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870 section 8 Infectious diseases loss, which occurs in up to 30% of Lassa fever patients, was recently shown in a mouse model to be associated with mild damage to the cochlear cells and significant degeneration of the spiral ganglion cells of the auditory nerve. The T-cell response to Lassa virus is sus- pected to play a role in the pathology. Likely developments in the near future The novel pyrazine derivative Favipiravir (T-705, Toyama Chemical Company Ltd), is likely to be tested in clinical trials for efficacy against Lassa fever. Given the success of the Ebola vaccine based on recombinant vesicular stomatitis virus (Ebola-VSV), a Lassa-VSV vaccine which has shown promise in nonhuman primates might ad- vance to the clinic as well. FURTHER READING Bonthius DJ, et al. (2007). Congenital lymphocytic choriomeningitis virus infection: spectrum of disease. Ann Neurol, 62, 347–55. Fischer SA, et al. (2006). LCMV in transplant recipients: transmission of lymphocytic choriomeningitis virus by organ transplantation.
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8.5.18 Filoviruses Jan H. ter Meulen ESSENTIALS Filoviruses are large RNA viruses, of which Ebola virus and Marburg virus cause the most severe forms of viral haemorrhagic fever and have been best-studied because of fear of their misuse as bioter- rorism agents. These are zoonotic viruses with reservoirs, most likely fruit-eating bats, in the rainforests of tropical Africa, where they cause sporadic infections and outbreaks among great apes and humans. Epidemiology—The primary mode of transmission of Ebola virus to humans often involves contact of hunters with dead animals that serve as amplifying hosts, especially gorillas, chimpanzees, and forest antelopes, whose meat is consumed as ‘bush meat’.
Contact with bats has been implicated for both Marburg and Ebola virus. However, the viruses are highly infectious and are transmitted from the index case and subsequently from person to person by all body fluids, including sweat, respiratory droplets, and semen. The viruses have been found to persist in convalescent patients for many months. Clinical features and therapy—Because filovirus infections cause a range of severe symptoms with overt haemorrhage occurring only in a subset of

patients, the terms Ebola virus disease and Marburg virus disease are now being used instead of Ebola or Marburg haemorrhagic fever. Clinical presentation of Ebola virus disease and Marburg virus disease is similar, initially as an influenza-like illness, often with gastrointestinal symptoms, followed by develop- ment of a maculopapular rash and haemorrhagic manifestations developing in approximately half of patients, including epistaxis, gum-bleeding, haematemesis, melaena, petechiae, and ecchymoses. There is no licensed specific antiviral treatment. Broad-spectrum antivirals, monoclonal antibodies and inhibitory RNAs have recently been evaluated in small studies or on a compassionate use basis with varying results. Intensive supportive care and treatment of compli- cations are very important to improve survival. Survivors often suffer for prolonged periods of time from various sequelae and may experi- ence relapses of symptoms, which collectively are called post-Ebola syndrome. The viruses can persist in semen for months, requiring precautions in convalescence to prevent sexual transmission. Diagnosis and prevention—The clinical diagnose of viral haem- orrhagic fever or Ebola virus disease/Marburg virus disease re- quires the immediate instalment of the strictest barrier nursing procedures and notification of public health authorities. Care must be taken in both drawing and handling blood specimens, which must be inactivated before performing routine laboratory tests, and samples must be shipped immediately to a reference laboratory for diagnosis by detection of virus by cell culture, viral antigen by enzyme-linked immunoabsorbent assay, and viral RNA by polymerase chain reaction. A prophylactic Ebola vaccine based on a recombinant, replication-competent vesicular sto- matitis virus has shown high efficacy in ring vaccination during the last epidemic and is anticipated to be licensed by Merck & Co. Introduction Filoviruses are large, enveloped, negative-stranded, nonsegmented RNA viruses with a characteristic thread-like morphology, hence the family name Filoviridae (Latin filum = thread). They comprise of five species of Ebola virus, named Zaire, Sudan, Tai Forest, Bundibugyo, and Reston, and one species of Marburg virus. They are now among the best-studied agents of viral haemorrhagic fevers, mainly because of fear of their misuse as bioterrorism agents (Chapter 10.5.13). The first appearance of these viruses was in Marburg, Germany, in 1967, when laboratory, medical, and animal care personnel exposed to tissues

