16 Viral Haemorrhagic Fevers

LUCILLE BLUMBERG | DELIA ENRIA | DANIEL G. BAUSCH

KEY POINTS

- Viral HF is an acute systemic febrile syndrome caused by over 30 viruses from four different virus families. Microvascular instability with capillary leak and impaired haemostasis are the pathogenic hallmarks.
- Mortality usually results from an intense inflammatory process akin to septic shock, with insufficient effective circulating intravascular volume leading to hypotension, cellular dysfunction and multi-organ system failure.
- Viral HF is characterized by a short incubation period (usually 1–2 weeks) followed by a rapidly progressive illness usually lasting no longer than 2 weeks. Initial signs and symptoms are usually very nonspecific and include fever, headache and myalgia, followed rapidly by gastrointestinal symptoms and, in some cases, rash and neurologic involvement. Severe cases develop haemodynamic instability, bleeding, shock and multi-organ system failure.
- Mortality rates range from less than 1% to over 80%, depending on the specific viral HF. Survivors generally make a full recovery with few sequelae. There is no chronic carriage of HF viruses. In most cases, infection is thought to confer lifelong immunity in survivors.
- The viruses that cause HF are zoonotic. Consequently, the endemic areas for the various viral HFs are limited to the distribution of their mammalian reservoirs and/or arthropod vectors. Although modern-day ease of travel has made it possible for cases of viral HF to be seen throughout the globe, imported cases remain extremely rare.
- The nonspecific clinical manifestations of viral HF make clinical diagnosis of single cases extremely difficult, especially early in the course of disease. The differential diagnosis is extremely broad. The occurrence of clusters of cases with a compatible clinical syndrome, especially involving healthcare workers, should raise suspicion of viral HF.
- Viral HF should be considered in febrile patients with a compatible clinical syndrome and history of travel and exposure, especially if the patient fails to respond to empiric treatment for the usual infectious diseases prevalent in the area. Despite the name, haemorrhage is not uniformly noted in viral HF and its absence should not be used to exclude the diagnosis.
- Typical laboratory findings in viral HF at presentation include lymphopenia, thrombocytopenia and elevated hepatic transaminases, with AST>ALT. Lymphocytosis and thrombocytosis may be seen in late stages.
- Although many HF viruses may be spread person-to-person, secondary attack rates are generally low as long as routine universal precautions are maintained in patient management. For added safety, specialized viral HF precautions are warranted when there is a confirmed case or high index of suspicion.
- Treatment of viral HF is generally supportive, following guidelines for the management of septic shock. The antiviral drug ribavirin and treatment with convalescent plasma have demonstrated efficacy in a few viral HFs.

Overview

INTRODUCTION

Viral haemorrhagic fever (HF) is a term first coined by Russian physicians in the 1940s to describe a syndrome comprised of fever, a constellation of initially nonspecific signs and symptoms, and a propensity for bleeding and shock. Viral HF may be caused by more than 30 different viruses from four taxonomic families: *Filoviridae*, *Arenaviridae*, *Bunyaviridae* and *Flaviviridae*, although not all members of these families cause viral HF (Table 16.1). Other common elements of viral HF include aspects of their pathogenesis, the fact that they are zoonoses (with the exception of dengue HF) and a tradition of naming HF viruses after the geographic origin of the first recognized case. Nevertheless, there are significant differences in the epidemiology, transmissibility, pathogenesis and clinical picture associated with each specific virus. We first present an overview of the characteristics common to all viral HFs followed by more detailed descriptions of some of the most frequent and important viral HFs. Detailed review of the classic mosquito-borne viral HFs – dengue HF and yellow fever – is provided in Chapters 14 and 15.

EPIDEMIOLOGY

Natural Maintenance and Transmission to Humans

With the exception of dengue virus, for which humans can now be considered to be the reservoir, HF viruses are zoonotic and are maintained in nature in mammals (Table 16.1).[1] The endemic area of any given viral HF is thus restricted by the distribution of its natural reservoir and/or arthropod vector although, for reasons that are often unclear, the distribution of the virus and disease are often less vast than that of the reservoir.

TABLE 16.1 Principal Viruses Causing Haemorrhagic Fever

Virus	Disease	Principal Reservoir/Vector	Geographic Distribution of Disease	Annual Cases	Disease-to-Infection Ratio	Human-to-Human Transmissibility	Case Fatality
Filoviridae							
Ebola[a]	Ebola HF	Fruit bat ('Egyptian fruit bat' or *Rousettus aegyptiacus*, perhaps others)	Sub-Saharan Africa	–[b]	1 : 1	High	25–85% depending upon species[b]
Marburg	Marburg HF	Fruit bat ('Egyptian fruit bat' or *Rousettus aegyptiacus*, perhaps others)	Sub-Saharan Africa	–[b]	1 : 1	High	25–85%[c]
Arenaviridae[d]							
OLD WORLD							
Lassa	Lassa fever	Rodent ('multimammate rat' or *Mastomys natalensis*)	West Africa	30 000–50 000	1 : 5–10	Moderate	25%
Lujo[e]	Lujo HF	Unknown. Presumed rodent	Zambia	Unknown	Unknown	Moderate-to-high	80%
NEW WORLD							
Junin	Argentine HF	Rodent ('corn mouse' or *Calomys musculinus*)	Argentine pampas	<50	1 : 1.5	Low	15–30%
Machupo	Bolivian HF	Rodent ('large vesper mouse' or *Calomys callosus*)	Beni department, Bolivia	<50	1 : 1.5	Low	15–30%
Guanarito	Venezuelan HF	Rodent ('cane mouse' or *Zygodontomys brevicauda*)	Portuguesa state, Venezuela	<50	1 : 1.5	Low	30–40%
Sabiá[f]	Brazilian HF	Unknown. Presumed rodent	Rural area near Sao Paulo, Brazil?	–[f]	1 : 1.5	Low?	33%
Chapare[g]	Chapare HF	Unknown. Presumed rodent	Cochabamba, Bolivia	Unknown	Unknown	Unknown	Unknown
Bunyaviridae							
OLD WORLD HANTAVIRUSES							
Hantaan, Seoul, Puumala, Dobrava-Belgrade, others	HF with renal syndrome	Rodents (see Table 16.6)	See Table 16.6	50 000–150 000	Hantaan: 1 : 1.5, Others: 1 : 20	None	<1–50%, depending on specific virus
NEW WORLD HANTAVIRUSES							
Sin Nombre, Andes, Laguna Negra, others	Hantavirus pulmonary syndrome	Rodents (see Table 16.6)	See Table 16.6	50 000–150 000	Sin nombre: 1 : 1, Others up to 1 : 20	None, except for Andes virus	<1–50%, depending on specific virus

TABLE 16.1 Principal Viruses Causing Haemorrhagic Fever—cont'd

Virus	Disease	Principal Reservoir/Vector	Geographic Distribution of Disease	Annual Cases	Disease-to-Infection Ratio	Human-to-Human Transmissibility	Case Fatality
Rift Valley fever	Rift Valley fever	Domestic livestock/ mosquitoes (*Aedes* and others)	Sub-Saharan Africa, Madagascar, Saudi Arabia, Yemen[g]	100–100 000[b,h]	1 : 100	None	Up to 50% in persons manifesting severe forms
Crimean-Congo HF	Crimean-Congo HF	Wild and domestic vertebrates/tick (primarily *Hyalomma* species)	Africa, Balkans, southern Russia, Middle East, India, Pakistan, Afghanistan, western China	~500	1 : 1–2	High	15–30%
Flaviviridae							
Yellow fever	Yellow fever	Monkey/mosquito (*Aedes aegypti*, other *Aedes* and *Haemagogus* spp.)	Sub-Saharan Africa, South America up to Panama	5,000–200 000[i]	1 : 2–20	No	20–50%
Dengue	Dengue HF	Human/mosquito (*Aedes aegypti* and *albopictus*)	Tropics and subtropics worldwide	Dengue HF: 100 000–200 000[h]	1 : 10–100 depending on age, previous infection, genetic background and infecting serotype	None	Untreated: 10–15% Treated: < 1%
Kyasanur Forest disease	Kyasanur Forest disease	Vertebrate (rodents, bats, birds, monkeys, others)/ tick (*Haemophysalis* species and others)	Karnataka State, India; Yunnan Province, China; Saudi Arabia[j]	~500	Unknown	Not reported, but laboratory infections have occurred	3–5%
Omsk HF	Omsk HF	Rodent/ticks (primarily *Dermacentor* and *Ixodes* species)	Western Siberia	100–200	Unknown	Not reported	1–3%

HF, haemorrhagic fever.

