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OSH Manual of Childhood Infections: The Blue Book (3 ed.)

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Viral Haemorrhagic Fevers

Chapter: Viral Haemorrhagic Fevers
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see also Chapters 13, 14, 34, 42

Name and Nature of Organisms

• Viral haemorrhagic fevers (VHFs) comprise a diverse group of infections characterized by febrile illnesses and in some, high case fatality rates. Many are transmitted from person

to person.

• The diseases include: Lassa fever, Ebola haemorrhagic fever, Marburg haemorrhagic fever, Crimean-Congo haemorrhagic fever (CCHF), the South American haemorrhagic fevers (Argentinian, Bolivian, Venezuelan and Brazilian), Kyasanur forest disease and Omsk haemorrhagic fever, and haemorrhagic fever with renal syndrome (HFRS). Some forms of dengue virus infection can lead to serious haemorrhagic disease, known as dengue haemorrhagic fever (DHF).

• The VHFs are caused by distinct RNA viruses that are members of four viral families: *Arenaviridae*, *Bunyaviridae*, *Filoviridae*, and *Flaviviridae*.

• Arenaviruses: six viruses are currently known to cause haemorrhagic disease in humans. The family is divided in Old World (Lassa and Lujo viruses), and New World (Junin, Machupo, Chapare, Guanarito and Sabiá viruses). All arenaviruses are enveloped, pleomorphic, bisegmented, single-stranded, 60 to >200nm.

• *Bunyaviridae*: The family includes CCHF virus (genus *Nairovirus*), and hantaviruses including Seoul, Puumala, Dobrava. The viruses are enveloped, segmented, and single-stranded, 90–120nm.

• *Filoviridae*: This family contains only Marburg and Ebola viruses. There are five subtypes of Ebola, four of which cause disease in humans; Sudan, Zaire, Cote d'Ivoire, and Bundibugyo. The fifth ebolavirus type, Reston, has been found in primates and pigs, and while inducing an antibody response in humans, has not thus far caused symptomatic infection. The viruses are enveloped, filamentous and non-segmented, 80 × 800–1000nm.

• *Flaviviridae*: This large family of viruses includes dengue and yellow fever viruses as well as the agents responsible for Kyasanur forest disease and Omsk haemorrhagic fever. There are four distinct serotypes of dengue virus (DEN 1, DEN 2, DEN 3, and DEN 4). They are enveloped, non-segmented, single-stranded, 50nm.

• The arenaviruses, filoviruses, and CCHF virus are classified as hazard group 4 as they present a serious hazard to laboratory workers.

Epidemiology

• ***Lassa fever*:** Reservoir is the multimammate rat (*Mastomys* species). Disease is endemic in West Africa, particularly Guinea, Liberia, Sierra Leone, and Nigeria. Many thousand cases are thought to occur each year in these endemic countries. Imported cases are rare, but have occurred in Europe, North America and elsewhere, almost exclusively in persons with high-risk occupations such as medical or other aid workers.

• ***Lujo virus*:** This has been recently described following a small outbreak in South Africa in 2008. The index case acquired infection in Zambia, and three secondary and one tertiary transmissions followed after the patient was repatriated to a hospital in South Africa. Four infections were fatal. Little is yet known of the epidemiology of this virus, but a rodent reservoir is likely.

• ***South American Arenaviruses*:** All are rodent borne (field voles, cane rats, cotton rats), and each virus occurs in a different country; Junin virus in Argentina, Machupo and Chapare viruses in Bolivia, Guanarito virus in Venezuela, and Sabiá virus in Brazil. Argentine HF (Junin virus) is the commonest of these, although its incidence has declined

since use of an effective vaccine. A resurgence of Bolivian HF was noted in 2007–8. Imported cases are very rare outside the Americas. Laboratory-acquired infections have occurred.

• ***Ebola*:** The reservoir is probably in bats; non-human primates and other mammals also susceptible. The four pathogenic subtypes are found in Central and West Africa: Republic of Congo, Democratic Republic of Congo, Gabon, Sudan, and Uganda. Ebola Reston has only been found in the Western Pacific and has not to date caused illness in humans. Sporadic outbreaks occur which may be extensive with hundreds of cases. Imported cases are very rare. Laboratory-acquired infections have occurred.

