larger genera are further subdivided into serogroups; orthobunyaviruses have at least 18 serogroups and Table 8.5.16.1 The family Bunyaviridae: its genera, serogroups, vectors, and viruses infecting humans Genus Serogroup Vector Viruses infecting humans Orthobunyavirus (over 150) Anopheles A (12) Mosquito

Tacaiuma Anopheles B (2) Mosquito Bakau (5) Mosquito Bunyamwera (33) Mosquito Bunyamwera, Calovo, Germiston, Ilesha, Maguari, Ngari, Shokwe, Tensaw, Wyeomyia Bwamba (2) Mosquito Bwamba, Pongola C group (14) Mosquito Apeu, Caraparu, Itaqui, Madrid, Marituba, Murutucu, Nepuyo, Oriboca, Ossa, Restan California (14) Mosquito California encephalitis, Guaroa, Inkoo, Jamestown Canyon, Keystone, La Crosse, snowshoe hare, Tahyna, trivittatus Capim (10) Mosquito Gamboa (8) Mosquito Guama (12) Mosquito Catu, Guama Koongol (2) Mosquito Minatitlan (2) Mosquito Nyando (2) Mosquito Nyando Olifantsvlei (5) Mosquito Patois (7) Mosquito Simbu (24) Mosquito Oropouche, Shuni Tete (5) Mosquito Turlock (5) Mosquito Unassigned (3) Mosquito Hantavirus (39) Hantaan (39) None Amur, Andes, Araraquara, Bayou, Bermejo, Black Creek, Canal Choclo, Dobrava, Hantaan, Juquitiba, Laguna Negra, New York, Lechiguanas, Maciel, Monongahela, Oran, Prospect Hill, Puumala, Saaremaa, Seoul, Sin Nombre Nairovirus (32) Crimean–Congo (3) Tick Crimean–Congo haemorrhagic fever, Hazara Dera Ghazi Khan (6) Tick Hughes (10) Tick Soldado Nairobi sheep disease (3) Tick Dugbe, Ganjam, Nairobi sheep disease Qalyub (3) Tick Sakhalin (7) Tick Avalon Thiafora (2) Tick Phlebovirus (57) Phlebotomus (44) Sandflya Alenquer, Candiru, Chagres, Corfou, Punta Toro, Rift Valley fever, sandfly fever Naples, sandfly fever Sicilian, severe fever with thrombocytopenia syndromea, Heartland, Toscana Uukuniemi (13) Tick Uukuniemi, Zaliv-Terpeniya Tospovirus (1) Thrips Unassigned (53) Mosquito Bangui, Kasokero, Tataguine Tick Bhanja, Issyk-kul Keterah, Tamdy, Wanowrie Numbers in parentheses indicate the approximate number of viruses in the genus or serogroup. Bold type indicates the type species and viruses causing major disease in humans. a Mosquito vector for Rift Valley fever virus; tick suspected for severe fever with thrombocytopenia virus and Heartland virus.

854 section 8 Infectious diseases nairoviruses have 7 (Table 8.5.16.1). Of over 60 Bunyaviridae that are known to infect humans, the type species and those causing major human diseases are shown in bold type in Table 8.5.16.1 and are described in more detail. Table 8.5.16.2 lists the distribution of the remaining viruses that cause minor human infections with their principal arthropod vectors. The habitats of the different viruses and their vectors range from arctic to tropical. The enzootic cycles of arbo- viruses are poorly understood. Most viruses undergo alternate cycles of replication in vertebrate and invertebrate hosts, but transovarial and transstadial transmission within some mosquitoes, ticks, and phlebotomine flies, and venereal transmission from vertically in- fected male mosquitoes to uninfected females is also known to occur. Most arboviruses have a narrow host range, occur within a limited area, and are transmitted by specific vectors to a limited number of vertebrate hosts, but some viruses infect a wider host range, are transmitted by more than one type of vector, and may occur in more than a single continent. Tick transmission predominates in Asia, but is unknown in South or Central America, and although some Bunyaviridae have been isolated in Australia, none is known to in- fect humans in that continent. Viruses of this family are among the most common, apparently emerging, diseases. Following viral entry, whether through the skin after the bite of an infected arthropod or by another route, there is replication in draining lymph nodes, which can be enlarged, and then viraemia. Symptoms develop when virus is deposited and replicates in other sites. The viruses are killed by bleach, phenolic disinfectants and detergents, autoclaving, boiling, and γ-irradiation. Enzymes such as nucleases also inactivate these viruses. Biosafety level 3 is recommended for handling most human pathogens with the ability to spread by aerosol (e.g. hantaviruses and Oropouche virus), but level 4 is required for Crimean–Congo haem- orrhagic fever virus. Added precautions are necessary when handling hantavirus-infected animals and virus concentrates. Genus Orthobunyavirus Viruses of the genus Orthobunyavirus are primarily transmitted by mosquitoes and can cause mild febrile disease