[a]Six species or sub-types of *Ebolavirus* with varying associated case-fatality ratios are recognized: Ebola Zaire, 85%; Ebola Sudan, 55%; Ebola Bundibugyo, 40%; Ebola Cote d'Ivoire, 0 (only one recognized case, who survived); Ebola Reston, 0 (not pathogenic to humans); Lloviu, no human infections recognized. All are endemic to sub-Saharan Africa, with the exceptions of Ebola Reston virus, which is found in the Philippines and Lloviu virus, which was detected in bats in Spain.

[b]Although some endemic transmission of the filoviruses (Ebola>Marburg) and Rift Valley fever virus occurs, these viruses have most often been associated with outbreaks. Filovirus outbreaks are typically less than 100 cases and have never been greater than 500.

[c]The case fatality ratio was 22% in the first recognized outbreak of Marburg HF in Germany and Yugoslavia in 1967 but has been consistently over 80% in outbreaks in central Africa where the virus is endemic. Possible reasons for this discrepancy include differences in quality of care, strain pathogenicity, route and dose of infection, underlying prevalence of immunodeficiency and co-morbid illnesses and genetic susceptibility.

[d]In addition to the arenaviruses listed in the table, Flexal and Tacaribe viruses have caused human disease as a result of laboratory accidents. Another arenavirus, Whitewater Arroyo, has been noted in sick persons in California but its role as a pathogen has not been clearly established.

[e]Discovered in 2008 in an outbreak of five cases (four of them fatal) in South Africa. The index case came to South Africa from Zambia.

[f]Discovered in 1990. Only three cases (one fatal) have been noted; two of them from laboratory accidents.

[g]Discovered in 2003 from a small outbreak in Cochabamba, Bolivia. Blood was obtained from one fatal case and Chapare virus isolated but few other details from the outbreak have been reported.

[h]Although Rift Valley fever virus can be found throughout sub-Saharan Africa, large outbreaks usually occur in East Africa.

[i]Based on estimates from the World Health Organization. Significant underreporting occurs. Incidence may fluctuate widely depending on epidemic activity.

[j]Numerous variants of Kyasanur Forest disease virus have been identified, including Nanjianyin virus in Yunnan Province, China and Alkhumra virus (also spelled 'Alkhurma' in some publications) in Saudi Arabia.

Few data are available on the precise modes of transmission from mammals to humans, but infection is presumed to most often result from inadvertent contact with virus-contaminated excreta of the reservoir, with inoculation into mucus membranes or broken skin. A few HF viruses are arboviruses, spread to humans by mosquitoes or ticks. Aerosol transmission has also been suggested for some viruses, but there are few data to confirm or refute this route of exposure.[2] Empiric observation in the field, including the general absence of clusters of cases in which no direct contact occurred, suggests that aerosol transmission is not a predominant mode of spread, if it occurs at all. Nevertheless, studies in non-human primates show that transmission of many HF viruses is possible when aerosols are artificially produced, with obvious implications for their potential use as bioweapons.[3,4]

Human-to-Human Transmission

Secondary human-to-human transmission occurs with many of the HF viruses, usually through direct contact with contaminated blood or body fluids (Table 16.1). Infection probably occurs most often through oral or mucous membrane exposure in the context of providing care to sick family members in the community or patients in a healthcare institution or during funeral rituals that entail the touching of the corpse prior to burial. Again, there are few data on aerosol spread, although the observation that infection is rare in healthcare workers taking precautions against contact, but not aerosol, transmission suggests that it is rare or non-existent. Large outbreaks are almost always the result of amplification in healthcare settings, in which basic infection control measures have broken down, usually in areas of extreme poverty or civil strife, resulting in the absence of gloves and other personal protective equipment and reuse of unsterilized needles.[5] The risk of transmission during the incubation period or from asymptomatic persons is negligible, although a case of Argentine HF was reported due to blood transfusion from a donor who was asymptomatic. Rarely, sexual transmission of HF viruses (best documented for Ebola, Marburg, Lassa and Junin viruses) during convalescence has been confirmed or strongly suspected.[6]

PATHOGENESIS AND PATHOLOGY

Knowledge of the pathogenesis of viral HF is based on limited data from humans combined with extrapolation from more extensive observations made in animal models.[7–9] Although details of the pathophysiology vary with the specific virus, microvascular instability and impaired haemostasis are the consistent hallmarks. Despite the term 'viral HF', external haemorrhage is not always seen and may even be rare in some viral HFs. Rather, the pathogenesis of viral HF appears to have much in common with septic shock. Mortality usually results not directly from exsanguination, but rather from an intense inflammatory process resulting in insufficient effective circulating intravascular volume leading to hypotension, cellular dysfunction and multi-organ system failure.

The interaction of virus with immune cells, especially macrophages and endothelial cells, results in cell activation and the unleashing of an inflammatory and vasoactive process consistent with the systemic inflammatory response syndrome. Although lymphocytes remain free of infection, they may be destroyed in massive numbers in some viral HFs through apoptosis, as seen in other forms of septic shock.

The synthesis of cell surface tissue factor triggers the extrinsic coagulation pathway. Impaired haemostasis may entail endothelial cell, platelet and/or coagulation factor dysfunction, depending upon the specific infecting virus. Disseminated intravascular coagulopathy (DIC) is frequently noted in some, but not all, viral HFs (Table 16.2).

After inoculation, the virus first replicates in dendritic cells and other local tissues, with subsequent migration to regional lymph nodes followed by dissemination through the lymph and blood monocytes to a broad range of tissues and organs,

TABLE 16.2 Pathobiological and Clinical Aspects of Viral Haemorrhagic Fevers

Disease	Incubation Period (Days)	Onset	Bleeding	Rash	Jaundice	Heart	Lung	Kidney	CNS	Eye
Filoviridae										
Ebola HF	3–21	Abrupt	++	+++	+	++?	+	+	+	+
Marburg HF	3–21	Abrupt	++	+++	+	++?	+	+	+	+
Arenaviridae										
Lassa fever	5–16	Gradual	+	+	0	++	+	0	+	0
Lujo HF	9–13	Abrupt	+	++	0	?	+	+	+	0
South American HFs[a]	4–14	Gradual	+++	+	0	++	+	0	+++	0
Bunyaviridae										
HF with renal syndrome	9–35	Abrupt	+++	0	0	++	+	+++	+	0
Hantavirus pulmonary syndrome	7–35	Gradual	0 (except for Andes virus infection)	0	0	+++	+++	+	+	0
Rift Valley fever[b]	2–5	Abrupt	++	+	++	+?	0	+	++	++
Crimean-Congo HF[c]	3–12	Abrupt	+++	0	++	+?	+	0	+	0
Flaviviridae										
Yellow fever	3–6	Abrupt	+++	0	+++	++	+	++	++	0
Dengue HF	3–15	Abrupt	++	+++	+	++	+	0	+	0
Kyasanur Forest disease	3–8	Abrupt	++	0	0	+	++	0	+++	+
Omsk HF	3–8	Abrupt	++	0	0	+	++	0	+++	+

CNS, central nervous system; HF, haemorrhagic fever; 0, sign not typically noted/organ not typically affected; +, sign occasionally noted/organ occasionally affected; ++, sign commonly noted/organ commonly affected; +++, sign characteristic/organ involvement severe.

[a]Data are insufficient to distinguish between the syndromes produced by the various New World arenaviruses.

[b]HF, encephalitis and retinitis may be seen in Rift Valley fever independently of each other.

[c]The incubation period of Crimean-Congo HF varies with the mode of transmission: typically 1–3 days after tick bite and 5–6 days after contact with infected animal blood or tissues.

including the liver, spleen, lymph nodes, adrenal glands, lungs and endothelium. Migration of tissue macrophages then results in secondary infection of permissive parenchymal cells. The most affected organs vary with the virus (Table 16.2). Tissue damage may be mediated through direct viral infection and necrosis or indirectly through the inflammatory process. Inflammatory cell infiltrates are usually mild.

Cellular immunity is thought to be the primary arm of protection in most viral HFs. With the exception of disease caused by the hantaviruses and some of the flaviviruses, the pathogenesis of viral HF appears to be unchecked viraemia, with most fatal cases failing to mount a significant antibody response. In some viral HFs virus replication and dissemination is facilitated by virus-induced suppression of the host adaptive immune response.

Virus rapidly clears from the blood upon symptom resolution in survivors, but clearance may be delayed (up to 3 months after acute infection) from a few immunologically protected sites, such as the kidney, gonads and chambers of the eye.[6,10] In contrast to the process described above, hantaviruses, yellow fever virus and dengue virus are usually cleared from the blood prior to the most severe phase of the disease. Here, the host immune response is thought to play a detrimental role.