 and blood from African Green monkeys (Cercopithecus aethiops) were infected. In 1976 and 1979, epidemics of a haemorrhagic disease with very high mortality in the northern Democratic Republic of the Congo (then Zaire) and in southern Sudan were found to be due to two strains of a related filoviruses, named Ebola virus. Over the next 10 years, rare, sporadic cases of filovirus infections in Africa were the only continuing evidence of the existence of these viruses. Another species of the virus, Ebola virus Reston was imported on four oc- casions between 1989 and 1996 with wild-caught monkeys (Macaca fascicularis) from Mindanao, Republic of the Philippines, to animal facilities in the United States of America and Italy. This virus, which is highly lethal for monkeys, has caused asymptomatic infections in pigs and animal keepers. Since 1990, both Ebola virus and Marburg virus disease have re-emerged across tropical Africa between lati- tudes 5° north and 5° south, causing several devastating outbreaks, and in December 2013 the Zaire strain of Ebola virus emerged in the forests of the Republic of Guinea, West Africa, and triggered the lar- gest and longest human epidemic of Ebola virus infection recorded to date. Across several countries in West Africa, over 28 000 people were infected and more than 11 000 died. This fatality rate of less than 50% was lower than in most previous outbreaks. Taken together, Ebola virus outbreaks or sporadic human cases have been recorded in Côte d’Ivoire, DRC, Gabon, Guinea, Liberia, Sierra Leone, Sudan, and northern Uganda and Marburg virus disease cases in Uganda, Kenya, Angola, and DRC. The largest Marburg virus disease outbreak to date has

occurred in Uige, Angola, with more than 250 people infected and a case-fatality rate of close to 90%. Bats or nonhuman primates represent the most likely species in- volved in the occurrence of sporadic human outbreaks. Zoonotic transmission to the human host likely occurs through hunting and meat consumption (‘bush meat’), while human-to-human transmission efficiently propagates Ebola virus through mucosal contact with infected body fluids. The risk of transmission con- tinues following death; hence, corpses remain at high risk and must be handled in accordance with full infection control procedures. Aetiology, genetics, pathogenesis, and pathology Filovirus infections are characterized by massive, unchecked, and destructive replication of virus in several organs, profound im- munosuppression due to infection of immune cells and apop- tosis of infected and noninfected cells, and triggering of a cascade of immune-mediated mechanisms resulting in a cytokine storm, endothelial damage, and coagulopathy culminating in shock and organ failure. The immunological and pathological events in end- stage filoviral disease resemble, in several aspects, those of bacterial sepsis: systemic inflammation (increased levels of proinflammatory cytokines, e.g. IL-6 and IL-8, and the anti-inflammatory cytokine IL-10), immune dysfunction (increased susceptibility to secondary bacterial infections, lymphocyte apoptosis), coagulopathy (in- creased D-dimers, thrombomodulin, ferritin, disseminated intra- vascular coagulation, thrombocytopenia), endothelial dysfunction (vascular leak with hypovolemia) and organ dysfunction (renal insufficiency, hepatic dysfunction, respiratory failure, neurologic dysfunction). Through minute lesions in the skin and mucosa, the pantropic filo- viruses infect initially dendritic cells, monocytes, and macrophages. Lymphocytes are spared from the infection. Ebola virus and Marburg virus disease infected dendritic cells fail to mature to the antigen-presenting stage and do not produce proinflammatory cyto- kines required for activation of natural killer cells and T cells. At the molecular level, the expression of viral proteins interferes with the production of interferon-α (IFN-α) and β, and with the ability of these and IFN-γ to induce an antiviral state in cells. Dendritic cells show no increase in costimulatory molecules such as CD40, CD86, and interleukin 12 (IL-12). The early immune response dysfunction originating in dendritic cells is aggravated by continued replication of filoviruses in monocytes and macrophages, accompanied by the secretion of noninhibited proinflammatory cytokines and activa- tion of polymorphonuclear leucocytes. This accumulated release of proinflammatory mediators culminates in a ‘cytokine storm’, causing thrombocytopenia and endothelial injury, for example, through the action of tumour necrosis factor-α (TNFα). Fatal human Ebola cases showed a marked elevation of serum levels of