or infections with cen- tral nervous system involvement. Two orthobunyaviruses, Akabane and Aino viruses in the Simbu serogroup, produce congenital de- formities in sheep, goats, and cattle in Japan, Australia, Africa, and the Middle East. However, there is no evidence that any member of the genus or family produces teratogenic effects in humans, but there is concern that Oropouche virus, a Simbu serogroup pathogen of Central and South America, may be a threat to pregnant women. Studies with Bunyamwera and similar viruses show reassortment within the three-segmented genome when two closely related vir- uses infect the same cell, either in nature or in the laboratory. When Fig. 8.5.16.1 Electron micrograph of Crimean–Congo haemorrhagic fever virus. Magnification × 400 000. Courtesy of Dr D. S. Ellis. Table 8.5.16.2 Bunyaviridae causing only mild or trivial infections in humans, arranged on a geographical basis Africa North America Central America South America Europe Asia Bangui (M) Avalon (T) Fort Sherman Alenquer (P) Bhanja (T) Batai (M) Bhanja (T) Keystone (M) Madrid (M) Apeu (M) Calovo (M) Bhanja (T) Dugbe (T) Prospect Hill Nepuyo Candiru (P) Corfou (P) Issyk-Kul (T) Germiston (M) Tensaw (M) Ossa (M) Caraparu (M) Tamdy (T) Ganjam (T) Ilesha (M) Trivittatus (M) Restan (M) Catu (M) Uukuniemi (T) Hazara (T) Kasokero (M) Soldado Guama (M, P) Keterah (T) Nairobi sheep disease Trivittatus (M) Guaroa (M) Wanowrie (T) Nyando (M) Itaqui Zaliv-Terpeniya (M, T) Pongola (M) Maguari (M) Shokwe (M) Marituba (M) Shuni (M) Murutucu (M) Tataguine (M) Oriboca Thiafora Restan (M) Wanowrie (T) Tacaiuma (M) Wyeomyia (M) M, virus transmitted by mosquitoes; P, virus transmitted by phlebotomine flies; T, virus transmitted by ticks.

8.5.16 Bunyaviridae 855 such events occur in nature they can impede the diagnosis and may lead to a change of virulence of the newly emerging virus. Laboratory studies of this phenomenon have been used to analyse the molecular basis of virulence for vertebrate and invertebrate hosts. Bunyamwera virus Symptoms A mild febrile illness, usually with headache, joint and back pains, sometimes with a rash, and occasionally with mild involvement of the central nervous system. Serological surveys indicate widespread human infection in sub-Saharan Africa, but it is rarely recognized. Laboratory infections have been recorded. A reassortant virus de- rived from Bunyamwera virus is Ngari virus. Ngari virus, a close relative to Cache Valley virus endemic in North America, was first isolated from male Aedes simpsoni mosquitoes in Southeastern Senegal in 1979 and has been associated with large outbreaks of viral haemorrhagic fever with gastrointestinal bleeding in Kenya and Somalia. Treatment and prognosis No treatment is necessary and the prognosis is normally good. California encephalitis, Inkoo, Jamestown Canyon, La Crosse, Tahyna, and snowshoe hare viruses The aforementioned viruses, and perhaps others currently unrecog- nized, are responsible for the clinical condition known as California encephalitis. The viruses are widely distributed throughout many parts of North America, Europe, and Eurasia. In the United States of America most reported human infections are due to La Crosse virus in North Carolina, Ohio, West Virginia, Tennessee, Wisconsin, and Minnesota, with nearly 700 neuroinvasive cases reported from 23 states from 2007 to 2016, or approximately 40–120 cases reported annually (Fig. 8.5.16.2). Most occurred in children, usually in boys, although Jamestown Canyon virus is found more often in adults. There is nearly always a history of outdoor exposure during warmer months in areas where woodland mosquitoes are prevalent. The in- cubation period is 5–15 days. Most cases of La Crosse encephalitis are relatively mild with headache, fever (2–3 days usually), and vomiting, progressing to lethargy, behavioural changes, and occasional brief seizures, followed by improvement. Severe cases (10–20%) are more frequent in children under 16 years old that develop sudden fever and headache, disorientation, and seizures during the first 24 h of illness, sometimes progressing to coma and requiring intensive supportive care. Overall, about