CLINICAL FEATURES

Viral HF is seen in both genders and all age groups, with a spectrum from relatively mild or even asymptomatic infection to severe vascular permeability with shock, multi-organ system failure and death. Although the clinical presentation may differ for each viral HF as it progresses, in most cases it is not possible to distinguish the various syndromes at presentation. Distinct phases of disease and recovery are classically described for HF with renal syndrome and yellow fever, although not seen in all cases. Biphasic illnesses are classically noted for the flavivirus HFs, in which a quiescent period of days (yellow fever and dengue) to weeks (Kyasanur Forest disease and Omsk HF) occurs, after which the most severe manifestations may set in, including haemorrhage, shock, renal failure and meningoencephalitis.

After an incubation period ranging from days to weeks, depending upon the infecting virus (Table 16.2), illness typically begins with fever and constitutional symptoms, including general malaise, anorexia, headache, myalgia, arthralgia, sore throat, chest or retrosternal pain and lumbosacral pain. Neck pain and stiffness, retro-orbital pain and photophobia are common in Rift Valley fever and may be noted in viral HFs, in which meningitis is common, such as Omsk HF and Kyasanur Forest disease. Orthostatic hypotension is common. Gastrointestinal signs and symptoms follow in the first few days of illness, including nausea, vomiting, epigastric and abdominal pain, abdominal tenderness, diarrhoea and constipation. Diarrhoea may become bloody in the later stages of disease. A misdiagnosis of appendicitis or other acute abdominal emergency sometimes occurs, prompting unneeded and dangerous (in terms of risk of nosocomial spread) surgical interventions. Conjunctival injection or haemorrhage is frequent. Various forms of skin rash, including morbilliform, maculopapular, petechial and ecchymotic, may be seen, depending on the specific viral HF (Table 16.2).

In severe cases, towards the end of the first week of illness, patients progress to vascular instability that may be manifested by facial flushing, oedema, bleeding, hypotension, shock and proteinuria. The likelihood of clinically discernible haemorrhage varies with the infecting virus (Table 16.2). Haematemesis, melena, haematochezia, metrorrhagia, petechiae, purpura, epistaxis and bleeding from the gums and venepuncture sites may develop, but haemoptysis and haematuria are infrequent. Significant internal bleeding from the gastrointestinal tract may occur even in the absence of external haemorrhage and misdiagnosis as peptic ulcer disease is common. Central nervous system manifestations, including disorientation, tremor, gait anomalies, convulsions and hiccups, may be noted in end-stage disease in some viral HFs, as is renal insufficiency or failure. Radiographic and electrocardiographic findings are generally nonspecific and correlate with the physical examination.[11] Pregnant women often present with spontaneous abortion and vaginal bleeding, with maternal and fetal mortality approaching 100% in the 3rd trimester.

Convalescence from viral HF may be prolonged, with persistent myalgia, arthralgia, anorexia, weight loss, alopecia orchitis, irritability and memory changes up to a year after infection. Nevertheless, in most cases there are no permanent sequelae. However, the psychological effects of viral HF may also be significant and often overlooked, with some patients experiencing depression or post-traumatic stress, as well as social stigmatization.

DIAGNOSIS

Differential Diagnosis

Many infectious and even non-infectious diseases can mimic viral HF, especially in the early stages, resulting in an extremely broad differential diagnosis that varies by geographic region (Table 16.3 and Figures 16.1–16.4). Initial misdiagnosis of more familiar syndromes is common. Malaria and bacterial septicaemia, including meningococcaemia, are among the most common, although malaria is unlikely to be the cause of severe illness in adults living in malaria-endemic areas. African tick-bite fever and other rickettsial illness should also be considered. Although confirmation of an alternative diagnosis renders viral HF less likely, the possibility of coinfection should be considered, especially taking into account that bacterial septicaemia can occur as a complication of viral HF. Furthermore, a positive test for malaria should not completely exclude viral HF, especially if the patient is not responding to anti-malarial drugs, since pre-existing parasitaemia may be common in holoendemic areas for malaria.

The presence or absence of certain clinical features can help rule out viral HF:

- Haemorrhage is almost never seen in the first few days of illness. Its presence at this early stage should suggest an alternative diagnosis, especially meningococcaemia.
- Although conjunctival injection and sub-conjunctival haemorrhage are frequent in viral HF, they are not accompanied by itching, discharge or rhinitis. The presence of these symptoms should suggest a more common viral upper respiratory tract infection, adenoviral or bacterial conjunctivitis or allergic rhinitis.
- With the exception of yellow fever, jaundice on presentation is not typical of viral HF and should suggest another diagnosis or a complicating factor such as underlying Gilbert's syndrome, drug reaction or co-infection with an

TABLE 16.3 Differential Diagnosis of Viral Haemorrhagic Fever

Disease	Distinguishing Characteristics and Comments
Parasites	
Malaria	Classically shows paroxysms of fever and chills; Haemorrhagic manifestations less common; Malaria smears or rapid test usually positive; Co-infection (or baseline asymptomatic parasitaemia) common; Responds to anti-malarials
Amoebiasis	Haemorrhagic manifestations other than bloody diarrhoea generally not seen; Amoebic trophozoites identified in the stool; Responds to anti-parasitics
Giardiasis	Positive stool antigen test and/or identification of trophozoites or cysts in stool; Responds to antiparasitics
African trypanosomiasis (acute stages)	Especially the east African form. Examination of peripheral blood smear/buffy coat may show trypanosomes
Bacteria (including Spirochetes, Rickettsia, Ehrlichia and Coxiella)	
Typhoid fever	Haemorrhagic manifestations other than bloody diarrhoea generally not seen; Responds to antibiotics
Bacillary dysentery (including shigellosis, campylobacteriosis, salmonellosis and enterohaemorrhagic *Escherichia coli* and others)	Haemorrhagic manifestations other than bloody diarrhoea generally not seen; Respond to antibiotics
Capnocytophaga canimorsus	Associated with dog and cat bites, typically in persons with underlying immunodeficiency, notably asplenic patients; Responds to antibiotics
Meningococcaemia	Bacterial-induced DIC may mimic the bleeding diathesis of viral HF; bleeding within the first 24–48 hours after onset of illness and rapidly progressive illness typical; Large ecchymoses typical of meningococcemia are unusual in the viral HFs except for Crimean-Congo HF; Rapid serum latex agglutination tests can be used to detect bacterial antigen in meningococcal septicaemia; May respond to antibiotics (critical to administer early)
Staphylococcaemia	Bacterial-induced DIC may mimic the bleeding diathesis of viral HF; May respond to antibiotics
Septic abortion	History of pregnancy and positive pregnancy test
Septicaemic or pneumonic plague	Bacterial-induced DIC may mimic the bleeding diathesis of viral HF; Large ecchymoses typical of plague are unusual in the viral HFs except for Crimean-Congo HF; Pneumonic plague may mimic HPS; May respond to antibiotics
Streptococcal pharyngitis	May mimic the exudative pharyngitis sometimes seen in Lassa fever
Tuberculosis	Haemoptysis of advanced pulmonary tuberculosis may suggest viral HF, but tuberculosis generally has a much slower disease evolution
Tularaemia	Ulceroglandular and pneumonic forms more common; Responds to antibiotics
Acute abdominal emergencies	Appendicitis, peritonitis and bleeding upper gastrointestinal ulcer
Pyelonephritis and post-streptococcal glomerulonephritis	May mimic HF with renal syndrome
Anthrax (inhalation or gastrointestinal)	Prominent pulmonary manifestations and widened mediastinum on chest X-ray in inhalation form; Responds to antibiotics
Atypical bacterial pneumonia (*Legionella, Mycoplasma, Chlamydophila pneumoniae* and *psittaci*, others)	May mimic hantavirus pulmonary syndrome; Exposure to birds and symptoms often not present until late in the illness in psittacosis; Respond to antibiotics
Relapsing fever	Recurrent fevers and flu-like symptoms, with direct neurologic involvement and splenomegaly; Spirochetes visible in blood while febrile; Responds to antibiotics
Leptospirosis	Jaundice, renal failure and myocarditis in severe cases; Responds to antibiotics
Spotted fever group rickettsia (including African tick bite fever, Boutonneuse fever, Rocky Mountain spotted fever)	Incubation period of 7–10 days after tick bite, compared with 1–3 days in Crimean-Congo HF; Necrotic lesions (eschar) typically seen at site of tick bite in some rickettsial diseases while there may only be slight bruising at the bite site in Crimean-Congo HF; Rash (if present) of Rickettsial infection classically involves palms and soles
Q fever (*Coxiella burnetii*)	Broad spectrum of illness, including hepatitis, pneumonitis, encephalitis and multisystem disease with bleeding; Responds to antibiotics
Ehrlichiosis	Responds to antibiotics
Viruses	
Influenza	Prominent respiratory component to clinical presentation; No haemorrhagic manifestations; Influenza rapid test may be positive; May respond to anti-influenza drugs
Arbovirus infection (including dengue and West Nile fever)	Encephalitis unusual, but when present may mimic the viral HFs with significant neurologic involvement (Kyasanur Forest disease, Omsk HF); Usually less severe than viral HF; Haemorrhage not reported
Viral hepatitis (including hepatitis A, B and E, Epstein-Barr and cytomegalovirus)	Jaundice atypical in HF except yellow fever; Tests for hepatitis antigens positive; Fulminant infection resembling viral HF may be seen in persons with underlying immune deficiencies
Herpes simplex or varicella-zoster	Fulminant infection with hepatitis (with/without vesicular rash); Elevated transaminases and leucopaenia typical; Disseminated disease may be noted in otherwise healthy persons; poor response to acyclovir drugs unless recognized early