IFN-γ, IL-2, and IL- 10, whereas elevated IFN-α, TNFα, and IL-6 were associated with fatalities in some, but not all, studies. Increased blood levels of ni- tric oxide, which has been shown to contribute to hypotension, cardiodepression, and vascular hyporeactivity in sepsis, were also found to be associated with mortality. The likely reason for the vari- ations of cytokine and chemokine release observed in vivo, as well as in experimentally infected primary human cells, is currently un- known genetic differences of the host. One study reported that HLA- B*07 and HLA-B*14 alleles were associated with survival, whereas HLA-B*67 and HLA-B*15 were associated with lethality in Ebola virus-infected patients. Both humans and experimentally infected nonhuman primates show massive apoptotic death of noninfected CD4+, CD8+, and NK cells in the blood and peripheral lymph nodes, a phenomenon which has been termed ‘bystander apoptosis’. Lymphocyte apoptosis was thought to be responsible for an elimin- ation of adaptive immune responses; however, studies in transgenic mice have not confirmed it as a major factor in the pathogenesis of disease. In addition, there appears to be also massive apoptotic death of infected macrophages. The expression of tissue factor is upregulated in infected monocytes and triggers the extrinsic pathway of coagulation. The procoagulant state amplifies the production of proinflammatory cytokines and

the development of vascular leakage, which further provokes activation of coagulopathy. The terminal stage of the disease is therefore charac- terized by plasma leakage, disseminated intravascular coagulopathy, and bleeding. It is thought that triggering the aforementioned cascade of events is more critical to the development of the observed pathology than direct organ damage due to cytopathic virus replica- tion. However, infection of the liver and adrenal glands impairs the synthesis of clotting factors and steroids, thus aggravating haemor- rhage and shock. Whether infection of endothelial cells contributes to the overall pathology remains controversial. At autopsy, both Marburg and Ebola-infected humans and pri- mates show widespread haemorrhagic diathesis of skin, membranes, and soft tissue. Extensive necrosis with little infiltration is seen in parenchymal cells of many organs, including liver, spleen, kidneys, and gonads. The most characteristic histopathological features are seen in the liver. Large disseminated deposits of viral antigen can be found in different organs, including the sweat glands and the skin. Virus is also detectable in pneumocytes and as cell-free virions in the alveoli.

872 section 8 Infectious diseases Spleen and lymph nodes show various degrees of lymphoid depletion with extensive vascular follicular necrosis. Fatal infection is marked by absence of specific IgG and presence of low levels of spe- cific IgM in only 30% of cases, whereas in human survivors early and increasing levels of Ebola-specific IgM and IgG is followed by activation of cytotoxic T cells. During two outbreaks in Gabon, asymptomatic seroconversion with polymerase chain reaction (PCR)-proven infection occurred in several people who mounted an early, strong but transient inflammatory response, with high levels of proinflammatory cytokines. This unexpected observation and data from animal models suggest that a tightly controlled, tran- sient early type I IFN and proinflammatory cytokine response can induce protective antiviral innate and adaptive immune responses. All of this points to great variability in individual host susceptibility to infection and reinfection based on innate immunity, as well as the viral load to which the individual is exposed during a challenge or rechallenge. The recent successful immunization against Ebola virus disease in animal models using different vaccine modalities revealed that humoural immunity plays the major role in protection against Ebola virus infection, whereas cell-mediated immunity plays a supporting role, becoming more prominent when vaccine induced antibody levels are suboptimal. Epidemiology Central African nonhuman primates and monkeys are victims of Ebola virus, as are other animals such as bushpigs, porcupines, and antelopes living in the tropical rainforest. Data from wildlife sur- veillance show that epizootics occur more often than previously thought and that Ebola virus has caused massive declines of gor- illas and chimpanzees. Phylogenetic analysis of the viruses further suggests that the outbreaks are epidemiologically linked and that Ebola virus, strain Zaire, has spread south-westward since 1976 in a wave-like manner from Yambuku, its site of appearance in the DRC, to the Republic of the Congo and to Gabon at a speed of