• ***Marburg*:** The reservoir is almost certainly fruit bats, and certain monkey species are susceptible to infection. Found in Central and West Africa: Kenya, Uganda, Democratic Republic of Congo, Angola. Sporadic cases and outbreaks occur, the largest of which was in Angola in 2004–5. Imported cases are very rare. Two cases occurred in 2008, one in Holland and one in the USA, and both followed a visit to a bat infested cave in the Maramagambo Forest, Uganda.

• ***CCHF*:** Reservoir in livestock, small mammals and birds; tick-borne. CCHF virus is the most widely distributed agent of severe haemorrhagic fever known and is enzootic from western China across to eastern Europe, the Middle East, and down to southern Africa. This range reflects the distribution of the *Hyalomma* ticks which are the main vector. Several hundred cases occur per year in Turkey, the Balkans, and southern parts of the Russian Federation. Epidemic years can occur. Imported cases appear to be rare.

• ***Hantaviruses*:** Rodent borne (various species including voles, mice, rats) and each virus has a specific rodent host. There is variable distribution in Europe, Asia, and the Americas depending on both viral and rodent species. Seoul virus is found worldwide, particularly in Asia, while Puumala and Dobrava virus occur in Europe. Puumala virus is responsible for a mild form of HFRS known as nephropathia endemica. About 150 000 cases of HFRS are thought to occur worldwide each year, and many thousand of those are in Europe.

• ***Dengue*:** A mosquito-borne infection transmitted by *Aedes* species, principally *Aedes aegypti* and *Aedes albopictus*. Dengue is endemic in over 100 countries in tropical and subtropical regions of the world. WHO estimates there are 750 million cases of dengue fever per year, of which up to 500 000 are DHF. Imported cases of dengue fever are relatively common in Europe, and cases of DHF are also seen.

• ***Omsk haemorrhagic fever/Kyasanur forest disease*.** These tick-borne infections are geographically limited to the western Siberia regions of Omsk, Novosibirsk, Kurgan, and Tyumen, and the Kyasanur Forest in southern India, respectively, and so are not considered further.

Transmission and Incubation Period

• ***Lassa fever*:** Virus is shed in the urine and droppings of infected multimammate rats, and most human infections arise through contact with materials contaminated by these. Person-to-person transmission also occurs via direct contact with body fluids (blood, semen, respiratory secretions, urine) of an infected person. Symptomatic patients are considered infectious, and urine may be intermittently positive for up to 2 months. Sexual transmission

is possible as virus remains detectable in semen for up to 3 months post-symptom onset. The incubation period is 7–10 days, with a range of 3–21 days.

• ***South American arenaviruses*:** Transmission to humans occurs via direct contact with infected rodents, or through inhalation of infectious rodent fluids and excreta. Argentine haemorrhagic fever is particularly seen in agricultural workers harvesting maize fields where rodents are plentiful. Person-to-person transmission has been documented with Junin and Machupo viruses. The incubation period is from 7 to 14 days, with a range of 5–21 days.

• ***Ebola and Marburg*:** The index case in an outbreak usually follows contact with an infected animal (a non-human primate or other mammal, or a bat). Virus is then transmitted to others through direct contact with the blood, secretions, organs or other body fluids of infected persons, or with fomites contaminated by body fluids. Symptomatic patients are considered infectious, and are most infectious as disease becomes severe. Infection in healthcare workers and caregivers has been a notable feature in outbreaks. Sexual transmission has been reported 3 months post onset of symptoms. The incubation period for Ebola is 2–21 days, and for Marburg is 3–10 days.

• ***CCHF*:** Infection is acquired through the bite or crushing of an infected tick, or through contact with blood of an infected animal. Person-to-person transmission occurs via direct contact with the blood, secretions, organs or other body fluids of infected persons; symptomatic patients are considered infectious. Nosocomial transmission remains a problem in endemic areas. The incubation period appears to vary with route of transmission. Following a tick bite, it is usually 1–3 days, and up to 9 days; but following contact with infected blood or tissues it is usually 5–6 days, up to 13 days.

• ***Hantaviruses*:** Virus is shed in urine, faeces, and saliva of the rodent host, and most human infections are thought to arise via inhalation of infected aerosols from these excreta. Person-to-person transmission is rare. The incubation period is 2–4 weeks for the viruses causing HFRS.