TABLE 16.3 Differential Diagnosis of Viral Haemorrhagic Fever—cont'd

Disease	Distinguishing Characteristics and Comments
HIV/AIDS	Seroconversion syndrome or HIV/AIDS with secondary infections, especially septicaemia
Measles	Rash may mimic that seen in early stages of some viral HFs and may sometimes be haemorrhagic; Prominence of coryza and upper respiratory symptoms in measles should help differentiate; Vaccine preventable
Rubella	Rash may mimic that seen in early stages of some viral HFs; Usually a mild disease; Vaccine preventable
Haemorrhagic or flat smallpox	Diffuse haemorrhagic or macular lesions; In contrast to the viral HFs, the rash may involve the oral mucosa, palms and soles; Smallpox in the wild has been eradicated
Alphavirus infection (including chikungunya and o'nyong-nyong)	Joint pain typically a predominant feature
Fungi	
Histoplasmosis	Pulmonary disease may mimic hantavirus pulmonary; Recent entry into mines or caves
Non-infectious Aetiologies	
Heat stroke	History for extreme heat exposure; Absence of sweating; Bleeding not typical but DIC may occur
Idiopathic and thrombotic thrombocytopenic purpura (ITP/TTP)	Presentation usually less acute than viral HF; May have prominent neurologic symptoms in TTP; Coagulation factors normal and DIC absent; Often respond to corticosteroids (ITP) or plasma exchange (TTP)
Acute glaucoma	May mimic the acute ocular manifestations of Rift Valley fever
Haematological malignancies (leukaemia, lymphoma)	May resemble leukemoid reaction occasionally seen in HF with renal syndrome
Drug sensitivity or overdose	Stevens–Johnson's syndrome and anticoagulant (warfarin) overdose
Industrial and agricultural chemical poisoning	Especially anticoagulants, although other symptoms of viral HF absent
Haematoxic snake bite envenomation	History of snake bite

DIC, disseminated intravascular coagulopathy; HF, haemorrhagic fever.

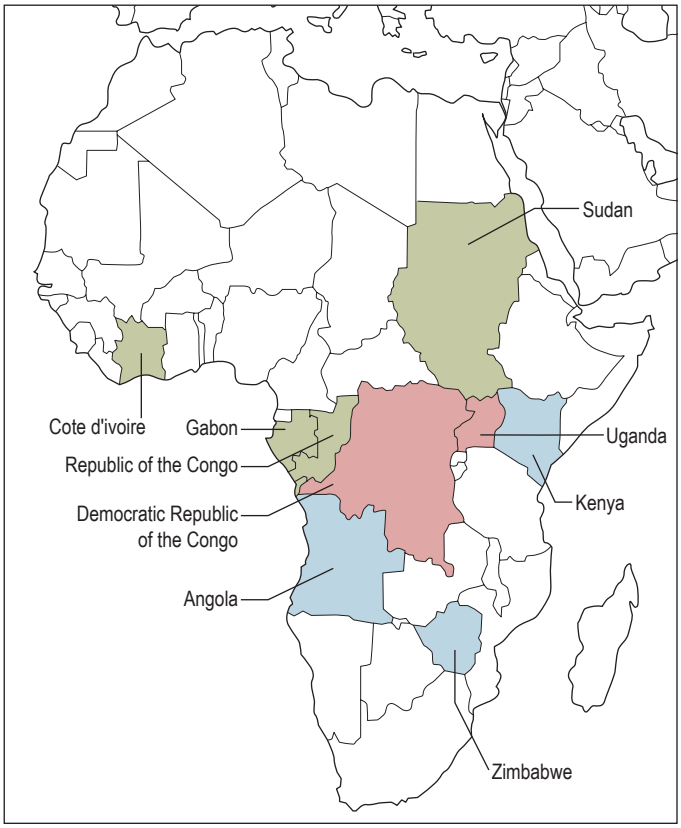

Figure 16.1 Endemic areas for filoviruses. Only filoviruses known to cause haemorrhagic fever are shown. Countries where Ebola and Marburg haemorrhagic fevers have been seen are indicated in green and blue, respectively, with countries in red indicating documentation of both diseases. Incidence and risk of disease may vary significantly within each country.

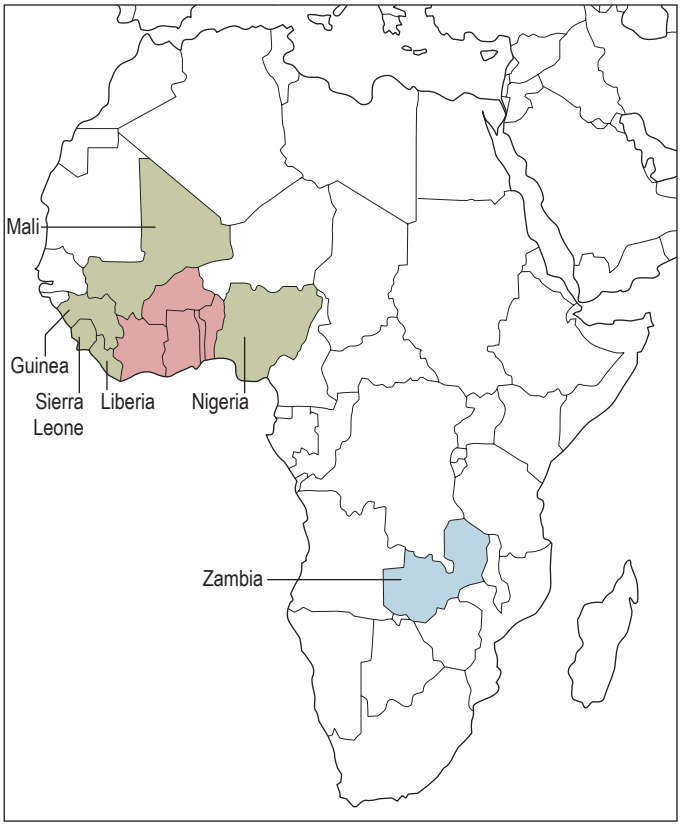

Figure 16.2 Endemic areas for Old World arenaviruses. Only the two arenaviruses, Lassa and Lujo, known to cause haemorrhagic fever are shown. Countries where clinical cases of Lassa fever have been confirmed are depicted in green. Indirect evidence, such as anecdotal reports or seroprevalence data, exists for most of the other countries in West Africa, shown in red. Endemic countries for Lujo virus are depicted by blue. Incidence and risk of disease may vary significantly within each country.

Figure 16.3 Endemic areas for New World arenaviruses. Only the arenaviruses known to cause haemorrhagic fever are shown. Incidence and risk of disease may vary significantly within each country.

organism causing hepatotoxicity or haemolysis, such as malaria.

- Although a dry cough may occasionally be noted in viral HF, sometimes accompanied by a few scattered rales on auscultation, with the exception of hantavirus pulmonary syndrome (HPS), prominent pulmonary symptoms or the presence of productive sputum are not typical of viral HF, although secondary bacterial infection producing these symptoms may occur as disease progresses.