50% of symptomatic children have seizures with status epilepticus in 10–15%. The case fatality rate approaches 1%. Residual seizures occur in 6–13%, persistent hemiparesis in about 1%, and cognitive dysfunction in a few. In appropriate epidemio- logical settings, the disease should be considered in children pre- senting with aseptic meningitis or encephalitis. In Europe, Tahyna virus is widely distributed in Austria, former Czechoslovakia, France, Germany, Italy, Norway, Romania, former Yugoslavia, and the former Soviet Union. Seroprevalence exceeds Fig. 8.5.16.2 La Crosse virus neuroinvasive disease average annual incidence per 100 000 population by county, 2007-2016. Counties are shaded according to incidences ranging from less than 1.00, 1.00 to 2.49 and greater than 2.50 per 100 000 population. Source: ArboNET, Centers for Disease Control and Prevention, accessed 28 June 2018.

856 section 8 Infectious diseases 95% in parts of former Czechoslovakia, and is about 50% in the Rhone valley in France and the Danube basin near Vienna, but overt disease is seldom recognized. Inkoo virus is prevalent in Finland and also in neighbouring regions of Russia. Most adult Lapps have antibodies. Small children may have signs of central nervous system involvement during acute infection. Antibodies reactive with California serogroup viruses have also been found in human sera collected in Sri Lanka, China, and in the far northern latitudes of Eurasia where several California serogroup viruses have been iso- lated from mosquitoes, some related to Inkoo and Tahyna viruses, but others to snowshoe hare virus. In another Russian study of c.50 people, mainly 14–30 years old, with infections caused by California serogroup viruses, about two-thirds had influenza-like illnesses without central nervous system involvement, while the remaining one-third had aseptic meningitis. Control, treatment, and prognosis Measures to limit mosquito breeding are useful in endemic regions. No vaccines are available, and there is no specific treatment. Fluid and electrolyte balance must be maintained, and anticonvulsive drugs might be required to control seizures. Oropouche virus Symptoms Before 1961, Oropouche virus was known to have caused only a mild fever in a single forest worker in Trinidad, but that year it was re- sponsible for a substantial epidemic in the Belém area of northern Brazil, where c.7000 people were affected. Over the ensuing decades, massive epidemics of febrile illness have been recorded throughout the Amazon Basin and beyond, with many thousands infected. Symptoms include headache, generalized pain including back pain, prostration, and fever (40°C). Rash, meningitis, or meningism occa- sionally accompany infection. Illness lasts from 2 to 5 days, occasion- ally with protracted convalescence. No fatalities have been reported. Control, treatment, and prognosis No vaccine is available. Transmission is probably by the biting midge Culicoides paraensis and outbreaks appear to be a consequence of agricultural development where accumulated organic waste from cacao and banana production provides ideal breeding sites for Culicoides, leading to massive populations and subsequent epidemic Oropouche disease. Measures to reduce Culicoides breeding may be beneficial. Treatment is supportive and the prognosis is good, al- though convalescence can be protracted. Genus Hantavirus Haemorrhagic fever with renal syndrome Hantaan virus of the genus Hantavirus is the cause of Korean haem- orrhagic fever in Korea. The Hantaan River is near the demilitarized zone between North and South Korea where the virus was first re- covered in 1976 from its rodent host Apodemus agrarius. The clin- ical diseases caused by Hantaan and related viruses in the Eurasian continent have long been known by different synonyms: epidemic haemorrhagic fever, Korean haemorrhagic fever, or nephropathia epidemica, but haemorrhagic fever with renal syndrome is pre- ferred. Four distinct viruses are responsible for most recognized cases: Hantaan virus, found primarily in Asia; Dobrava virus in an enclave of disease in the Balkan region and sparsely elsewhere in Europe; Puumala virus in Scandinavia, western Russia, and much