• ***Dengue*.** Infection follows the bite of an infective *Aedes* mosquito. Person-to-person transmission does not occur, although during the viraemic phase blood is infective for biting mosquitoes. The incubation period is 4–7 days, with a range of 3–14 days.

Clinical Features and Sequelae

• ***Lassa fever*:** Clinically infection ranges from mild to asymptomatic (80% of cases) to a severe fulminating infection. Onset is gradual with fever, chills, malaise, headache, myalgia, and sore throat. Nausea, vomiting, diarrhoea or cough may be present, and exudative pharyngeal inflammation is common. In severe cases, shock, encephalopathy, renal and circulatory failure may develop progressing to severe haemorrhage. Overall the mortality rate is 1–3%, but is around 15% in hospitalized cases. Mortality rates are high (730%) in the third trimester of pregnancy, and fetal death approaches 100%. The most notable complication is acute hearing loss and sensorineural hearing deficit occurs in 25–30% of patients and may persist for life. It does not appear to be associated with disease severity.

• ***South American haemorrhagic fevers*:** The clinical picture is consistent for all these viruses: onset is gradual with fever, malaise, myalgia, back pain, and headache. Petechiae and haemorrhage develop after a few days, and neurological manifestations may follow

with tremor of hands and tongue, seizures, and coma. Blood loss is usually minor, but the haematocrit rises as capillary leak syndrome becomes more severe. Renal impairment is very common in Argentine haemorrhagic fever. Overall mortality rates vary from 5% to 30%, and are highest in the third trimester of pregnancy. Fetal mortality is high.

• ***Ebola and Marburg*:** Onset is sudden with headache, high fever, and back pain. Prostration follows rapidly with pharyngitis, vomiting, severe watery diarrhoea, conjunctivitis, and a measles-like rash. Neurological manifestations include severe lethargy, irritability, and confusion. Haemorrhagic manifestations develop after 75 days, and may progress to severe blood loss and death. Overall the mortality rates are very high; between 50% and 90%. Fetal loss is common when infection occurs during pregnancy. Convalescence is slow and debilitating, and survivors may have prolonged amnesia.

• ***CCHF*:** Onset is sudden with fever, myalgia, dizziness, neck pain and stiffness, backache, headache, sore eyes, and photophobia. Nausea, vomiting, diarrhoea, and sore throat may also occur. Haemorrhagic manifestations develop after 75 days and may be extensive with petechial rash, bruising, ecchymoses and generalized bleeding of the gums and orifices. In severe cases multiorgan failure develops. Up to 50% of cases are fatal, but mortality rates vary considerably.

• ***HFRS*:** These are a group of clinically similar illnesses characterized by fever, headache, malaise, gastrointestinal symptoms, and renal impairment. Onset is sudden. Petechial and conjunctival haemorrhage may precede periods of hypotension followed by hypovolaemic shock. Most infections do not exhibit overt signs of bleeding or internal haemorrhage. The mortality rate is up to 15%, but in Europe, Puumala virus infection is generally a mild disease (nephropathia endemica) that is rarely haemorrhagic and has a case fatality rate <1%.

• ***Dengue fever/DHF*.** Most dengue infections are either asymptomatic, or a febrile influenza-like illness. However, DHF is a potentially fatal complication of classical dengue fever, the pathogenesis of which is still unclear. Strain variability may have a role, but the main hypothesis surrounds the immune response to sequential infections with different viral serotypes. Dengue fever starts with fever, nausea, severe headache, and back pain. Acute illness is relatively short-lived although incapacitating. DHF is typically seen in children <15 years old and is characterized by rapid deterioration and prostration, with haemorrhage and shock secondary to circulatory collapse. Petechiae and ecchymoses appear. Mortality rates of DHF can exceed 20% in the absence of circulatory support, but are <2% with appropriate management.

Diagnosis

• For all the hazard group 4 haemorrhagic fever viruses, diagnostic testing must be carried out in a designated laboratory with containment level 4 facilities.

• The diagnosis of a VHF should be considered in all patients returning from an endemic area and presenting with compatible symptoms.

• In the first few days of illness, diagnosis is achieved by virus detection in blood or tissue samples—virus isolation; detection of viral antigens in tissue by immunofluorescence or EIA; detection of viral nucleic acid by PCR.