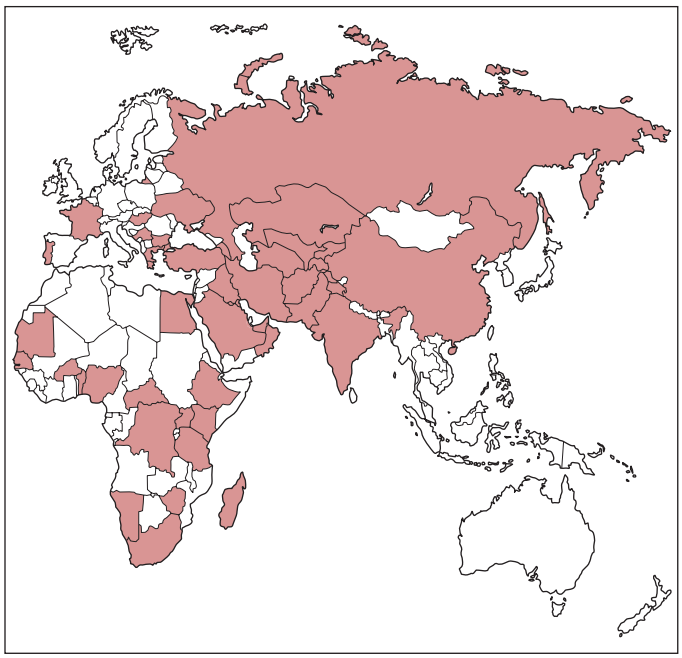

Figure 16.4 Endemic areas for Crimean-Congo haemorrhagic fever virus. Incidence and risk of disease may vary significantly within each country. Variable intensity of surveillance may underlie the absence of confirmed cases in some countries.

Clinical Diagnosis

The nonspecific clinical manifestations of most viral HFs make a clinical diagnosis and detection of single cases extremely difficult, especially early in the course of the disease when haemorrhage and other more identifiable manifestations are usually absent. A detailed epidemiological history and physical examination, along with preliminary basic laboratory results (Table 16.4) are critical in initial consideration of the diagnosis, including details of travel, possible exposures, occupational risks and details of the progression of illness (e.g. timing of haemorrhage relative to onset of illness). A diagnosis of viral HF should be considered in patients with a clinically compatible syndrome who, within the incubation period for the particular viral HF in question (Table 16.2):

- Reside in or travelled to an area where a viral HF is known or suspected to be endemic (Table 16.1 and Figures 16.1–16.4)
- Had potential direct contact with blood or body fluids of someone with a suspected or confirmed viral HF during their acute illness. This group is most often comprised of healthcare workers and laboratory personnel or persons caring for family members at home or preparing bodies for burial
- Had contact with live or recently killed animals in a viral HF-endemic area (although it should be recognized that direct contact with the animal reservoir is not usually reported even in confirmed cases of viral HF). Animals and arthropods in question include non-human primates, rodents, bats, livestock, ticks and mosquitoes, depending upon the viral HF in question. Food potentially recently contaminated by these animals could also be a source of infection
- Worked in a laboratory or animal facility where HF viruses are handled
- Had sex with someone recovering from a viral HF in the last 3 months.

The index of suspicion should be especially high for persons in specific high-risk occupations, including abattoir workers, veterinarians and farm workers, hunters and taxidermists. Acts of bioterrorism must be considered if viral HF is strongly suspected in a patient without any of the aforementioned risk factors, especially if clusters of cases are seen. It should be noted that even persons who meet the above criteria most commonly have a disease other than viral HF, so alternative diagnoses should always be aggressively sought and specific treatment instituted.

Laboratory Diagnosis

If viral HF is still suspected after the initial work-up and laboratory testing, prompt diagnostic laboratory testing is imperative. Rapid access to specialized laboratory testing will vary according to region and is especially a problem in resource-limited areas. Unfortunately, no commercial assays are available for the viral HFs, with the exception of various kits with varying sensitivity and specificity for the serologic diagnosis of dengue fever and HPS. The absence of commercial assays poses a major impediment to both patient diagnosis and research. Recombinant-protein and virus-like particle-based assays for the viral HFs are being developed which may eventually relieve

TABLE 16.4 Indicated Clinical Laboratory Tests and Characteristic Findings in Patients with Viral Haemorrhagic Fever

Test	Characteristic Findings and Comments
Leukocyte count	Early: moderate leukopenia (except for hantavirus infection, in which early leukocytosis with immunoblasts are classically noted); Later: leukocytosis with left shift; Granulocytosis more suggestive of bacterial infection
Haemoglobin and haematocrit	Haemoconcentration (especially noted in haemorrhagic fever with renal syndrome and hantavirus pulmonary syndrome)
Platelet count	Mild-to-moderate thrombocytopenia
Electrolytes	Sodium, potassium and acid–base perturbations, depending upon fluid balance and stage of disease
BUN/creatinine	Renal failure may occur late in disease.
Serum chemistries (AST, ALT, amylase, gamma-glutamyl transferase, alkaline phosphatase, creatinine kinase, lactate dehydrogenase, lactate acid)	Usually increased, especially in severe disease; AST > ALT; A lactate level greater than 4 mmol/L (36 mg/dL) may indicate persistent hypo-perfusion and sepsis. Lactate dehydrogenase is typically markedly increased in hantavirus pulmonary syndrome
Sedimentation rate	Normal or decreased
Blood gas	Metabolic acidosis may be indicative of shock and hypoperfusion
Coagulation studies (PT, PTT, fibrinogen, fibrin split products, platelets, D-dimer)	DIC common in Ebola, Marburg, Lujo virus, Crimean-Congo HF and New World arenavirus infections
Urinalysis	Proteinuria common; Haematuria may be occasionally noted; Sediment may show hyaline-granular casts and round cells with cytoplasmic inclusions
Blood culture	Useful early to exclude viral HF and later to evaluate for secondary bacterial infection; Blood should be drawn before antibiotic therapy is instituted
Stool culture	Useful to exclude viral HF (in favour of haemorrhagic bacillary dysentery)
Thick and thin blood smears	May aid in the diagnosis of blood parasites (malaria and trypanosomes) and bacterial sepsis (meningococcus, capnocytophaga and anthrax); All negative in viral HF unless coinfection
Rapid test, PCR or other assay for malaria	Negative in viral HF unless coinfection with malaria
Febrile agglutinins or other assay for *Salmonella typhi*	Negative in viral HF unless coinfection with *S. Typhi*

ALT, Alanine aminotransferase; AST, aspartate aminotransferase; DIC, disseminated intravascular coagulation; viral HF, viral haemorrhagic fever.

this bottleneck, as well as further improve sensitivity and specificity. Meanwhile, various 'in-house' assays have been developed and are performed in a few specialized laboratories.

The enzyme-linked immunosorbent assay (ELISA), reverse transcriptase polymerase chain reaction (RT-PCR) and cell culture are the mainstays of diagnosis.[12] Although extensive validation of these assays has not been conducted, sensitivities and specificities are generally considered to be over 90%. The immunofluorescent antibody test (IFA) may also be employed but is not as routinely sensitive or specific and is more subjective in its interpretation, varying with the experience of the technician.[13] Post-mortem diagnosis of some viral HFs may be established by immunohistochemical staining of formalin-fixed tissue, especially skin, liver and spleen.[14] All confirmed cases of viral HF should be reported immediately to government health authorities as well as to the World Health Organization in keeping with International Health Regulations. No test can reliably be used to diagnose viral HF before the onset of illness. Consequently, testing of contacts or other asymptomatic persons is not recommended, even if the suspicion of infection is high.

Acute Febrile Stage. In the acute febrile phase of the disease, viral HF is usually diagnosed by identifying virus, virus antigen or nucleic acid in the specimen. These measures also provide prognostic value, since high levels of virus, antigen or nucleic acid in the blood correlate with a poor prognosis in most viral HFs. Serum is the most reliable sample to test, but the virus can be variably isolated from throat washings, urine, CSF, breast milk and various other tissues.[6] ELISAs are high throughput and ELISA antigen tests and RT-PCR can usually be done in a few hours. Multiplex PCR assays have been developed that may allow for simultaneous testing for the HF viruses as well as the many diseases in the differential diagnosis. Furthermore, these assays can be performed with inactivated specimens using standard equipment present in most diagnostic laboratories. In contrast, propagation of most HF viruses in cell culture requires a high containment facility and 2–10 days to detect virus growth, depending on the specific virus and titre in the sample. However, ELISAs may lack sensitivity relative to RT-PCR and cell culture. Nevertheless, cell culture should not be omitted whenever possible because HF viruses have occasionally been isolated from specimens for which ELISA antigen, antibody and RT-PCR tests were all negative – a finding attributable to virus concentrations in the test sample that were below the threshold of detection of these assays or the presence of variant or novel viruses that were not detectable with the antigens and primer sets employed.[15]

Failure to appreciate the intricacies and limitations of the various laboratory assays has occasionally led to false-negative diagnoses and increased risk of nosocomial transmission. Inhibitory substances circulating in the blood have been shown to cause false-negative RT-PCR results in viral HF. Thus, appropriate inhibition controls must be included in all RT-PCR assays.

Although virus is usually present in high titre and relatively easy to detect in the blood of persons with severe disease (with the exception of *Flavivirus* and *Hantavirus* infections), viraemia may be of very short duration or even absent in surviving cases or very early in the course of disease. If clinical suspicion of viral HF remains high, despite a negative result, tests should be repeated in 1–2 days and, if necessary, again in convalescence.