of Europe; and Seoul virus, probably found globally wherever un- controlled populations of Rattus norvegicus exist. A few cases of haemorrhagic fever with renal syndrome have been associated with Saaremaa virus in Europe and Amur virus in Asia. Hantaan and Dobrava viruses cause severe life-threatening disease with mortality of about 5%, reaching up to 30% in select populations. Puumala virus infections are less severe, although patients still re- quire admission to hospital, but fewer than 1% of admitted patients die. Seoul virus is thought to be the least severe of the pathogenic strains of Old World hantaviruses, although it has been associated with human deaths. Each hantavirus is associated with a particular rodent host: Hantaan virus with the striped field mouse Apodemus agrarius; Dobrava virus with the yellow-necked mouse Apodemus flavicol- lis; Puumala virus with the bank vole Myodes glareolus; and Seoul virus with the Norway rat Rattus norvegicus. Humans are infected by aerosols of rodent excreta, or rarely by rodent bites. It is seen among adult men in rural environments and may be an occupa- tional disease. Those at greatest risk include farmers, woodcutters, shepherds, and, especially, soldiers in the field. Most hantavirus disease is seasonal, with a peak incidence in late autumn and early winter, although the Balkan form is found most often during summer months in Greece and adjacent countries. Symptoms The incubation period for hantaviruses is variable; it is usually 12–16 days but it can be up to 2 months. Severe disease, typically associated with Hantaan or Dobrava virus infections in Asia or the Balkans, is characterized by five phases: 1 Febrile: 3- to 7-day duration 2 Hypotensive: lasting from a few hours to 3 days 3 Oliguric: from 3 to 7 days 4 Diuretic: from a few days to weeks 5 Convalescent: prolonged Signs and symptoms of the febrile phase include fever, mal- aise, headache, myalgia, back pain, abdominal pain, nausea and vomiting, facial flushing, petechiae, and conjunctival haemorrhage (Fig. 8.5.16.3). In the hypotensive phase, patients have nausea, vomiting, tachycardia, hypotension, blurred vision, haemorrhagic signs, and shock. About one-third of fatalities occur during this phase. In the oliguric phase, nausea and vomiting may persist and blood pressure may rise. Renal failure develops with anuria, and about one-third of cases have severe haemorrhage (epistaxis, gastrointestinal, cutaneous, or bleeding at other sites). Nearly half of the deaths occur during the oliguric phase. In the diuretic phase, urine output increases to several litres per day. Convalescence is protracted and it might be months before full strength and function are regained. Not all the phases are seen in the less severe forms of the disease. The milder forms of haemorrhagic fever with renal syndrome, such as nephropathia epidemica due to Puumala virus, follow a similar

 but less severe course, with abrupt onset of fever of 38–40°C, head- ache, malaise, backache, and generalized abdominal pain. Back or loin pain is especially common. Signs of renal failure are usually not as pronounced, and the need for renal dialysis varies. Transient blurred vision occurs in about 10% of cases. Infection due to Seoul virus follows a similar course, but may present with more evidence of liver involvement. There is no evidence of person-to-person transmission. Treatment and prognosis Admission to hospital, avoidance of trauma and unnecessary movement, close observation, and careful supportive care are es- sential for patient survival. Treatment is phase specific, with special attention to fluid balance and volume, and control of hypotension and shock. Renal dialysis may be required. Antiviral therapy using ribavirin has been shown to be effective if started early in disease. Recovery is protracted but usually complete, with the exception of Seoul virus infection which might carry an increased risk of chronic renal disease, hypertension, or stroke. Hantavirus pulmonary syndrome Hantavirus pulmonary syndrome, first reported from the United States of America in 1993, also occurs in Canada, Central and South America. The initial cases had a mortality of more than 50%, but rates have declined to

20–40% as clinical experience has increased. Most disease was reported from the western United States of America and Canada, and more recently from Argentina, Chile, Brazil, and other Central and South American countries. Sin Nombre virus was first associated with hantavirus pulmonary syndrome, but many add- itional hantaviruses have now been recognized as likely causes of this syndrome (Table 8.5.16.1). As Old World hantaviruses are generally associated with specific microtine rodents (subfamilies Arvicolinae and Microtinae: voles, lemmings, muskrats, rats, and their allies, dis- tributed worldwide), so each American hantavirus appears to be as- sociated with a specific sigmodontine host (Sigmodontinae: cotton rats and their allies found in the western hemisphere). Apparent human-to-human transmission of Andes virus occurred during an outbreak in southern Argentina, including transmission to medical staff. Protective precautions are recommended when treating sus- pected cases of hantavirus pulmonary syndrome. Symptoms Symptoms are primarily those of acute unexplained adult respira- tory distress syndrome and cardiogenic shock, rather than the expected renal disease. Nonspecific prodromal features of fever, myalgia, and malaise may last 3–5 days, with nausea, vomiting, and abdominal pain, often accompanied by dizziness. On admis- sion, physical examination of patients with confirmed infection reveals fever (more than 38°C), tachycardia (more than 100 beats/ min), tachypnoea (more than 20 breaths/min), and often hypo- tension (systolic pressure less than 100 mmHg), with audible rales in the chest. Laboratory findings include hypoxia, leukocytosis, haemoconcentration, thrombocytopenia, atypical lymphocytosis, elevated transaminases, and prolonged prothrombin time. Chest radiography shows progression from subtle interstitial findings to bilateral frank pulmonary oedema; pleural effusions are usually pre- sent (Fig. 8.5.16.4). Thrombocytopenia and haemoconcentration are independent statistical predictors of hantavirus pulmonary syn- drome, although not infallible. In a patient with rapidly progressive pulmonary oedema, a blood smear showing four of the following five characteristics is a highly sensitive and specific means of establishing the diagnosis of hantavirus pulmonary syndrome: (1) thrombocyto- penia, (2) haemoconcentration, (3) lack of toxic granulation in neu- trophils, (4) more than 10% immunoblasts, and (5) myelocytosis. Disease progresses rapidly once the lungs begin to fill, and death is commonly seen 24–48 h after admission, or sooner if there is hyp- oxia or circulatory failure. The severity of disease correlates with the degree of pulmonary oedema on chest radiography. Hypotension and shock may occur independently in patients whose hypoxaemia is medically controlled. Treatment and prognosis Treatment is supportive, ideally in a modern intensive care unit, with careful management of hypoxia, fluid balance, and shock. About two-thirds of patients require intubation and mechanical (a) (b) Fig. 8.5.16.3 Patient with acute Korean haemorrhagic fever, showing extensive conjunctival haemorrhages (a) and facial swelling (b). Courtesy of Professor H. W. Lee.