approxi- mately 50 km per year. This argues against the hypothesis that Ebola virus-Z was resident, but undetected, in the central African forest block before the mid-1970s. The exact source of the 2014 outbreak in West Africa has not been confirmed but likely involves exposure to a colony of Angolan free-tailed bats (Mops condylurus) roosting in a tree. Evidence has also accumulated that fruit-eating bats (Hypsignathus monstrosus, Epomops franqueti, Myonycteris torquata and others) are one, but possibly not the primary, natural reservoir of Ebola virus, and hunting of bats for human consumption has been linked to an Ebola virus outbreak in DRC in 2007. Recently, Ebola virus Reston was detected in domestic swine in the Philippines and a few asymptomatic human infections were reported. The pathogen- icity of the virus for these animals and their possible role in a trans- mission cycle are currently not known. The primary mode of transmission of Ebola virus

to humans often involves contact of hunters with dead animals, especially chimpan- zees, whose meat is consumed as ‘bush meat’. In several outbreaks, however, the mode of infection of the index case could not be elu- cidated. The index cases usually transmit the virus to caring family members, often women, who come into contact with blood and body fluids. These are highly infectious, so that the average rate of secondary cases generated from the index case is around 10–20%, but might be considerably higher. Occasionally, the virus has been spread through sexual contact. Nosocomial spread through im- properly sterilized reusable syringes or other medical equipment has caused explosive Ebola epidemics in Sudan and the Democratic Republic of the Congo. The mortality among surgical staff operating on Ebola virus disease patients misdiagnosed as having acute ab- dominal conditions was also extremely high. Nursing activities and preparing the corpse for burial carry a high risk of infection, as do burial practices which include touching of the corpse and collectively washing hands in a common bowel thereafter. There is no epidemio- logical evidence that Ebola or Marburg viruses are transmitted as true, small particle aerosols between humans. However, direct mu- cosal exposure to droplets generated by a patient during coughing poses a considerable risk of infection. A meta-analysis of all publi- cations on the household secondary attack rate (SAR) during Ebola epidemics estimated the overall SAR at 12.5%, with the greatest risk factor being the provision of nursing care (SAR, 47.9%). According to this analysis, 27.1% of all Ebola infections are asymptomatic and these individuals are unlikely to transmit the virus. Ebola virus has been cultured from aqueous humour, saliva, breast milk, urine, and semen of infected patients; in addition, viral RNA has been found in stool, tears, and sweat, and in rectal, conjunc- tival, vaginal, and skin swabs. Because large amounts of virus can be found in skin, and sweat may contain the virus, touching an infected person might result in transmission. Infected persons can shed virus for prolonged periods of time after infection (several weeks to months). The virus has been cultured from semen up to 82 days after illness onset. Sexual transmission has, so far, only been documented in a single case, based upon which infectious virus may persist in semen for 179 days. Mother-to-child transmission by breastfeeding in survivors of Marburg virus has been reported, and the potential for transmission through breast milk has also been suggested for Ebola. Viable Zaire Ebola virus was detected in aqueous humour 14 weeks after the onset of Ebola virus disease and 9 weeks after the clearance of viremia. However, samples of conjunctivae and tears tested negative for Ebola virus, which supports previous studies sug- gesting that patients who recover from Ebola virus disease pose no risk of spreading the infection through casual contact. Marburg virus disease epidemiology is similar to that of Ebola virus. Evidence of infection has been detected in fruit-eating bats (Rousettus aegyptiacus) from Uganda and Kenya, and in insectiv- orous bats in DRC (Miniopterus inflatus, Rhinolophus elocuens). However, epizootics have not been observed in mammals. Contact with bats during mining activities was reported for several index cases of Marburg haemorrhagic fever, in accordance with cave roosting of R. aegyptiacus, a habit that is not observed in the bat spe- cies implicated in Ebola virus transmission. Until 2000, the viral ori- gins of cases could be traced to eastern Africa. However, in 2005 the largest outbreak of Marburg haemorrhagic fever occurred in Uige, Angola, expanding the known range of the disease to the far western edge of the Congo basin. Continuing population movements in cen- tral Africa, destruction of the rainforest, and increased consumption of ‘bush meat’ increase the likelihood of future filovirus outbreaks. In 2008 a fatal and a nonfatal case of Marburg haemorrhagic fever occurred in the Netherlands and the United States of America, respectively, imported by tourists who had visited a bat-roosting cave in Uganda (Python cave, Queen Elizabeth Park). Touching bat

