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862 section 8 Infectious diseases Crimean–Congo haemorrhagic fever Bente DA, et al. (2013). Crimean–Congo hemorrhagic fever: history, epidemiology, pathogenesis, clinical syndrome and genetic diver- sity. Antiviral Res, 100, 159–89. Conger NG, et al. (2015). Health care response to CCHF in US soldier and nosocomial transmission to health care providers, Germany, 2009. Emerg Infect Dis, 21, 23–31. Swanepoel R (1995). Nairovirus infections. In: Porterfield JS (ed) Exotic viral infections, pp. 285–93. Chapman & Hall, London. Sandfly fever, Rift Valley fever, and severe thrombocytopenia syndrome Bartelloni PJ, Tesh RB (1976). Clinical and serologic responses of vo- lunteers infected with phlebotomus fever virus (Sicilian type). Am J Trop Med Hyg, 25, 456–62. Bird BH, McElroy AK (2016). Rift Valley fever virus: unanswered questions. Antiviral Res, 132, 274–80. Madani TA, et al. (2003). Rift Valley fever epidemic in Saudi Arabia: epidemiology, clinical and laboratory characteristics. Clin Infect Dis, 37, 1084–92. Mansfield KL, et al. (2015). Rift Valley fever virus: a review of diagnosis and vaccination, and implications for emergence in Europe. Vaccine, 33, 5520–31. McMullan LK et al. (2012). A new phlebovirus associated with severe febrile illness in Missouri. N Engl J Med, 367, 834–41. Yu X-J, et al. (2011). Fever with thrombocytopenia associated with a novel Bunyavirus in China. N Engl J Med, 364, 1523–32. 8.5.17 Arenaviruses Jan H. ter Meulen ESSENTIALS Arenaviruses are zoonotic RNA viruses that are distributed worldwide and are adapted to various rodent genera. Some are highly patho- genic and cause haemorrhagic fevers that are endemic in restricted regions of a few countries. Humans are thought to become infected mainly through inhalation of aerosolized rodent urine or dust par- ticles to which infectious urine has dried, or by ingestion of contamin- ated foodstuff: prevention therefore depends on rodent control and avoidance of contact with rodents, their excreta, and nesting materials. Clinical approach—because arenaviruses cause diseases that start insidiously and therapy is life-saving, they should be considered in all patients with fever of unknown origin and a history of possible exposure in the well-known endemic areas. Specific infections Lassa fever—reservoir is a small rodent (Mastomys natalensis); occurs
regularly in rural areas of Nigeria, Liberia, Sierra Leone, and the Republic of Guinea, but may occur also in other West African countries. Clinical picture is highly variable and can be difficult to distinguish from other febrile infections, but may include chest pain, nausea/vomiting/ diarrhoea/abdominal pain, facial swelling, pulmonary oedema, and bleeding. Case fatality is 15–30%, but may be reduced by up to 90% through prompt administration of ribavirin. Irreversible sensorineural deafness is a frequent complication. Body fluids of patients are highly infectious and Lassa virus has been transmitted directly from person- to-person, hence strict ‘barrier nursing’ measures are required and (if possible) patients with severe disease and bleeding should be man- aged in a negative-pressure room by personnel wearing appropriate protective gear, including

respiratory filters; postexposure prophylaxis with ribavirin should be considered. No vaccine is available. Lymphocytic choriomeningitis virus infection—reservoir is the house mouse. Most commonly causes an influenza-like illness, some- times with subsequent aseptic meningitis or encephalomyelitis. Intrauterine infection has resulted in nonobstructive hydrocephalus with periventricular calcifications, chorioretinitis, and psychomotor retardation. Use of ribavirin has not been systematically evaluated. South American haemorrhagic fevers—the reservoir(s) for Argentinian haemorrhagic fever is the vesper mouse, for Bolivian haemorrhagic fever Calomys callosus, and for Venezuelan haem- orrhagic fever the cotton rat and the cane mouse. These cause an influenza-like illness with marked skin erythema and (in almost half of cases) haemorrhagic manifestations; a late neurological cerebellar syndrome occurs in about 10%. Treatment with convalescent-phase plasma is very effective in Argentinian haemorrhagic fever, and ribavirin may be effective. A live attenuated vaccine for Argentinian haemorrhagic fever is licensed in Argentina. Introduction Arenaviruses are pleomorphic enveloped negative-stranded seg- mented RNA viruses with a characteristic internal granular structure, hence their family name Arenaviridae (Latin areno- sus = sandy). A newly suggested taxonomy divides the Arenaviridae family into the genera Mammarenavirus and Reptarenavirus, whose reservoirs are mainly rodents and reptiles (i.e. snakes), respectively. Mammalian arenaviruses are grouped into New World and Old World arenaviruses based on their geographical distributions as well as their serological and phylogenetic differences. While most of these viruses do not cause human disease, nine species are as- sociated with neurological and haemorrhagic diseases in humans. Lymphocytic choriomeningitis virus (LCMV) is distributed world- wide and occasionally causes acute central nervous system (CNS) disease and congenital malformations and has been transmitted through solid organ transplantation. Lassa virus in West Africa, and Junin, Machupo, Guanarito, Sabia, and Chapare viruses in South America cause viral haemorrhagic fevers. Certain rodent species are the principal hosts of arenaviruses and shed them lifelong in high titres in their urine. Humans are thought to become infected mainly through inhalation of aerosolized rodent urine or dust particles to which infectious urine has dried, or by ingestion of contaminated foodstuff. Human-to-human transmission occurs with some of the viruses. In geographically confined endemic rural areas, sporadic infections with these viruses occur regularly and are often linked to seasonal agricultural activities. Novel related viruses are emerging from time to time in previously unaffected areas. In 2000, three patients from California were fatally infected with a novel arena- virus related to Whitewater Arroyo virus, originally isolated from