The diagnosis of viral HF can usually be safely discarded if virus, antigen or nucleic acid cannot be detected in blood during the first 7 days of illness and IgM antibody is negative (see below).

False-positive results due to contamination are also a concern with RT-PCR due to its extreme sensitivity, especially when the assay is being performed in more rudimentary facilities in developing countries, where separate spaces for sample preparation and amplification and the routine use of positive and negative controls is not always possible. In the worst case, outbreaks or even bioterrorism could be falsely declared. The use of one-step assays, sequencing of PCR products to distinguish them from reference strains, targeting different portions of the genome and use of multiple supporting diagnostic methods can minimize the risk of false-positives.

Sub-acute and Convalescent Stages. In the sub-acute and convalescent stages of illness, viral HF can be diagnosed through identification of IgM and IgG antibody, respectively, in the blood through ELISA or IFA. Antibody seroconversion (usually interpreted as a fourfold increase in titre) on acute and convalescent serum specimens has also been used to retrospectively diagnose acute disease when assays for detection virus, nucleic acid or antigen are not available. Demonstration of neutralizing antibody can increase the specificity of ELISA antibody results but neutralization assays are not uniformly standardized, are cumbersome to perform and, because they require the use of live virus, must be done in a high containment laboratory for many of the viruses in question. Consequently, they are infrequently performed. The timing of appearance of IgM and IgG antibodies and their duration after infection has not been systematically studied and likely varies with the specific virus. In survivors, IgM generally appears in the first days or weeks of illness and lasts for months after infection, while IgG typically appears during convalescence and is thought to last years, if not decades.

MANAGEMENT AND TREATMENT

Because of their potential severity, risk of secondary spread, high degree of public scrutiny and unfamiliarity on the part of most physicians, consultation with infectious disease specialists or other clinicians with experience in the diagnosis and treatment of viral HFs should be sought when the diagnosis is suspected. The process of performing a work-up for non-viral HF aetiologies, while assuring that proper safety precautions are maintained, nosocomial spread avoided and undue panic is minimized, is a delicate one. The casual inclusion of viral HF in the differential diagnosis has the potential to induce considerable anxiety in patients, hospital staff and the general community. When to 'sound the alarm' of viral HF is a case-by-case decision left to the treating physician in consultation with experts in the field. Knowledge that most viral HFs are rare and that routinely practiced universal precautions are protective in the vast majority of cases (see below) should offer reassurance.

In remote areas of Africa, access to basic laboratory tests and diagnostic tests for the broad range of diseases included in the differential diagnosis of viral HF is very limited and empiric treatment to cover the usual range of infectious agents is the norm. Admission to an isolation ward is based on relatively nonspecific clinical and epidemiological features. Access to accurate on-site specialized diagnostics, typically PCR, may reduce the number of patients potentially exposed to HF viruses in the isolation ward.

Treatment of viral HF can be divided into general supportive measures, antiviral drugs, antibody therapy (including both human convalescent plasma and laboratory-generated mono- and polyclonal antibodies), immune modulators and coagulation modulators.[16–18] However, very few controlled trials in humans have been performed for any treatment strategy for viral HF.

General Supportive Measures

Treatment of viral HF generally follows the guidelines for the management of septic shock.[19] Where possible patients with viral HF should be treated in an intensive care unit since severe microvascular instability, often complicated by vomiting, diarrhoea, decreased fluid intake and third-spacing, may require continuous monitoring and aggressive fluid replacement. Because of the risk of bleeding at insertion sites, intravascular haemodynamic devices are contraindicated. Haemodynamic status should instead be monitored by blood pressure cuff or other non-invasive means. Intramuscular and subcutaneous injections should also be avoided due to the risk of haematoma. Even in resource-limited settings basic supportive care can be safely implemented if contact precautions and sound infection control practices are maintained.

Fluid Management. Fluid management in viral HF poses a particular challenge. Aggressive fluid replacement is warranted and may prevent shock and DIC. However, overaggressive and unmonitored rehydration may lead to significant third-spacing and pulmonary oedema, given the impaired cardiac function present in some viral HFs, especially HPS. Fluid and blood pressure management guidelines for septic shock are recommended for viral HF due to the common elements in the pathogenesis of these two conditions, although there are no efficacy data on their use in viral HF. Crystalloids (Ringers lactate or normal saline) and, if necessary, vasopressors, should be infused to maintain central venous pressure between 8–12 mmHg or mean arterial blood pressure above 65 mmHg in adults. Early use of vasopressors, especially dopamine and norepinephrine, may diminish the risk of fluid overload. Dobutamine should be added if the above measures, and blood transfusion when warranted, fail to maintain the target blood pressure and adequate organ perfusion. Peritoneal and haemodialysis have been used in patients with HF with renal syndrome without major complications, but there is little published experience in other viral HFs. Extreme caution is warranted with this and all procedures that involve potential exposure to blood to avoid virus transmission to healthcare workers.

Clinical Laboratory Findings. A broad range of clinical laboratory parameters should be monitored closely (Table 16.4). Blood samples for clinical laboratory testing can be inactivated by the addition of detergents, such as Triton X-100, although the effect of such inactivation steps on the various possible parameters to be measured has not been firmly established. The anorexia, vomiting and diarrhoea of viral HF frequently result in hypokalaemia, so regular potassium supplementation may be needed, keeping a close eye on renal function, which is often compromised in late disease.

Blood Products and Management of Disseminated Intravascular Coagulopathy. Transfusions, preferably with packed red blood cells, should be used to maintain a haematocrit over 30% while avoiding volume overload, taking into account that chronic anaemia due to malaria and malnutrition may be frequent in patients in certain geographical areas. The possibility of DIC should be assessed through the relevant laboratory parameters (D-dimers are an especially early and sensitive indicator, Table 16.4) if bleeding and thrombocytopenia persist, with transfusion of platelets and/or fresh frozen plasma as required. Transfusion of platelet concentrate (1–2 U/10 kg) should be considered when the platelet count is <50 000/μL in a bleeding patient or <20 000/μL without bleeding. The platelet count should generally rise by at least 2000/μL per unit of platelets transfused, although a lesser response may occur if there is ongoing DIC and platelet consumption. Impaired platelet aggregation may promote haemorrhage in some viral HFs, especially Lassa fever, even when platelet counts are not drastically low. Transfusion of fresh frozen plasma (FFP) (15–20 mL/kg) should be considered when bleeding is present and fibrinogen levels are <100 mg/dL. Fibrinogen concentrates (total dose 2–3 g) or cryoprecipitates (1 U/10 kg) may be administered instead of FFP, although FFP has the theoretical advantage of containing all coagulation factors and inhibitors deficient in DIC but no activated coagulation factors. Vitamin K may be given, especially if underlying malnutrition or liver disease is suspected.

Antibiotics. Patients should be immediately covered with appropriate broad-spectrum antibiotics and/or antiparasitics, with specific consideration of coverage for malaria and tick-borne rickettsial diseases, until a diagnosis of viral HF can be confirmed (Table 16.3). These drugs should be stopped once the diagnosis of viral HF is established unless there is evidence of co-infection. Secondary bacterial infection should be suspected and antibiotics given when patients have persistent or new fever after about 2 weeks of illness, when most viral HFs have either resulted in death or are resolving.

Oxygenation and Ventilation. With the exception of HPS, impaired gas exchange is not typically a prominent feature of viral HF, especially in the absence of iatrogenic pulmonary oedema. Oxygen should be administered by nasal cannula or face mask to patients with unfavourable parameters. Intubation and mechanical ventilation should be avoided because of the risk of barotrauma and pleural-pulmonary haemorrhage except in HPS, in which mechanical ventilation may be life-saving. When required, low tidal volumes (i.e. lung-protective ventilation) are best.

Pain Control and Ulcer Prophylaxis. Acetaminophen, tramadol, opiates or other analgesics should be used for pain control. Salicylates and non-steroidal anti-inflammatory drugs should be avoided due to the risk of bleeding. Prophylactic therapy for stress ulcers with H2 receptor antagonists is appropriate.

Management of Seizures. Seizures sometimes occur in late-stage viral HF and can usually be managed with benzodiazepines or phenytoin, with careful attention to possible respiratory depression. The use of sedatives and neuromuscular blocking agents should be minimized, but haloperidol or a benzodiazepine may be used.

Nutrition. Attention should be given to adequate nutrition, especially if the patient's course is prolonged or the patient is malnourished. Gut feeding is preferable to parenteral alimentation. Nasogastric tubes may be theoretically indicated for patients unable to eat, but there is little practical experience with their use in viral HF. Exacerbation of gastrointestinal bleeding and heightened risk of transmission to healthcare workers during tube placement are concerns.