8.5.18 Filoviruses 873 excrement or being hit by low-flying bats were identified as possible risk factors for acquisition of the infection. Recently, a genetically distinct filovirus was discovered in Spain in dead insectivorous bats (Miniopterus schreibersii) and named Lloviu virus. There is currently no evidence of human infections with this virus. Prevention In endemic areas, avoidance of contact with bats and their excrements, with dead and diseased monkeys, and control of monkey sellers are currently the only feasible options for prevention. In case of outbreaks, interruption of person-to-person spread of the virus is essential for control. Early institution of safe and orderly care of the ill, using barrier nursing and disinfection procedures, should be set up with effective surveillance of high-risk contacts and prompt isolation of further cases (e.g. barrier nursing, guidelines from the Centers for Diesase Control and Prevention (CDC) and World Health Organization (WHO); see Chapter 8.5.17 and Box 8.5.17.1). In fully equipped hospitals, patients must be placed in negative-pressure rooms and all personnel must wear protective gear with FP3 filters for respiratory protection (Fig. 8.5.18.1). Cutaneous or mucosal contact with blood or body fluids from an Ebola patient poses a high risk. Contacts must be followed up for development of persistent high fever for 3 weeks from the last date of contact by daily temperature measurement. Development of vaccines against filoviruses has recently made astonishing progress, driven by the public health emergency of the West African Ebola virus outbreak in 2014/15. Two recom- binant viral vectored vaccines, a replication defective adenovirus and a replication-competent vesicular stomatitis virus (VSV) each expressing the glycoprotein of Ebola virus were tested during the outbreak. The latter was recently reported to have 100% efficacy in the preliminary analysis of a phase 2/3 trial employing a ring- vaccination cluster-randomized design during the Ebola virus epi- demic in Guinea and its licensure could be as early as 2018. The manufacturer Merck & Co. has made the vaccine available during 2016 for ring vaccinations following the occurrence of several iso- lated cases of Ebola virus disease in West Africa after the epidemic had been declared over, and again in 2018 in the most recent out- break of Ebola in the DRC. Its single-dose regimen and proof of effectiveness from 10 days postimmunization make it an attractive candidate for use in an outbreak campaign. A drawback of this vac- cine is that is requires storage at –70 oC. Protection against Marburg virus disease infection in animal models has been much easier to achieve using a variety of vac- cines, including recombinant proteins, than against Ebola virus. This is probably due to the slightly slower replication of the virus in these models. Given the success with the VSV-vectored Ebola virus vaccine (see earlier), this approach will likely be extended to a multifilovirus vaccine comprising of three species of Ebola virus and of Marburg virus disease. Clinical features Marburg virus disease and Ebola virus cause identical clinical dis- eases. After an incubation period of 5 to 12 days, the disease starts suddenly with fever, headache, myalgia, and extreme fatigue. Early signs also include conjunctivitis, bradycardia, and sore throat, often associated with severe swelling and dysphagia, but no exudative pharyngitis. Severe nausea, vomiting, abdominal pain, and profuse watery diarrhoea are common (Fig. 8.5.18.2). Around the fifth day, a perifollicular, nonitching, maculopapular rash frequently appears on the trunk, back, and shoulders, spreading to the face and limbs and becoming confluent (Fig. 8.5.18.3). It may be difficult to see and has a measles-like appearance on dark skin. The rash fades in 3–10 days and is followed by a desquamation in survivors. In about half of the patients, haemorrhagic manifestations occur between the fifth and seventh day, including epistaxis, gum-bleeding, haematemesis (Fig. 8.5.18.4), melaena, petechiae, ecchymoses (Fig. 8.5.18.5), haem- orrhages from needlesticks and post-mortem evidence of visceral Fig. 8.5.18.1 Personal protective equipment in use in Sierra Leone during Ebola epidemic in 2015. Courtesy of Dr Alastair Moore.