 ventilation. Fluid loss into the lungs leads to haemoconcentration, but infusion of fluids exacerbates pulmonary oedema; therefore, fluids should be administered cautiously with careful monitoring. Limited experience suggests that intravenous ribavirin has little ef- fect on the course of hantavirus pulmonary syndrome, perhaps be- cause of the speed with which the disease progresses. Control Prevention involves avoidance of infected rodents either through effi- cient rodent control programmes in cities, for Seoul virus, or mainten- ance of clean campsites so that waste food is not allowed to accumulate and attract rodents. Nationally approved inactivated vaccines, reported to be safe and effective against hantaviruses, are available for use in Asia. Genus Nairovirus The genus Nairovirus, named after Nairobi sheep disease, is an acute haemorrhagic gastroenteritis affecting sheep and goats in East Africa, with transmission by the

sheep tick Rhipicephalus appendiculatus. It has caused laboratory infections, but the genus includes Crimean– Congo haemorrhagic fever virus and several other viruses known to infect humans; for example, Ganjam virus, almost indistinguish- able from Nairobi sheep disease virus but first isolated in India from Haemaphysalis intermedia ticks collected from healthy goats; Hazara virus, recovered from Ixodes redkorzevi ticks collected from the vole Alticola roylei in a subarctic habitat at an altitude of 3660 m in the Kaghan valley of Hazara district, Pakistan; Dugbe virus, isolated in Nigeria from Amblyomma variegatum ticks collected from healthy cattle; and Soldado virus, repeatedly isolated from a variety of bird ticks but recently linked to a mild illness in humans. Crimean–Congo haemorrhagic fever virus The virus was first recognized as a cause of an acute febrile haemor- rhagic disease affecting humans in the Crimean region of the former Union of Soviet Socialist Republics, transmitted by ticks and carrying a mortality of 5–30%. In Africa, Congo virus was first isolated in the then Belgian Congo (now Democratic Republic of the Congo) from the blood of a local 13-year-old boy, and it caused a moderately severe laboratory infection. Related viruses were isolated in Uganda where more laboratory infections occurred, one of which ended fatally after a severe haematemesis. In Asia, a virus indistinguishable from Congo virus was isolated from pools of ticks collected from a variety of wild and domestic animals in western Pakistan. Crimean haemorrhagic fever virus was later proved to be serologically indistinguishable from Congo virus, hence the use of the term Crimean–Congo haemor- rhagic fever virus. Different strains of this virus have been associated with outbreaks of severe and sometimes fatal disease in the Crimea, Rostov, and Astrakhan regions of Russia, in Albania, Bulgaria, and the Balkans, in East, West, and South Africa, in Iran, Iraq, and western Pakistan, and in China. From 2002 to 2015, c.9700 cases were re- ported in Turkey, although it was virtually unknown there previously. A U.S. soldier serving in Afghanistan was infected in 2009, treated at a medical facility in Germany, but died. Two healthcare providers had nosocomial infections with mild or no symptoms. In 2016, two cases of Crimean–Congo haemorrhagic fever, including one fatal infection, were diagnosed in Spain. The virus had been detected in Hyalomma lusitanicum ticks from Spain 4 years earlier. Most infec- tions are seen among farmers or abattoir workers and acquired by tick bites or exposure to viraemic animal blood, but infections have occurred in both hospitals and laboratories. Symptoms The incubation period is 3 to 7 days. Fever usually starts suddenly and is normally continuous, although occasionally it is remittent or biphasic. Other clinical features are headache, nausea, vomiting, joint pains, backache, photophobia, circulatory disorders, thrombocytopenia, and leukopenia. Haemorrhagic manifestations are common. Patients show cutaneous petechiae and extensive ecchymoses, and bleed from nasal, gastric, intestinal, uterine, and urinary tract mucosae (Fig. 8.5.16.5). Patients may present with acute abdominal pain, mimicking an acute surgical emergency, and operating room staff have become infected and died through exposure to infected blood or secretions at operation. The mortality is about 5–30%, but may be up to 40% or higher in hos- pital or nosocomial outbreaks. Transient hair loss has been reported. Control, treatment, and prognosis No internationally licensed vaccine is available. Avoidance of tick bites may reduce the risk of infection. In hospital outbreaks, meticu- lous attention to the containment of infected secretions is essential and barrier nursing should be used. Overt disseminated intravas- cular coagulation usually indicates a poor prognosis, and haema- temesis, melaena, and somnolence are significantly more common in fatal cases. Supportive therapy is essential, with monitoring of