8.5.17 Arenaviruses 863 rodents in New Mexico. In 2008, a novel, genetically distinct, and highly pathogenic arenavirus (named Lujo virus) was isolated from a Zambian patient hospitalized with a fatal Lassa fever-like illness in South Africa, who transmitted the infection to several care givers. Aetiology, genetics, pathogenesis, and pathology Common to all arenavirus haemorrhagic fevers is disruption of vas- cular endothelial integrity, originating most likely from the release of endogenous mediators from infected macrophages or endothe- lial cells, and resulting in extravasations of fluid into extravascular spaces (‘capillary leakage syndrome’). Coagulation disorders are subtler than in filovirus infections and disseminated intravascular coagulopathy is not observed. Platelets are dysfunctional despite their adequate or only mildly depressed numbers, and evidence for a soluble protein inhibitor of platelet function, presumably of host origin, has been described in Lassa virus and Junin virus infections. Experimentally, Lassa virus-infected nonhuman primates also showed a marked decrease in endothelial prostacyclin production. Arenaviruses initially infect macrophages and immature dendritic cells, compromising the ability of the latter to mature and stimu- late T-cell

responses. Infected dendritic cells seem to be eliminated by immunopathological mechanisms, correlating with a decline in the number of T lymphocytes and destruction of the architecture of lymphatic organs, which may explain the overall poor immune response throughout the course of Lassa virus infection. Studies of human survivors of Lassa virus infections indicate a general im- munosuppression characterized by low levels of type I IFN and pro- inflammatory cytokines such as tumour necrosis factor α (TNFα) or interleukin 1β (IL-1β). Altered levels of IFNγ-induced protein 10 (IP-10), IL-6 or IL-8 are observed in fatal Lassa virus cases and the reduction of cytokines is paralleled by a reduced expression of costimulatory proteins in DCs, such as CD86, which results in the failure to activate CD4+ and CD8+ T lymphocytes. In LCMV and Lassa virus infections, neutralizing antibody re- sponses are absent or appear late, likely due to masking of neutral- izing epitopes by heavy glycosylation of the viral envelope protein. In contrast, infection with Junin virus induces neutralizing anti- bodies. Hence, immune plasma is used for passive immune therapy of this disease. Arenaviruses replicate in many epithelial cell types with only modest cytopathic effect and there is ominous absence of an inflam- matory response in infected organs. Autopsy of Lassa virus-infected nonhuman primates shows pulmonary congestion, pleural effusion, and pericardial oedema, and effusion. Major microscopic lesions are necrotizing hepatitis and interstitial pneumonia. The degree of hepatic damage is not sufficient to implicate hepatic failure as the cause of death. In Junin virus infection, there are large areas of intra- alveolar or bronchial haemorrhage, petechiae on organ surfaces, and ulcerations of the digestive tract, although bleeding is not massive. Pneumonia with necrotizing bronchitis or pulmonary emboli is ob- served in half of the cases. Haemorrhage and a lymphocytic infiltrate have been observed in the pericardium, and splenic haemorrhage is common. Renal damage occurs in about half of the fatal cases and consists of severe structural damage in the distal tubular cells and collecting ducts with relative sparing of the glomeruli and proximal tubules. Neurological involvement during the acute phase of the disease is common in the South American haemorrhagic fevers, but there is no evidence of direct viral infection of the CNS. In Lassa fever, neurological complications, mainly sensorineural deafness, are very common during convalescence and are thought to be due to immunopathology. There is evidence that Lassa virus persists, at least for some time, because it has been isolated in human urine for up to 60 days. In one report of a fatal human LCMV infection there was peri- vascular macrophage infiltration in multiple areas of the brain and antigen was observed in the meninges and cortical cells. LCMV has been recovered from the CNS of newborn children with malformations. Epidemiology Lassa fever Clinical cases of Lassa fever are reported regularly in rural areas of Nigeria, Liberia, Sierra Leone, and the Republic of Guinea, but might also occur in other West African countries. Rare cases and evidence of exposure of humans have been documented in neighbouring countries (i.e. Benin, Burkina Faso, Côte d’Ivoire, Ghana, Mali, and Togo) and in some of them Lassa virus has been isolated from ro- dents. The reservoir of Lassa virus is a small rodent (Mastomys natal- ensis) that lives in and around human dwellings. In West Africa, 300 000 to 500 000 Lassa virus infections are estimated to occur annually, resulting in approximately 150 000 clinical cases, ranging in severity from flu-like illness to haemorrhagic fever, and approxi- mately 5000 deaths. In endemic areas, 75% of all Lassa virus infec- tions are probably asymptomatic, with an overall mortality of 1–5%. Lassa fever patients are not infectious during the incubation period and quite close contact with body fluids is required for person-to-person spread of the virus. However, airborne transmission, prob- ably through direct contact with droplets produced during heavy coughing and presumably originating from Lassa pneumonitis, has been reported in a few instances. It has recently been estimated in an endemic area that up to 20% of hospitalized Lassa fever cases origin- ated from human-to-human transmission in the