874 section 8 Infectious diseases haemorrhagic effusions. While clinically significant haemorrhage occurs in only a minority of patients, coagulopathy appears to be a typical feature of Ebola virus disease. Dehydration and prostration are frequent; patients show the ghost-like facial expression typical of the disease. During the first week, the temperature remains high around 40°C, falling by lysis during the second week, to rise again between days 12 and 14. Other clinical signs during the second week include hepatosplenomegaly, oedema, orchitis, scrotal or la- bial reddening, myocarditis, and pancreatitis. Jaundice is not a fea- ture. A poor prognosis is marked by haemorrhagic signs, oliguria or anuria, chest pain, shock, tachypnoea, and neurological symp- toms (sudden hearing loss, blindness, painful paraesthesia, intract- able hiccups). Death in shock usually occurs 6–9 days after onset of clinical disease. Infection in pregnancy results in high maternal mortality and virtually 100% fetal death. Central nervous system in- volvement has led to hemiplegia and disorientation, and sometimes frank psychosis. Causes of death remain poorly understood but are likely to be due (in combination or alone) to a combination of septic shock (leaky gut?) and multiorgan failure (direct cytopathic effect). The recovery of Marburg and Ebola disease is prolonged with arth- ralgia or persistent arthritis, ocular disease (ocular pain, photo- phobia, hyperlacrimation, loss of visual acuity, uveitis), hearing loss, and orchitis occurring as late manifestations. Neurological ab- normalities in survivors seem to be frequent; on neurological exam most common findings reported are abnormal smooth pursuits and saccades, tremor, abnormal reflexes, and sensory abnormal- ities. In a minority of survivors ongoing seizures, evidence of stroke (including hemiparesis, hemianopsia, and cranial nerve abnormal- ities), and parkinsonism have been described. Other symptoms of the so-called post-Ebola syndrome include abdominal pain, anorexia, Fig. 8.5.18.2 Severe vomiting and diarrhoea in a patient with Ebola virus disease in Sierra Leone. Courtesy of Dr Alastair Moore. Fig. 8.5.18.3 Rash of Ebola haemorrhagic fever acquired through a laboratory accident. Courtesy of Professor D. I. H. Simpson. Fig. 8.5.18.4 Haemorrhage and oedema of face and neck in Marburg haemorrhagic fever. Courtesy: Professor S. Stille. Fig. 8.5.18.5 Ecchymoses in a patient with Ebola virus disease. Courtesy of Professor D. I. H. Simpson.

8.5.18 Filoviruses 875 headache sleep disturbances, dizziness, itchiness/rashes, impotence, numbness, retroorbital pain, and muscular weakness. Serious but re- versible personality changes have been recorded in a few survivors, namely confusion, anxiety, depression, and aggressive behaviour. Blindness has been reported as a sequel. Preliminary data from a study tracking 1500 Ebola survivors for up to 5 years in Liberia (PREVAIL) show that 68% have neurological complications, 60% eye problems, and 55% musculoskeletal disorders. Both Ebola virus and Marburg virus disease have been iso- lated from the anterior chamber of the eye and from seminal fluid many weeks after the onset of clinical disease and there have been documented cases of sexual transmission. The shedding of Ebola virus RNA has been detectable in semen and vaginal fluid by PCR for many months, with approximately one-quarter of the nine par- ticipants of one study having positive findings on quantitative RT- PCR at 7–9 months after onset, but not by virus isolation. Patients should, therefore, refrain from sexual activities during early conva- lescence. Another lesson to emerge from the 2014 epidemic is that some survivors experience serious symptoms after their recovery from the main disease episode, suggesting that viral persistence in certain compartments of the body is more serious in some survivors than previously recognized. A British nurse who developed Ebola virus meningitis more than 9 months after surviving acute Ebola virus disease was readmitted 14 months past the initial infection to a high-containment unit for treatment of late disease complications. Ebola virus can persist in the central nervous system