Fig. 8.5.16.4 Chest radiograph of a patient with early hantavirus pulmonary syndrome (left), and the same patient 24 h later (right) showing development of bilateral perihilar alveolar oedema. Courtesy of Dr Loren Ketai.

8.5.16 Bunyaviridae 859 fluid and electrolyte balance. The antiviral ribavirin has been recommended, however, efficacy is circumstantial. Limiting injections and avoidance of aspirin or other drugs affecting coagulation may reduce bleeding. Patients who recover can have residual polyneuritis persisting for months, but eventual recovery is to be expected. Laboratory investigations with live virus require biological safety level 4 containment. Genus Phlebovirus At least ten different phleboviruses are known to infect humans (see Table 8.5.16.1). Pappataci fever, sandfly fever, or phlebotomus fever was recognized as a clinical entity in the Mediterranean area during the 19th century, and the association with Phlebotomus papa- tasi sandflies was demonstrated by showing that filtrates of human blood reproduced the disease in human volunteers. It was thought that humans were the only vertebrate host, but antibody studies in- dicate that gerbils, cattle, and sheep may also be infected. Sandfly fever Naples virus was isolated from human serum collected during an outbreak of sandfly fever in Naples, and the sandfly fever Sicilian virus was isolated from American troops with a similar disease in Palermo, Sicily. The two viruses have many common properties, but are serologically quite distinct. Sandfly fever is widespread throughout the Mediterranean area, and also occurs in Iran, Turkey, Bangladesh, India, Pakistan, and the southern states of Russia. Toscana virus, serologically related to the Naples virus, is found in countries bordering the Mediterranean; it is notable for its ability to infect the central nervous system, especially in central Italy where it is thought to be responsible for at least 80% of acute summertime infections of the central nervous system in children. The viruses that cause sandfly fever do not occur in the New World, but in South and Central America a similar clinical condition follows infection with Alenquer, Candiru, Chagres, and Punta Toro viruses. Rift Valley fever has long been known as a disease of domestic animals, mainly sheep, in East Africa, which occasionally spreads to farm workers and others handling infected animals. The infec- tion is endemic, but seldom recognized, in many wild game ani- mals in Africa. Rift Valley fever virus differs from the sandfly fever viruses, Punta Toro virus, and most other members of the genus in being normally transmitted by mosquitoes rather than sandflies. Uukuniemi and Zaliv-Terpeniya viruses are tick-transmitted; the only evidence that Uukuniemi virus can infect humans is the finding of specific antibodies in some human sera collected in Estonia and in former Czechoslovakia. Severe fever with thrombocytopenia syndrome virus and Heartland virus are a newly discovered tick- borne phleboviruses found in China, South Korea and Japan, and the United States of America, respectively, and primarily affecting farmers living in rural areas. Zaliv-Terpeniya virus was isolated from bird ticks collected on an island in the Sea of Okhotsk, Sakhalin region, and there is some evidence that it may be pathogenic to humans. Sandfly fever Naples virus and sandfly fever Sicilian virus Symptoms After an incubation period of 2–6 days, fever starts abruptly with chills, nausea and vomiting, epigastric pain, and often severe gen- eralized headache leading to incapacitating prostration. Fever of 38–40°C usually resolves after 2–3 days, but may be biphasic and persist for a week. There is no rash, but small haemorrhages into the skin and mucous membranes may be seen. Photophobia and eye pain occur, lymphadenopathy is often seen, and the liver may be tender although jaundice is rare. The disease is self-limiting, with complete recovery. No deaths have been attributed to either sandfly fever Naples virus, or sandfly fever Sicilian virus. Rift Valley fever virus Following its initial isolation in 1930 as the agent of enzootic hepa- titis of domestic animals in Kenya, Rift Valley fever virus was rec- ognized as the cause of sporadic human infections in East, Central, and West Africa, with a particular tendency to infect laboratory workers handling the virus. In East and Central Africa, the virus has been isolated from a variety of mosquito species and it is capable of persisting in mosquito eggs during the dry season, emerging when larvae hatch in the rainy season. From 1951 to 1956 there were severe epizootics