community. Most of these seem to have been caused by a few ‘super spreaders’, as only 5% of human cases resulted in an effective reproduction number greater than 1, with a maximum value of up to 12. Expatriates working in endemic areas have imported Lassa fever into Europe and North America. Lymphocytic choriomeningitis virus infection The distribution of LCMV is highly variable within populations of its natural host Mus musculus. From infected mouse colonies, LCMV spreads to humans in rural settings or when human habi- tats are substandard in urban areas. Infected laboratory and pet rodents have also been associated with disease in humans, and aerosol transmission might have occurred. Clinical cases of LCMV infection seem to be rare in the United States of America, even though 9.0% of house mice and 4.7% of residents had measurable antibodies in the Baltimore area in the 1990s. Person-to-person spread has not been demonstrated. Intrauterine LCMV infection has resulted in fetal or neonatal death, as well as hydrocephalus and chorioretinitis in infants, and the virus may be a more frequent cause

 disease in newborns than previously recognized. Two clus- ters of transplantation-associated transmission of LCMV have been reported. Argentine haemorrhagic fever The endemic area of Argentine haemorrhagic fever (caused by Junin virus) comprises the provinces of Buenos Aires, Córdoba, Santa Fe, and La Pampa. The major rodent hosts of Junin virus are the agrarian rodents (vesper mice) Calomys musculinus and C. laucha. Most human cases are male agricultural workers. About 21 000 cases have been reported since the early 1960s, averaging about 360 a year with wide annual fluctuations. Peak incidence is during summer and early autumn. Overall human antibody preva- lence is about 12% and about 30% had no history of typical illness. Occasional hospital or family epidemics have occurred, but cases have not been observed outside of Argentina. Recent introduction of a live attenuated vaccine has reduced the incidence of the disease dramatically. Bolivian haemorrhagic fever Bolivian haemorrhagic fever (caused by Machupo virus) is limited to rural areas of Beni department in Bolivia. The only known res- ervoir is Calomys callosus. The largest known epidemic of Bolivian haemorrhagic fever, involving several hundred cases, followed a marked and unusual increase in the Calomys population in homes in the town of San Joaquin in 1963 and 1964. This seems to have been a unique event, and there were almost no further cases until 1994, when there was an outbreak in north-eastern Bolivia. Since all ages and both sexes are affected, it can be assumed that most patients were infected in their homes. Person-to-person spread is rarely re- ported. A novel virus, tentatively designated Chapare virus, was iso- lated from a fatal haemorrhagic fever case near Cochabamba. The virus is genetically related to Sabia virus from Brazil; its rodent host and geographical distribution are currently unknown. Venezuelan haemorrhagic fever Venezuelan haemorrhagic fever (caused by Guanarito virus) is en- demic to the southern and south-western parts of Portuguesa state and adjacent regions of Barinas state in Venezuela. From 1989 to 1995, a total of 105 confirmed or probable cases of Venezuelan haemorrhagic fever were reported, of which 34% were fatal. All ages and sexes were infected suggesting that transmission had occurred in and around houses. The incidence peaked each year between November and January, during the period of major agricultural activity. In addition, epidemic activity of the illness appears cyc- lically every 4 to 5 years. The cotton rat Sigmodon alstoni and the cane mouse Zygodontomys brevicauda are the rodent reservoirs. Seroprevalence in humans living in the state of Portuguesa is below 2%. Human-to-human transmission has not been reported. Other arenavirus infections Sabia virus was isolated in 1990 from a fatal case in São Paulo, Brazil. Its natural distribution and host are still unknown. One patient who acquired the infection in the laboratory treated himself immediately with ribavirin, and made a rapid and full recovery. Whitewater Arroyo virus was isolated in 1996