Management of Pregnant Patients. Uterine evacuation in pregnant patients appears to lower maternal mortality and should be considered given the extremely high maternal and fetal mortality associated with viral HF. However, this procedure must be performed with extreme caution, since it can be considered high-risk with regard to potential nosocomial transmission and may also induce additional maternal haemorrhage.

Antiviral Drugs

Ribavirin. The only currently available antiviral drug for any viral HF is the guanosine analogue ribavirin. Data from the few randomized controlled clinical trials that have been performed combined with empiric observation and anecdotal evidence suggest that ribavirin is efficacious in the treatment of Lassa fever, the South American HFs and HF with renal syndrome.[20] Treatment as early as possible in the course of the diseases is imperative. The mechanism of action is unknown, although lethal mutagenesis is suspected. Although frequently given, more data are needed to make conclusions on ribavirin's efficacy for Crimean-Congo HF. In vitro data show activity against Omsk HF virus as well, but clinical studies have not been performed. Ribavirin is not efficacious and should not be used for Ebola or Marburg HF.

The standard dosing schedule of ribavirin for viral HF is presented in Table 16.5, although pharmacokinetic and pharmacodynamic experiments in relation to each HF virus have not been performed. Although few data are available oral ribavirin may also be effective in some cases, but less so than the intravenous (IV) form, most likely because, with a first-pass metabolism of 50%, the serum concentration achieved through oral administration is on the borderline of the mean inhibitory

TABLE 16.5 Ribavirin Therapy for Viral Haemorrhagic Fever

Indication	Route	Dose	Interval
Treatment	IV[a]	30 mg/kg (max. 2 g)[b]	Loading dose, followed by:
	IV[a]	15 mg/kg (max. 1 g)[b]	Every 6 hours for 4 days, followed by:
	IV[a]	7.5 mg/kg (max. 500 mg)[b]	Every 8 hours for 6 days
Prophylaxis	PO	35 mg/kg (max. 2.5 g)[b]	Loading dose, followed by:
	PO	15 mg/kg (max. 1 g)[b]	Every 8 hours for 10 days

IV, intravenous; PO, oral administration.
[a]The drug should be diluted in 150 mL of 0.9% saline and infused slowly.
[b]Reduce the dose in persons known to have significant renal insufficiency (creatinine clearance of less than 50 mL/min).

concentration of ribavirin for many HF viruses.[21] Furthermore, absorption of oral ribavirin from the gut may also pose a barrier given the vomiting and diarrhoea often present in viral HF. Until more data are available on the efficacy of the oral route, the entire treatment course of ribavirin should be administered IV when possible.

Major adverse effects due to short-term ribavirin therapy are rare.[21,22] The main side-effect is a dose-dependent, mild-to-moderate haemolytic anaemia that infrequently necessitates transfusion and disappears with cessation of treatment. Rigors may occur when ribavirin is infused too rapidly. Relative contraindications include severe anaemia or haemoglobinopathy, coronary artery disease, renal insufficiency, decompensated liver disease, breast-feeding and known hypersensitivity. Jaundice may develop in patients with Gilbert's syndrome. Although findings of teratogenicity and fetal loss in laboratory animals have rendered ribavirin technically contraindicated in pregnancy, its use must still be considered as a life-saving measure given the extremely high maternal and fetal mortality associated with viral HF in pregnancy.

Haemoglobin, haematocrit and bilirubin levels should be checked at initiation of ribavirin therapy and then every few days, with consideration of transfusion of packed red blood cells if significant anaemia develops. Because of the long terminal half-life (~24 hours) and large volume of distribution, ribavirin may still have effect for hours or even days after cessation, particularly in red blood cells where it accumulates.

Patent issues and high cost (up to US$1000/patient from most pharmaceutical sources in Europe and North America) have historically severely limited availability of IV ribavirin. However, the patent is now expired and the World Health Organization has applied to add the drug to the list of essential medicines, which will hopefully significantly lower cost and improve availability. Meanwhile, many countries in Africa import the drug from less-expensive makers in China and Russia.

Other Antiviral Drugs. A number of experimental therapies for viral HFs have shown in vitro activity and, in some cases, therapeutic benefit in animal studies, including nucleoside analogues, inhibitors of S-adenosyl-l-homocysteine hydrolase, small inhibitory RNAs, phosphorodiamidate morpholino oligomers, antisense compounds, tyrosine kinase inhibitors and various other small molecules. None are yet approved or available for clinical use in humans.[16,23]

Antibody Therapy

Although cellular immunity is thought to be the primary arm of protection in most viral HFs, treatment with convalescent immune plasma has often been tried. With the exception of Argentine HF, for which efficacy is clear, there are few controlled trials or objective data on its benefit. Furthermore, there are significant logistical challenges inherent in the use of convalescent immune plasma, including risk of concomitant transmission of other blood-borne pathogens and lack of an existing bank of immune plasma for this purpose. With the exception of treatment of Argentine HF, this therapy should be reserved for severe and refractory cases when ribavirin is not an option, either because it is not available or because the patient has a viral HF for which ribavirin is not efficacious. Numerous mono- and polyclonal antibody preparations for the viral HFs have been tested in animal models over the years, with varying degrees of success.

Immune Modulators

Increasing understanding of the systemic inflammatory response syndrome underlying septic shock and by extension viral HF, has renewed interest in the use of immune modulating drugs for these syndromes. However, trials of various immune modulators in septic shock, including ibuprofen, corticosteroids, anti-TNFα, nitric oxide inhibitors, statins (HMG-CoA reductase inhibitors) and interleukins have not shown conclusive benefit. Ribavirin combined with interferon (IFN)-αcon-1, a consensus IFN, diminished mortality and disease severity in a hamster arenavirus model.[24] Although approved for clinical use in humans, IFN-αcon-1 has not been tested in human viral HF, perhaps in part due to its high cost, systemic toxicity and need for repeated doses. These problems can potentially be overcome through the delivery of a recombinant, replication-deficient type 5 human adenovirus that encodes and elicits the production of IFN-αcon-1 from infected cells. Other immunomodulating approaches being explored include those that enhance immune recognition of infected cells and dampen immune responses through the blockage of toll-like receptors. Corticosteroids should not be administered in viral HF unless adrenal insufficiency is demonstrated, target blood pressure is not maintained despite adequate fluid repletion and vasopressors, or in conjunction with mannitol if cerebral oedema is suspected.

Coagulation Modulators

A growing body of literature suggests that disturbances in the procoagulant–anticoagulant balance play an important role in the mediation of septic shock. Although controversial, recombinant activated protein C, a serine protease that plays a central role in anticoagulation, may be efficacious for some patients with septic shock. Nevertheless, the drug should still be considered experimental for viral HF.[25] At first glance, the major adverse effect of activated protein C – serious bleeding (including intracranial haemorrhage) that has been reported in up to 5% of treated patients – would seem to contraindicate its use in viral HF. However, the mechanism of the drug may not be via direct anticoagulation, but rather through modulation of inflammation. Conceivably, early use could mitigate the pathogenic processes in viral HF that ultimately result in haemorrhage with no additional risk of bleeding due to the drug itself. Other coagulation-modifying drugs that have been explored anecdotally in human cases or in animal models for the viral HFs, with varying degrees of efficacy, include rNAPc2, a potent experimental recombinant inhibitor of the tissue factor/factor VIIa coagulation pathway, recombinant factor VIIa itself (paradoxically, since it would have the opposite effect of rNAPc2), heparin sulphate and antithrombin III. All must presently be considered experimental.

Management of Convalescence

Since the clinical status of patients with viral HF generally correlates with the level of viraemia and infectivity, patients who have recovered from their acute illness can safely be assumed to have cleared their viraemia and can be discharged from the hospital without concern of subsequent transmission at home. However, because of potential delayed virus clearance in the urine and semen, abstinence or condom use is recommended for 3 months after acute illness. Transmission through toilet facilities has not been noted. Nevertheless, simple precautions

to avoid contact with excretions in this setting are prudent, including separate toilet facilities and regular hand-washing. Breast-feeding should be avoided during convalescence unless there is no other way to support the baby. Clinical management during convalescence includes the use of warm packs, acetaminophen, non-steroidal anti-inflammatory drugs, cosmetics, hair-growth stimulants, anxiolytics, antidepressants, nutritional supplements and nutritional and psychological counselling as indicated.