and be trig- gered to reactivate or to escape immune surveillance, or both. It is not clear how, or whether, post-Ebola virus disease immunity is af- fected by the stage of treatment or type of therapy given. Haematological studies reveal early leucopenia, thrombocyto- penia accompanied by abnormal platelet aggregation, subsequent relative neutrophilia, and the appearance of atypical lymphocytes. Liver enzymes are elevated (AST/SGOT >ALT/SGPT) consistent with histopathological evidence of hepatitis (Fig. 8.5.18.6), but al- kaline phosphatase and bilirubin levels are usually normal or only slightly elevated. Disseminated intravascular coagulation is a prom- inent manifestation of Ebola virus infection in primates (prolonged prothrombin (PT) and partial thromboplastin time (PTT), D-dimers, fibrin split products), and elevated D-dimers and thrombocytopenia are consistently observed in early stages of illness in humans. Fibrin deposition has been documented at autopsy. Detailed studies of the coagulation disorder have been performed in two patients treated in intensive care in the United Kingdom and both had evidence of a consumptive coagulopathy. As this resolved, thromboelastography demonstrated that both developed a marked hypercoaguable state, which was treated with low molecular weight heparin. Neither case developed any clinical evidence of venous thromboembolic disease or complications from anticoagulation. Currently the frequency of occurrence and clinical importance of the hypercoagulable state is unknown. In nonhuman primates, a rapid decline in plasma protein C levels was observed in Ebola virus infection, preceding clinical symptoms. Differential diagnosis and criteria for diagnosis Clinically, filovirus infections can be confused with nonviral in- fections such as severe malaria, typhoid fever, shigellosis (‘diarrhée rouge’ in francophone Africa), leptospirosis, rickettsial diseases, meningococcaemia, Gram-negative sepsis, and other conditions re- sulting in disseminated intravascular coagulation. There is overlap of clinical presentation with other viral haemorrhagic fevers. Ebola virus disease or Marburg virus disease should be suspected in a pa- tient living in or coming from, within the incubation period, a known endemic area (currently Angola, Côte d’Ivoire, the Democratic Republic of the Congo, Gabon, Sudan, Kenya, and Uganda, Guinea, Sierra Leone, Liberia, Ivory Coast) and presenting with other- wise unexplained high fever (above 38.5°C) and vascular involve- ment (subnormal blood pressure, postural hypotension, petechiae, haemorrhagic diathesis, flushing of face and chest, nondependent oedema). Reported contact with another viral haemorrhagic fever patient or a known viral haemorrhagic fever vector is obviously a very important risk factor. During outbreaks, more specific case def- initions are typically being developed (see Box 8.5.18.1). The case definition for suspected Ebola virus infection might change during the course of an outbreak and differ from that of pre- vious outbreaks. Because viral haemorrhagic fever is a purely clinical diagnosis which requires the immediate instalment of barrier nursing proced- ures and notification of public health authorities, rapid laboratory con- firmation is mandatory. Care must be taken in drawing and handling blood specimens since virus titres can be extremely high and the virus is stable for long periods, even at room temperature. During the first week of clinical illness, virus is easily detected by cell culture, viral antigen by enzyme-linked immunoabsorbent assay, and viral RNA by PCR, and commercially available field tests to detect antigen in blood or cadaveric oral fluids (OraQuick Ebola Rapid Antigen test, Orasure Fig. 8.5.18.6 Hepatic histology in Ebola haemorrhagic fever. Courtesy of Professor D. I. H. Simpson. Box 8.5.18.1 Signs and symptoms for suspecting Ebola virus infection during the 2014 outbreak (developed by WHO, CDC USA, Médecins Sans Frontières) 1 Fever + contact with a known Ebola virus disease case, or 2 Fever + at least three of the following: Headaches, lethargy, dyspnoea, dysphagia, dyspepsia, loss of appetite, myalgia/arthralgia, vomiting, diarrhoea, hiccups, or 3 Any person with unexplained bleeding, or 4 An unexplained death

876 section 8 Infectious diseases Technologies Inc, USA) or RNA in blood (RealStar Zaire EBOV PCR, Altona Diagnostics, Germany) have recently been used successfully to identify EBOV during the 2018 outbreak in DRC. Impressively, the circulating Ebola virus strain could be sequence-confirmed by a local laboratory within 10 days using nanopore-sequencing tech- nology (MinION device, Oxford Nanopore Technologies, UK). Blood samples must be handled and shipped to a reference labora- tory using special precautions (triple packaging: primary, secondary, and outer container with absorbent material in between) and must be inactivated for performing routine laboratory tests (Chapter 8.5.17, Table 8.5.17.1). In fatal human Ebola virus cases, antiviral IgM and IgG antibodies were detected in 46% and 30% of patients, respectively. However, in the age of rapid and accurate molecular diagnostics, ser- ology does not play a major role in diagnosis of the disease. Virus can also be visualized by immune-histochemistry in formalin-fixed skin biopsies taken from the axilla or nape of the neck. For handling of clinical specimens from suspected cases, see Chapter 8.5.17, Table 8.5.17.1. Treatment Conceptually, therapy of Ebola virus disease and Marburg virus dis- ease consists of specific antiviral approaches, modulation of the host immune response, and symptomatic treatment. Currently, no specific