in lambs in southern Africa, and many human cases oc- curred. Further human cases with several deaths were seen in South Africa in 1975, and a major outbreak occurred in East Africa fol- lowing El Niño flooding in 1997 to 1998, apparently seeding a ‘virgin (a) (b) Fig. 8.5.16.5 Turkish patients with Crimean–Congo haemorrhagic fever showing petechiae (a) and extensive ecchymoses (a, b) on the arms and thorax. Courtesy of Professor D. I. H. Simpson.

 soil’ outbreak in Saudi Arabia and Yemen in 2000. In 1997–1998 and 2006–2007 there were epizootics in Kenya, Tanzania, Burundi, and Somalia. In the recent epidemic, 684 cases with 155 deaths were re- ported in Kenya (case fatality 23%), 264 cases with 109 deaths in Tanzania (case fatality 41%), and 114 cases with 51 deaths in Somalia (case fatality 45%). Heavy rains in East Africa during 2006–2007 triggered another outbreak with many human and animal cases. Continuing the roughly 10 year cycle, an outbreak affecting humans and domestic animals was reported in north-eastern Kenya in 2018. In the Central African Republic in 1969, a virus isolated from Mansonia africana mosquitoes and named Zinga virus was associ- ated with several cases of haemorrhagic fever; Zinga virus was later shown to be a strain of Rift Valley fever virus. In West Africa, Rift Valley fever virus was isolated from mosquitoes in Nigeria and from bats in Guinea, but despite the presence of antibodies in human sera collected in Nigeria and Senegal, human disease was unrecognized until 1987 when a substantial epidemic occurred in Mauritania, with further epi- demics in following years. In 1977 the virus spread, apparently for the first time, into Egypt, producing a major epizootic in domestic ani- mals, principally sheep and goats but also cattle, and causing about 600 human deaths within 3 months. The virus has been detected intermit- tently since then in Egypt. The principal known vector is the mosquito Culex pipiens. Both the Egyptian and the Mauritanian epidemics ap- peared to be linked to major ecological changes following the construc- tion of the Aswan Dam on the Nile and dams on the Senegal River. Symptoms After an incubation period of 3–6 days, fever starts abruptly with shivering, nausea and vomiting, epigastric pain, arthralgia, and often severe generalized headache. The fever may be biphasic, with temperatures between 38 and 40°C, and may remain elevated for at least a week. There is no rash, but small haemorrhages appear on mucous membranes. Photophobia and eye pains occur. There may be conjunctival inflammation, and a central serous retinitis leading to central scotoma and sometimes to retinal detachment can occur late in disease. The fundus may show macular exudates that are slow to disappear. There is often a lymphadenopathy and although the liver is frequently involved and may be tender, jaundice is rare. Convalescence may be protracted but is usually uncomplicated. A few patients develop severe disease with haemorrhage, enceph- alitis, or eye lesions. Haemorrhagic disease presents as mentioned, but progresses with cutaneous and mucous membrane petechiae, ecchymoses (Fig. 8.5.16.6a), gastrointestinal haemorrhage, and jaundice with severe liver and renal dysfunction often progressing to disseminated intravascular coagulation, hepatorenal syndrome, and death. Patients with encephalitis usually recover from acute febrile disease only to present within a few days to 2 weeks later with head- ache, meningism, confusion, and fever, often leading to residual defects or ending in death. Ocular complications are characterized by rapid onset of decreased visual acuity with scotomas due to ret- inal haemorrhage, exudates, and macular oedema (Fig. 8.5.16.6b). These are also seen after apparent recovery from the initial disease. About one-half of these patients have some degree of permanent visual loss. Death from Rift Valley fever was rarely recognized be- fore the 1977 outbreak in Egypt, but the Mauritanian epidemics with mortality due to jaundice and haemorrhagic manifestations, and the recent East African and Arabian Peninsula outbreaks with several hundred suspect fatalities establish it as a life-