from white- throated wood rats or pack rats (Neotoma albigula and Neotoma spp.) collected in McKinley County, New Mexico. A related virus caused three fatal human infections in California in 1999 and 2000; they are believed to be rare events because the abundance and habits of wood rats suggest that potential contact with humans is limited. One patient reportedly cleaned rodent droppings in her home during the 2 weeks before illness onset; no history of rodent contact was solicited for the other two patients. Several other arenaviruses isolated from North American rodents have not yet been shown to cause human infections. Dandenong virus, a new arenavirus related to LCMV, has recently been isolated in Australia from patients who had received organ trans- plants from a deceased donor who had travelled in Eastern Europe. Prevention Rodent control In endemic areas, rodent control is essential and direct contact with rodents, their excreta, and their nesting materials should be avoided. Management of infected patients Safe and orderly care of the ill and adequate disinfection proced- ures should be instituted early (barrier nursing, guidelines from Centres for Disease Control and World Health Organization, see Box 8.5.17.1), with effective surveillance of high-risk contacts and prompt isolation of further cases. Direct person-to-person trans- mission occurs in Lassa fever and, although rare, has been docu- mented for some New World viruses. Nosocomial transmission can occur through direct contact with an infected patient’s blood, urine, or pharyngeal secretions. If possible, patients with severe disease and bleeding should be placed in a negative-pressure room and all personnel should wear protective gear with P3 filters for respiratory protection. High-risk contacts are associated with percutaneous or mucosal contact with blood or body fluids. Medium-risk contacts (unprotected contact with blood or body fluids) may safely be ob- served for development of persistent high fever for 3 weeks from the last date of contact by daily temperature measurement and tele- phone reporting. Ribavirin postexposure prophylaxis There are no evidence-based data to support oral ribavirin as postexposure prophylaxis, but, anecdotally, a German physician seroconverted asymptomatically under ribavirin prophylaxis after examining a coughing Lassa fever patient without respiratory pro- tection and gloves (medium-risk contact). Prophylaxis should be given to high-risk contacts of Lassa fever and South American haemorrhagic fever patients, and offered to medium-risk contacts of Lassa fever patients on an individual basis. One recommended dosage is 600 mg orally four times a day for 10 days. Temporary side effects of this regimen were rash, tachycardia, myalgia, diar- rhoea, and abdominal pain. In one case, there may have been an association between ribavirin and worsening of a pre-existing tachyarrhythmia. Among 16 people there were reversible increases in plasma bilirubin concentrations in 11 and a decrease in haemo- globin concentration in 9. One person stopped prophylaxis after 4 days because of jaundice, and in another the serum lipase concen- tration increased.

8.5.17 Arenaviruses 865 Vaccines Experimental vaccines based on different viral vector systems have protected against lethal challenge with Lassa virus in animal models. The most impressive results to date have been obtained with a replication competent recombinant vaccine based on ves- icular stomatitis virus, which also forms the backbone of an Ebola vaccine that showed efficacy in a phase 2 trial. A single injection of this vaccine expressing the Lassa virus glycoprotein protected non human primates against lethal challenge and was cross-protective against several Lassa virus strains. A live attenuated vaccine (can- didate No. 1) against Junin virus is licensed in Argentina and pro- duced by the Maiztegui Institute, Pergamino. It was tested in over 200 000 volunteers, showed an estimated effectiveness of 95.5%, and may be cross-protective against Machupo virus only. The Salk Institute, Swiftwater, PA, also produced some quantities of the vaccine, which has an investigational new drug status from the United States Food and Drug