• Serological testing by detection of IgM and IgG antibodies in serum by ELISA or

fluorescent antibody test (FAT). IgM may be detectable very soon after symptom onset. For dengue diagnosis, serological cross-reactions with other flaviviruses must be rigorously excluded.

• There may be a number of possible differential diagnoses depending on the country of exposure, including malaria, typhoid, leptospirosis, rickettsial infections.

• Dual pathology is possible.

Management and Treatment

• Seek advice as soon as possible, and transfer patient to a specialist unit if appropriate

• For Lassa, CCHF, Ebola, Marburg, and South American arenaviruses, patients must be managed in strict isolation (in a negative pressure room if available), with full infection control precautions. Contacts should be restricted to essential personnel only, and invasive procedures including venepuncture should be minimized.

• Symptomatic and supportive treatment is essential, particularly fluid and electrolyte balance, replacement of plasma loss during period of capillary leakage, volume replacement, and replacement of coagulation factors and platelets.

• The supportive care of patients critically ill with a VHF should be the same as the conventional care provided to patients with other causes of multisystem failure.

• Renal failure with oliguria is a prominent feature of HFRS and may be seen in other VHFs as intravascular volume depletion becomes more pronounced. In HFRS, the management of oliguria may require haemodialysis or peritoneal dialysis.

• Monitor platelets and haematocrit, and virological indices (i.e. PCR positivity and viral load) in blood and urine.

• In severe cases, therapy will be required for shock and blood loss.

• Antiviral therapy with ribavirin is recommended for Lassa fever, Argentine HF (and is probably effective for other arenaviruses), and CCHF.

• IV ribavirin should be given early in the course of disease. There is some evidence that ribavirin treatment reduces renal complications in HFRS.

• Convalescent immune plasma has been used with beneficial effect against Argentine haemorrhagic fever, but is only available in Argentina.

• No antiviral therapeutic options currently exist for other haemorrhagic fevers.

Prevention

Lassa and Other Arenaviruses, CCHF, Ebola, Marburg

• Strict barrier precautions when managing patients are essential to minimize exposure of healthcare workers, other hospital staff, and family members, and thus prevent nosocomial transmission. Non-essential staff and visitors should be restricted.

• All persons entering the room must be gloved and gowned, with face shields and eye protection for those coming within 1m (3ft).

- Prevention of percutaneous injuries associated with the use and disposal of sharps is vital.
- Keep laboratory tests to the minimum necessary for clinical management in order to reduce potential exposures to laboratory staff. Samples must be appropriately labelled and the laboratory alerted as to their high-risk status.
- Standard protocols for laundry, cleaning, and disinfection may be followed where there is no contamination by blood/body fluids.
- Safe and effective disinfection and decontamination procedures are required for materials contaminated with blood/body fluids (including personal protective equipment, linens, fomites, equipment, and patient samples sent for diagnostic investigations). Persons carrying out decontamination must be appropriately protected. Contaminated environmental surfaces should be cleaned with hypochlorite solution (5000ppm available chlorine), unless the contamination is heavy, in which case hypochlorite solutions containing 10 000ppm available chlorine should be used. Where possible, contaminated materials and samples should be double-bagged then autoclaved or incinerated.
- Contact tracing: All persons having contact with the case since they became symptomatic must be identified and risk assessed. Those with close contact must be monitored by daily temperature checks for 21 days following their last contact.
- There is no evidence to suggest that postexposure prophylaxis with ribavirin is effective.
- No vaccines are currently available, except for Argentine haemorrhagic fever. This vaccine is only available in Argentina, where it has been used since the 1990s, and been responsible a decrease in incidence of this disease.
- Prevention of naturally acquired cases in endemic areas—control of rodent and insect vectors, rodent-proof storage containers, and avoidance of insect bites or exposure to body fluids of infected animals.

Dengue and Hantavirus

- Normal control of infection procedures apply when managing patients.
- Contact tracing not required.
- No vaccines currently available.
- Prevention of naturally acquired cases in endemic areas—control of rodent and insect vectors, rodent-proof storage containers, and avoidance of insect bites.

Further Reading

Howard CR. *Viral Haemorrhagic Fevers, Perspectives in Medical Virology*, Volume **11**. 2003, Elsevier.