threatening infection. Control, treatment, and prognosis Veterinary vaccines have been used for some years, and formalin- inactivated vaccines have also had limited use for the prevention of disease in laboratory workers and others exposed to high risk of in- fection. Improved vaccines based on molecular techniques are under development. Treatment is supportive. Although there are no reports of nosocomial transmission, barrier nursing would be a sensible precaution. Severe fever with thrombocytopenia syndrome virus Severe fever with thrombocytopenia syndrome first came to the at- tention of Chinese health officials in 2009 when cases appeared in rural areas of Henan and Hubei provinces in central China. Recently cases were diagnosed in South Korea and Japan. Adult farmers appear to be at greatest risk. Severe fever with thrombocytopenia syndrome virus was isolated from ticks (Haemaphysalis longicor- nis), but not from mosquitoes, and molecular characterization of the virus suggests that it is distantly related both to viruses of the sandfly fever complex and to Uukuniemi virus. In cen- tral China between 2011–2016 over 5300 laboratory-confirmed cases were reported, most occurred from May to July, with about 75% of patients over 50 years of age. Transmission by tick bite (a) (b) Fig. 8.5.16.6 Severe Rift Valley fever. (a) Cutaneous petechiae and ecchymosis. (b) Severe central retinal lesion. Courtesy of Professor D. I. H. Simpson.

 is suspected; however, person-to-person transmission has been reported following contact with bloody secretions or vomited blood of patients. Symptoms Symptoms of Severe fever with thrombocytopenia syndrome in- clude fever, thrombocytopenia, and leucopenia, followed by multiorgan failure in severe cases. Patients may present with fever, fatigue, conjunctival congestion, diarrhoea, abdominal pain, pro- teinuria, and haematuria in addition to thrombocytopenia and leucopenia. Multiorgan failure may develop, rapidly leading to death in 12–47% of hospitalized cases based on limited data. Characteristics of less severe disease among nonhospitalized cases have yet to be determined. A robust humoral immune response oc- curs and neutralizing antibodies persist in surviving patients for at least 1 year. Onset of disease occurred 6–13 days after contact with blood of infected persons where person-to-person transmis- sion was suspected. Control, treatment, and prognosis Assuming transmission from infected ticks, control and prevention should focus on avoidance of tick bite. Barrier nursing and standard precautions against contact with blood and other potentially infec- tious bodily fluids are prudent precautions. There is no vaccine and no specific treatment and susceptibility to antiviral drugs like ribavirin has yet to be evaluated. Laboratory testing of clinical specimens and experimental manipulation of severe fever with thrombocytopenia syndrome virus should be done under appropriate containment. Heartland virus A novel phlebovirus was recently isolated from two patients seen independently from north-western Missouri, United States, and each hospitalized with fever, fatigue, diarrhoea, moderate to se- vere thrombocytopenia and leukopenia. Both reported a history of recent tick bite prior to onset of illness. Both patients noted fa- tigue, short-term memory difficulty, and anorexia following hos- pital discharge. Additional cases were diagnoses in 2012–2013 and fatal infections have occurred. Virus was isolated from leukocytes collected from both patients on day 2 of hospitalization and found by phylogenetic analysis to be a novel phlebovirus closely related to severe fever with thrombocytopenia syndrome virus. Heartland virus was detected in nymphs of the tick, Amblyomma america- num. Epidemiological and clinical characteristics of human in- fection due to Heartland virus, as well as optimum treatment and prevention remain to be determined. Unassigned viruses and viruses causing only minor disease in humans The great majority of the viruses listed in Table 8.5.16.2 cause only a mild febrile illness, but the following show certain additional features. Bhanja virus (Phlebovirus) This virus was first isolated from Haemaphysalis intermedia ticks collected from healthy goats in India, but has since

been isolated in Sri Lanka, Africa, and Europe. Infection of goats is widespread in Italy and the Balkans where there have been several reported human cases, including some with severe neurological disease. Laboratory infections have also occurred. Bhanja virus is related to Heartland and severe thrombocytopenia syndrome viruses. Bwamba virus (Orthobunyavirus) This was first isolated in Uganda in 1941 and is very widespread throughout sub-Saharan Africa. More than 75% of adult human sera collected in Nigeria and over 95% of human sera collected in Uganda and Tanzania have antibodies against Bwamba virus. The original cases showed fever, headache, generalized pain, and con- junctivitis but no rash, although a rash has been described in the Central African Republic. No fatalities have been reported. Nyando virus (Orthobunyavirus) This virus was first isolated from mosquitoes in Kenya. It has since been isolated from humans in the Central African Republic where it caused fever, myalgia, and encephalitis. Tataguine virus (unassigned) This causes fever, rash, and joint pains in at least five African coun- tries (Cameroon, Central African Republic, Ethiopia, Nigeria, and Senegal). Wanowrie virus (unassigned) This virus was first isolated in India from Hyalomma marginatum ticks collected from sheep. It has also been isolated in Egypt and Iran, and in Sri Lanka where it was recovered from the brain of a 17-year-old girl who died following a 2-day fever with abdominal pain and vomiting. FURTHER READING

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