Administration for high-risk populations. Clinical features Lassa fever The clinical picture of Lassa fever is highly variable and may be very difficult to distinguish from other febrile infections. Following an incubation period of 7–21 days, Lassa fever begins insidiously with fever, weakness, malaise, severe usually frontal headache, and a painful sore throat. One-half of patients develop joint and lumbar pain and a nonproductive cough. Severe retrosternal chest pain, nausea with vomiting or diarrhoea, and abdominal pain are also common. Respiration rate, pulse rate, and temperature are elevated, and blood pressure may be low. There is no characteristic rash; petechiae and ecchymoses are not seen. About one-third of patients will have conjunctivitis. More than two-thirds of patients have pharyn- gitis, one-half with exudates; the posterior pharynx and tonsils are dif- fusely inflamed and swollen, but there are few ulcers or petechiae (Fig. 8.5.17.1). The abdomen is tender in half of the patients. Neurological signs in the early stages are limited to a fine tremor, most marked in the lips and tongue. Thirty per cent (30%) of patients progress to a prostrating illness 6–8 days after onset of fever, usually with persistent vomiting and diarrhoea. Patients are often dehydrated with elevated haematocrit. Proteinuria occurs in two-thirds of patients, with mod- erately elevated blood urea nitrogen. About one-half of Lassa fever pa- tients have diffuse abdominal tenderness without localizing signs or loss of bowel sounds. The severe retrosternal or epigastric pain seen in many patients may be due to pleural or pericardial involvement. Facial and conjunctival swelling develop, and severe pulmonary oedema and adult respiratory distress syndrome are common in fatal cases, with gross head and neck oedema, stridor, and hypovolaemic shock (Fig. 8.5.17.2a, b). Renal and hepatic failure are not seen. Bleeding is seen in only 15–20% of patients and is restricted to mucosal surfaces, conjunctiva, and gastrointestinal and/or genital tracts. Over 70% of patients have abnormal electrocardiograms (nonspecific ST-segment and T-wave abnormalities, ST-segment elevation, generalized low voltage complexes, and changes reflecting electrolyte disturbance), but none correlate with disease severity or outcome. There is no Box 8.5.17.1 Principles of barrier nursing in resource-poor settings (World Health Organization) Protective clothing • Double gloves • (Single-use) gown • Plastic apron • Mask (P3 protection) • Goggles • Disinfect within isolation area or destroy (single-use) material Handwashing • After each patient contact or contact with infected material • Rinse in disinfectant, then wash with soap and water • Disinfectant/washing facilities must be located just outside isolation rooms Instruments • Individual thermometer for each patient, keep in receptacle with disinfectant • Disinfect stethoscope and sleeve of sphygmomanometer between each use • Place all reusable instruments in disinfecting fluid after use Bed covering and linen • Use of plastic sheet to cover and protect entire mattress is essential • Disinfect after discharge or death of the patient • Place bedding and linen in plastic bag for sterilization (soak in disin- fectant, boil, or autoclave) Food • Food should be supplied by hospital, not relatives • Each patient must have own eating utensils • Wash and disinfect in isolation area • Dispose of uneaten food Charts/records • Keep outside isolation area Disinfection methods • Household bleach—viruses causing viral haemorrhagic fevers are killed by exposure to a 1:10 solution for 1 min, or to a 1:100 solution for 10 min • Heat sterilization—if autoclave not available, boil at 100°C for 20 min Fig. 8.5.17.1 Lassa fever: pharyngitis. Copyright D. A. Warrell.

 clinical evidence of myocarditis. Neurological signs are infrequent but carry a poor prognosis; they progress from confusion to severe en- cephalopathy with or without general seizures and without focal signs (Fig. 8.5.17.3). There has been a report of an imported fatal Lassa fever case presenting with only neurological symptoms. Cerebrospinal fluid is usually normal, apart from a few lymphocytes. Pneumonitis and pleural and pericardial rubs

develop in early convalescence in about 20% of hospitalized patients, sometimes associated with congestive cardiac failure. Lassa virus is present in the breast milk of infected mothers, and neonates are therefore at risk of congenital, intrapartum, and puer- peral infection. Lassa fever may be difficult to diagnose in children. In very young babies marked oedema has been reported. Laboratory findings A normal mean white blood cell count on admission to hospital (6×109/litre) may mask early lymphopenia with later relative or abso- lute neutrophilia as high as 30×109/litre. Thrombocytopenia is mod- erate, even in severely ill patients, but platelet function is markedly depressed. The ratio of aspartate aminotransferase (AST, SGOT) to alanine aminotransferase (ALT, SGPT) is as high as 11:1. Prothrombin times, glucose, and bilirubin levels are nearly normal, excluding bio- chemical hepatic failure. Platelet and fibrinogen turnover are normal and there is no indication of disseminated intravascular coagulopathy. Complications and sequelae Nearly 30% of patients develop unilateral or bilateral deafness beginning during convalescence. About one-half show a near or complete recovery after 3–4 months, but the other one-half re- main permanently deaf. Many patients also show transient cere- bellar signs during convalescence, particularly tremors and ataxia. Other complications include uveitis, pericarditis, orchitis, pleural effusion, ascites, and acute adrenal insufficiency. Prognosis The case fatality rate of hospitalized patients in West Africa is approximately 15%, but it exceeds 50% in patients with haemor- rhage. CNS manifestations carry a poor prognosis. Lassa fever is a common cause of maternal mortality in parts of West Africa. Mortality is 20% in the first trimester and 30% in the second tri- mester of pregnancy, with fetal loss occurring in 87%, apparently not varying with the trimester. Mortality was reduced fourfold in women who spontaneously or were therapeutically aborted. High viral titres in serum (exceeding 104 TCID50/ml), AST (SGOT) raised above 150 U/litre, and bleeding, each worsen the prognosis, with the combination of high viral titres and high AST (SGOT) carrying a risk of death of approximately 80%. High neu- trophil counts (more than 30 × 109/litre) may be observed in these patients. In a recently published series of 284 Lassa fever patients treated in a dedicated facility in Nigeria, overall case-fatality rate was 24%, with a 1.4 times increase in mortality risk for each 10 years of age, reaching 39% for patients older than 50 years. 28% of patients had acute kidney injury, which was strongly associated with poor outcome, and 37% had CNS manifestations, respect- ively. Normalization of creatinine concentration was associated with recovery. Elevated serum creatinine (OR 1·3; p=0·046), as- partate aminotransferase (OR 1·5; p=0·075), and potassium (OR 3·6; p=0·0024) were independent predictors of death. Fig. 8.5.17.3 Lassa fever: generalized oedema and encephalopathy in a pregnant woman in Sierra Leone. Copyright D. A. Warrell. (a) (b) Fig. 8.5.17.2 (a) Lassa fever: facial and generalized oedema and hypovolaemic shock in a pregnant woman in Sierra Leone. (b) Lassa fever: facial oedema in a child. (a) Copyright D. A. Warrell. (b) Courtesy of Dr S. Mardel.