antiviral licensed therapy is available. However, several small mol- ecule and biological drugs were evaluated in small trials during the recent outbreak in West Africa, or were given on a compassionate use basis. Favipiravir (T-705) is a broad-spectrum antiviral developed by Toyama Chemical Co Ltd., which has been approved in Japan and is now in phase III of clinical development in the United States for the treatment of complicated or resistant influenza. In a noncomparative, proof-of-concept trial, in which all patients received favipiravir along with standardized care (10-day treatment with a loading dose of 6000 mg on day 1 and a maintenance dose of 2400 mg/day for adults), it had no effect on survival in patients with a viral load of greater than 7.7 log 10 copies/ml. However, it had a possible effect on patients with lower viral loads (20% mortality in treatment group vs. 30% in pretrial controls). Toxicity was not reported in this trial. TKM-Ebola, devel- oped by Arbutus biopharma (formerly known as Tekmira), belongs to a new therapeutic class based on RNA interference technology. This drug is composed of two small interfering RNAs (siRNAs), which si- lence the Ebola virus viral polymerase and VP35 genes by inhibiting mRNA translation and enhancing host cell-mediated viral mRNA destruction. As siRNAs are very unstable, they are encapsulated and protected in lipid nanoparticles coated with polyethylene glycol mol- ecules. TKM-Ebola has been used in the United States in two adult patients as compassionate treatment in combination with extensive supportive care and convalescent plasma. The two patients survived despite severe disease-related clinical and biological alterations. A phase II, single-arm clinical trial in Sierra Leone to evaluate the ef- ficacy of TKM-Ebola in patients was discontinued because of a low probability of demonstrating an overall therapeutic benefit. ZMapp is a cocktail of three humanized monoclonal antibodies with strong neutralizing in vitro and in vivo activity against the Zaire strain of Ebola virus. In a randomized controlled trial in West Africa, mortality in the ZMapp-treated participants who received a fixed dose of 50 mg/ kg administered every 3 days was 40% lower (8 of 36; 22% mortality) than in participants receiving standard of care alone (13 of 35; 37%). However, due to a smaller-than-intended sample size because of en- rolment problems, this difference did not reach statistical significance. Serum from Ebola virus survivors contains varying levels of low titre neutralizing antibodies and Ebola virus-infected nonhuman primates have been successfully treated up to 48 hours after a lethal Ebola virus challenge with multiple doses of concentrated, species- matched, polyclonal immunoglobulin G obtained from vaccinated rhesus macaques that had survived challenge with a lethal Ebola virus dose. In a nonrandomized, comparative study in West Africa, 84 patients of various ages (including pregnant women) with con- firmed Ebola virus disease received two consecutive transfusions of 200–250 ml of ABO-compatible convalescent

plasma, with each unit of plasma obtained from a separate convalescent donor. The transfusions were initiated on the day of diagnosis or up to 2 days later. No significant improvement in survival was observed in the treated group (risk of death 31% vs. 38% in control group), however, the level of neutralizing antibodies against Ebola virus in the plasma was unknown at the time of administration. A summary of all experimental Ebola virus drugs which were evaluated in clinical trials during the last epidemic has been re- cently published (Cardile et al., 2017). Among the post-exposure treatments monoclonal antibodies seem to demonstrate the highest level of efficacy, whereas for relapsed or convalescent patients who are shedding filoviruses faviparivir, siRNAs and or the adenosine analogue GS-5734 (Remdesivir, Gilead Sciences) may be more appropriate. Fluid, electrolyte, respiratory, and osmotic imbalances should be managed carefully. Patients may require full intensive care sup- port, including mechanical ventilation, along with blood, plasma, or platelet replacement. The maintenance of intravascular volume is a particular challenge, but every effort is justified since the crisis is short lived, and complete recovery can be expected in survivors. Treatment of all concurrent (tropical) infections is important. Recommendations on how to best treat Ebola patients requiring critical care delivered by experienced multidisciplinary teams (e.g. using Trexler isolator tents), have been published (Fig. 8.5.18.7). Meticulous adherence to infection prevention guidelines and thor- ough training of staff is key to prevent nosocomial infections.
Fig. 8.5.18.7 An example of an isolation unit for transporting a patient with Ebola virus disease. Courtesy of Dr Alastair Moore.

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