8.5.17 Arenaviruses 867 In most patients with imported Lassa fever treated in developed countries, diagnosis and ribavirin therapy have often been delayed, and the patients have died despite full supportive care. Lymphocytic choriomeningitis virus infection An influenza-like illness is the most common clinical presentation of LCMV. Fever (up to 40°C) with rigors is always present. Frequently noted are malaise, retro-orbital headache, photophobia, lumbar myalgias, anorexia, nausea, bradycardia, and pharyngeal injection without exudate. Mild non-tender cervical or axillary lymphaden- opathy may occur. Up to 50% of patients have vomiting, sore throat, and dysaesthesias, and onequarter of patients complain of chest pains and cough, associated with pneumonitis. Arthritis, parotitis, orchitis, myocarditis, rash, and alopecia have also been noted. In some pa- tients, the disease is biphasic with subsequent aseptic meningitis of about one week’s

duration or encephalomyelitis in a smaller number of cases. Other neurological manifestations such as myelitis, Guillain– Barré syndrome, and sensorineural deafness have been reported. The onset of CNS disease can also occur without any prodrome. Intrauterine infection This has resulted in nonobstructive hydrocephalus with periven- tricular calcifications, chorioretinitis, and psychomotor retardation. No cardiac abnormalities were observed. Some mothers had a his- tory of febrile illness during pregnancy. Transplantation-associated lymphocytic choriomeningitis virus infection In two clusters of cases, the solid organ transplant recipients had abdominal pain, altered mental status, thrombocytopenia, elevated aminotransferase levels, coagulopathy, graft dysfunction, and either fever or leukocytosis within 3 weeks after transplantation. Diarrhoea, peri-incisional rash, renal failure, and seizures were variably present. Seven of the eight recipients died 9–76 days after transplantation. Prognosis Patients with aseptic meningitis almost always recover without sequelae, but 25–30% of patients with encephalitis have neurological residua. South American haemorrhagic fevers In Argentine and Bolivian haemorrhagic fevers, after an incubation period of 7–16 days, there is insidious development of malaise, chills, fever, severe myalgia, anorexia, lumbar pain, epigastric pain, abdom- inal tenderness, conjunctivitis, retro-orbital pain often with photo- phobia, and constipation. Nausea and vomiting occur frequently after 2–3 days of illness. There is no lymphadenopathy, spleno- megaly, sore throat, or cough, but there is high fever (up to 40°C), marked erythema of the face, neck, and thorax, and conjunctivitis (Fig. 8.5.17.4). Respiratory symptoms are uncommon. Petechiae ap- pear by the fourth or fifth day of the illness. There may be a pharyn- geal enanthema, but pharyngitis is uncommon. The infection either resolves after about 6 days or progresses to severe disease. South American haemorrhagic fevers are associated with haemorrhagic manifestations in nearly half of patients: gingival haemorrhages (Fig. 8.5.17.5), epistaxis, metrorrhagia, petechiae (Fig. 8.5.17.6), ecchymoses, purpura, melaena, and haematuria. Severe cases have nausea, vomiting, intense proteinuria, microscopic haematuria, Fig. 8.5.17.4 Argentine haemorrhagic fever: facial swelling and erythema. Courtesy of Professor D. I. H. Simpson. Fig. 8.5.17.5 Argentine haemorrhagic fever: petechial haemorrhages. Courtesy of Professor D. I. H. Simpson. Fig. 8.5.17.6 Argentine haemorrhagic fever: gingival bleeding. Courtesy of Professor D. I. H. Simpson.

 oliguria, and uraemia. Fatal cases develop hypotensive shock, hypo- thermia, and pulmonary oedema. Renal failure has been reported but glomerular filtration rates, renal plasma flow, and creatinine clear- ance are usually normal. There is some electrocardiographic evidence of myocarditis. Fifty per cent of patients have neurological symptoms during the second stage of illness, such as tremors of the hands and tongue, progressing in some patients to delirium, oculogyration, and strabismus. Meningeal signs and cerebrospinal fluid abnormalities are rare. This late neurologic syndrome can also follow treatment with immune plasma, the usual treatment in endemic areas. The clinical presentation of Venezuelan haemorrhagic fever is similar. Patients are toxic and usually dehydrated, with pharyngitis, conjunctivitis, cervical lymphadenopathy, facial oedema, or petechiae. Laboratory findings Thrombocytopenia (below 150 × 109/litre) and neutropenia (range 0.8–6.6 × 109/litre) are almost invariable. Bleeding and clot retrac- tion times are concomitantly prolonged. Although reductions of levels of factors II, V, VII, VIII, and X, and of fibrinogen are observed, alterations in clotting functions are usually minor and full-blown disseminated intravascular coagulopathy is not a feature. Complications and sequelae A late neurological syndrome in about 10% of cases, consisting mainly of cerebellar signs, is associated with treatment using high-titre antiserum. Among survivors of South American haem- orrhagic fevers, convalescence typically takes 1–3

months, with weight loss, fatigue, autonomic instability, and occasional hair loss. Mild permanent damage to acoustic centres has been detected in a small group of patients. Prognosis In endemic areas, the case fatality rate of Argentine haemorrhagic fever is 15–30% for untreated hospitalized patients and 1% for pa- tients who received plasma therapy. CNS manifestations carry a poor prognosis. The case fatality rate of Bolivian haemorrhagic fever is higher. In one series of hospitalized patients with Venezuelan haemorrhagic fever, the case fatality rate was reported to be 33% despite vigorous supportive care. Argentine haemorrhagic fever is reported to be severe in pregnancy. Whitewater Arroyo-like virus Illnesses were associated with nonspecific febrile symptoms including fever, headache, and myalgias. Within the first week of hospitalization, lymphopenia was observed in all three patients, and thrombocytopenia (30–40 ×109/litre) was seen in two. All three pa- tients had acute respiratory distress syndrome and two developed liver failure and haemorrhagic manifestations. All patients died 1–8 weeks after becoming unwell. Criteria for diagnosis and differential diagnosis Due to the variable clinical presentation of arenavirus infections, the diseases should be suspected in any patient presenting with a severe fe- brile illness and evidence of vascular involvement (low blood pressure, postural hypotension, petechiae, haemorrhagic diathesis, flushing of face and chest, nondependent oedema). Sore throat, abdominal symptoms, and CNS symptoms are likewise important. For many re- gions in the world, the major differential diagnosis is malaria. Lassa fever Lassa fever should be suspected in a patient living in or coming within the incubation period (7–21 days) from rural areas in Sierra Leone, Liberia, Nigeria, the Republic of Guinea, and adjacent terri- tories, and presenting with otherwise unexplained high fever (above 38.5°C), pharyngitis with dry cough and chest pain, or abdom- inal pain and diarrhoea, facial oedema, mucosal bleeding, or CNS symptoms. In West Africa, fever with pharyngitis, proteinuria, and retrosternal chest pain had a predictive value for Lassa fever of 81% and a specificity of 89%. Due to the variable clinical picture of Lassa fever, there are many differential diagnoses including severe mal- aria, typhoid fever, rickettsial diseases, relapsing fevers, shigellosis, leptospirosis, meningococcaemia, and gram-negative sepsis. Viral haemorrhagic fevers such as yellow fever, Rift Valley fever, and Marburg and Ebola virus infections are much more likely to cause haemorrhage, disseminated intravascular coagulopathy, and severe liver dysfunction than Lassa fever. South American haemorrhagic fevers These should be considered in patients coming from endemic areas of Argentina (particularly male agricultural workers), Bolivia, Venezuela, and Brazil who present with unexplained fever and a bleeding diathesis. Differential diagnoses are similar to those for Lassa fever and, in addition, yellow fever and dengue fever must be considered. Appearance of the blanching maculopapular rash and a shorter duration of fever differentiate dengue from the early stages of arenavirus infections. The combination of a platelet count of less than 100 × 109/litre and a white blood cell count of less than 2.5 × 109/litre has a sensi- tivity of 87% and a specificity of 88% for Argentine haemorrhagic fever. These criteria are recommended when screening Argentine haemorrhagic fever patients for treatment with immune plasma or ribavirin in endemic areas. LCMV infection should be considered in patients presenting in autumn or winter with a biphasic disease characterized by fever and persistent meningeal signs, particularly if there is a history of rodent contact. Other rat bite fevers (Chapter 8.6.31) enter the differential diagnosis. Laboratory diagnosis Laboratory diagnosis of arenavirus infection is by isolation of virus from serum, demonstration of a fourfold rise in antibody titre, or high-titre IgG antibody with virus-specific IgM antibody in asso- ciation with compatible clinical disease. More recently, detection of viral sequences by reverse transcriptase–polymerase chain reaction (RT-PCR), or by detection of viral proteins using an enzyme-linked immunosorbent assay system have been introduced. In LCMV in- fection, viremia can persist for approximately

15 days. Virus titres in the cerebrospinal fluid are lower and present for a shorter period of time. Indirect fluorescent or complement fixation antibodies appear 2–3 weeks after the onset of the illness and reach their peak titres 5–6 weeks after the onset of illness before becoming undetectable after a few months. Neutralizing antibodies appear 2–6 weeks after onset of symptoms and persist for 6 months to 5 years. Acute and convalescent sera can be tested for increases in antibody titres, and

8.5.17 Arenaviruses 869 an increase in the specific IgM in blood and cerebrospinal fluid is diagnostic. For handling of clinical specimens from suspected cases, see Table 8.5.17.1. Treatment Lassa fever While the broad-spectrum antiviral ribavirin has been evaluated in Lassa fever patients and is currently recommended for treat- ment, recent studies have also shown very good efficacy of the drug Favipiravir in animal models. Favipiravir (T-705) is a broad- spectrum antiviral developed by Toyama Chemical Co Ltd. It has been approved in Japan and is now in phase III of clinical develop- ment in the United States for the treatment of complicated or re- sistant flu. Ribavirin is effective but must be given as early as possible while laboratory confirmation of the diagnosis is pending. It is ad- ministered by intravenous infusion as a 2-g loading dose followed by 1 g every 6 h for 4 days, then 0.5 g every 8 h for 6 more days. Another recommended intravenous regimen is an initial dose of 30 mg/kg fol- lowed by 15 mg/kg every 6 h for 4 days, followed by 7.5 mg/kg every 8 h for 6 days. Rigors can occur if the drug is infused too rapidly. Oral ribavirin doses are a 2-g loading dose followed by 4 g/day in four div- ided doses for 4 days followed by 2 g/day for six doses. Oral ribavirin is believed to be only half as effective as intravenous therapy. A five- to tenfold decrease in the case fatality ratio was demonstrated in pa- tients treated with ribavirin compared to untreated patients when therapy was given within the first 6 days of illness. Patients with high AST (SGOT) and viraemia, who were treated within the first 6 days of illness, had a 5 to 9% case fatality, and a 26–47% fatality when treated after 6 days, compared with 52–78% when untreated. Ribavirin is contraindicated in early pregnancy because of potential teratogenicity, but the fetus rarely survives the infection. Fluid, elec- trolyte, respiratory, and osmotic imbalances should be corrected, and full intensive care support, including mechanical ventilation, offered as required. However, even vigorous support might be insuf- ficient to prevent fatal progression of advanced disease. Interferon-α has shown efficacy against arenaviruses in animal models but only if given within a couple of days of challenge. A syn- ergistic effect with suboptimal doses of ribavirin was observed. Lymphocytic choriomeningitis virus infection Ribavirin treatment has not been evaluated in human CNS disease caused by LCMV. In a cluster of transplantation-associated systemic LCMV infections, one recipient, who received ribavirin and reduced levels of immunosuppressive therapy, survived. South American haemorrhagic fevers Convalescent-phase plasma has been shown to be highly successful in Argentine haemorrhagic fever, reducing the mortality from 15– 30% to 1% in patients treated in the first 8 days of illness. Efficacy is directly related to the concentration of neutralizing antibodies, and delayed treatment is less successful. Availability of appropriately screened plasma may, however, be a problem. Ribavirin is effective against the causative Junin virus in experimentally infected pri- mates, but does not prevent CNS involvement. In one small double- blind trial with 18 patients, mortality was 12.5% in those treated compared to 40% in the placebo group. One human case of Bolivian haemorrhagic fever has been successfully treated with ribavirin and Venezuelan haemorrhagic fever is also likely to respond. Other issues Lassa fever is a truly neglected re-emerging disease that has a consid- erable impact on West African healthcare systems and the economy of affected rural areas. The absence of local diagnostic capacity and the high price of intravenous ribavirin preparations are the main barriers to the introduction of specific therapy to endemic areas. Areas of uncertainty or controversy The

pathogenic events leading to plasma leakage, bleeding, and shock are not well understood in arenavirus infections, compared to filoviruses The pathological basis of the sensorineural hearing Table 8.5.17.1 Inactivation of blood/serum from viral haemorrhagic fever patients for laboratory analysis Material Examination Inactivation Blood Thick film Add formalin to a final concentration of 1% to solution used for lysis of erythrocytes Blood Thin film Methanol fixation Blood Leucocyte count 1:100 in 3% acetic acid, 15 min room temperature Serum/plasma Serological tests Heat for 60 min at 60°Ca 0.25% β-propiolactone (final concentration), 30 min 37°C Serum/plasma Clinical chemistry Heat for 60 min at 60°Cb 0.25% β-propiolactone (final concentration), 30 min 37°Cc 0.1% Triton X-100 (final concentration), 60 min room temperatured a Loss of reactivity. Heating at 56°C for 1 h preserves antibody reactivity better but leaves sample with residual infectivity. Only recommended if sample can be safely handled in biological safety level 2 cabinet (laminar air flow). b No influence on sodium, potassium, magnesium, urea, creatinine, urate, bilirubin, glucose, C-reactive protein. Reduced levels of bicarbonate, aspartate aminotransferase, calcium, phosphate, albumin, total protein. Measurement not possible for alkaline phosphatase, alanine aminotransferase, γ-glutamyl transpeptidase, creatine kinase. c Liver enzyme values reduced by 20%. pH and bicarbonate not useful. d Influence on clinical chemistry not evaluated.

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