PREVENTION

Patient Isolation, Personal Protective Equipment and Nursing Precautions

Infection control of HF viruses relies on classic public health principles of identification and isolation of infected persons. Given the difficulty of clinical diagnosis, all patients with a syndrome clinically compatible with a viral HF should be presumed infectious and isolated until a specific diagnosis is made. It is prudent to place the patient in a negative airflow room when available despite the lack of evidence for natural aerosol transmission between humans. Hermetically sealed isolation chambers are not required and may have profound negative psychological effects on the patient. Although specific viral HF isolation precautions (consisting of surgical mask, double gloves, gown, protective apron, face shield and shoe covers) to prevent contact and droplet exposure to blood and bodily fluids are advised for added security, experience has shown that routine universal precautions are protective in most cases (Figure 16.5).[26] Access to the patient should be limited to a small number of designated staff and family members with specific instructions and training on viral HF infection control guidelines and the use of personal protective equipment. Use of sharps should be minimized and immediate disposal in a sharps box strictly enforced. If the patient is being seen in a facility where mosquito bites are likely, such as the open air wards common in developing countries, insecticide-treated bed nets and/or room screens should be employed to prevent transmission of arthropod-borne HF viruses.

Figure 16.5 Personal protective equipment for the management of viral haemorrhagic fever. Relative to goggles, face shields have the benefits of less fogging, greater protection of the mucus membranes and a better view of the healthcare worker's face, facilitating communication with the patient.

Contact Tracing

Persons with unprotected direct contact with someone during the symptomatic phase of a human-to-human communicable HF virus should be monitored daily for evidence of disease for the duration of the longest possible incubation period starting after their last contact (Table 16.2). Contacts should check their temperature daily and record the results in a log. Despite the lack of evidence for transmission during the incubation period, it is usually recommended that exposed persons remain at home during this time and avoid close contact or activities with household members that might result in exposure to bodily fluids, such as sex, kissing and sharing of utensils. Hospitalization or other confinement of asymptomatic persons is not warranted, but persons who develop fever or other signs and symptoms suggestive of viral HF should be immediately isolated until the diagnosis can be ruled out.

Post-exposure Prophylaxis

Although oral ribavirin has been used as post-exposure prophylaxis for various viral HFs, there are no data on efficacy, dose or duration of administration of the drug for this purpose.[21] Adverse events reported with oral ribavirin, which include nausea, vomiting, dry mouth and metallic taste, myalgia, fatigue, diarrhoea, abdominal pain, headache, jaundice, skin rash, tachycardia, anaemia, thrombocytosis and neurological perturbations (including mood and sleep disturbances), can be mistaken for the early manifestations of viral HF, causing considerable emotional stress and confusion.[22]

Given the lack of efficacy data, generally low secondary attack rates for the HF viruses and the risk of adverse effects, post-exposure ribavirin should be reserved for definitive high-risk exposure to arenaviruses, Crimean-Congo HF virus or Old World hantaviruses, defined as one of the following: (1) Penetration of skin by a contaminated sharp instrument (e.g. needle stick injury); (2) Exposure of mucous membranes or broken skin to blood or bodily secretions (e.g. blood splashing in the eyes or mouth); (3) Participation in emergency procedures without appropriate personal protective equipment (e.g. resuscitation after cardiac arrest, intubation or suctioning) and (4) Prolonged (i.e. hours) and continuous contact in an enclosed space without appropriate personal protective equipment (e.g. a healthcare worker accompanying a patient during medical evacuation in a small airplane).[21] In estimating the risk of infection, clinicians should realize that the most infectious patients are those with severe clinical conditions, usually late in the course of illness. Prophylaxis should not be used when the only exposure was during the incubation period or during convalescence after fever has subsided.

Oral ribavirin should be started immediately after the exposure, but not before counselling between the patient and the physician. Because of the high first-pass metabolism of oral ribavirin, relatively high doses are needed to provide serum levels in the range of the minimum inhibitory concentration of most HF viruses (Table 16.5). The drug should be taken with food. A baseline haemoglobin and haematocrit should be drawn and therapy reconsidered if significant anaemia is present. The patient should be informed that minor adverse effects often occur. If not already performed, the index case should be tested for viral HF, with cessation of ribavirin if the results are negative. Persons taking prophylaxis who develop manifestations of viral HF should also be immediately laboratory tested by the

most rapid and sensitive method, usually RT-PCR and converted to IV ribavirin unless the disease can be readily excluded.

Environmental Shedding and Disinfection

The lipid envelope of all HF viruses is relatively easily disrupted, generally limiting virus viability outside a living host.[1] When shed naturally in animal excreta or human body fluids, which would then dry, infectivity appears to be on the order of hours to days, varying with the specific virus and environmental conditions. However, HF viruses have been isolated from samples kept for weeks at ambient temperatures if stored hydrated in a biological buffer, such as blood or serum. Little concern is required regarding HF viruses seeping into ground-water or posing any long-term risk through casual exposures in the general environment, where harsh thermal and pH conditions would likely readily inactivate them.

When contamination may have recently occurred, such as in homes or hospitals treating persons with viral HF, disinfection is warranted. HF viruses can be inactivated by exposure to temperatures above 60°C for 1 hour, gamma irradiation, ultraviolet light (surface disinfection only) and by a wide variety of chemical treatments. Sodium hypochlorite (i.e. household bleach) is the most readily available effective inactivation method, although it is corrosive with repeated use.[26] Bleach solutions should be prepared daily; starting with the usual 5% chlorine concentration, a 1:100 (1%) solution should be used for reusable items such as medical equipment, patient bedding and reusable protective clothing before laundering. A 1:10 (10%) bleach solution should be used to disinfect excreta, corpses and items to be discarded. Workers cleaning areas potentially contaminated by the excreta of small mammals should wear protective materials (gloves and surgical mask) let the area aerate before entering, then spray the area with the 10% bleach solution and let it sit on the surface for at least 15 minutes before mopping or wet sweeping. A site with appropriate security should be dedicated for waste disposal if routine autoclaving is not available. Specific guidelines exist regarding handling and burial of corpses of victims of viral HF.

Vaccines and Reservoir and Vector Control

See individual disease sections for details.

Filovirus Diseases: Ebola and Marburg Haemorrhagic Fevers

The filovirus infections (from the Latin *filo* for 'thread', referring to their filamentous shape), Marburg and Ebola HFs, are perhaps the most severe and feared of all viral HFs. The Filoviridae are comprised of six species of *Ebolavirus* and one *Marburgvirus*, with relatively consistent case fatality ratios associated with each virus (Table 16.1). Although the Marburg genus is limited to a single species, Lake Victoria Marburg virus, numerous strains have been recognized, with possible differences in virulence. All of the known human pathogenic Filoviruses are endemic only in sub-Saharan Africa (Figure 16.1).

EPIDEMIOLOGY

Recent evidence strongly implicates fruit bats as the filovirus reservoir, with human infection likely from inadvertent exposure to infected bat excreta or saliva.[27–30] Miners, spelunkers, forestry workers and others with exposure in environments where bats typically roost are at risk. The association between exposure in caves and mines and *Marburgvirus* infection is particular strong.[31,32] Non-human primates, especially gorillas and chimpanzees and other wild animals may become infected and serve as intermediate hosts that transmit filoviruses to humans through contact with their blood and bodily fluids, usually associated with hunting and butchering.[33,34] These wild animals are presumably also infected by exposure to bats and develop severe and usually fatal disease similar to human viral HF.[35] *Zaire ebolavirus* has caused large die-offs of central chimpanzees and western lowland gorillas in central Africa.[36] Filovirus outbreaks tend to occur at the end of the rainy season.

Filoviruses are probably the most transmissible of all HF viruses, although attack rates are still generally only 15–20% in outbreaks in Africa and much lower if proper universal precautions are maintained.[37] In most outbreaks it appears that there is a single or very few introductions from a zoonotic source into humans followed by nosocomial amplification in a setting of inadequate universal precautions, usually in rural areas of countries where civil unrest has decimated the healthcare infrastructure (Figure 16.1). The largest outbreak of Ebola HF to date was 425 cases in Uganda in 2000–2001 and, of Marburg HF, 252 cases in Angola in 2004–2005. Filovirus outbreaks appear to be occurring more frequently since the mid-1990s, perhaps reflecting societal changes in Africa where healthcare seeking at hospitals, which may sometimes lack appropriate infection control measures, becomes more frequent. Enhanced surveillance for viral HF may also play a role.

PATHOGENESIS AND PATHOLOGY

After initial infection through an as yet unknown receptor, filoviruses disseminate to virtually all organs, causing widespread but focal tissue damage.[8,38] Necrosis is greatest in the liver, spleen, kidney and gonads and is associated with high levels of virus or viral antigen in these organs, suggesting a direct viral-induced effect. Hepatocellular necrosis, Councilman bodies, microvesicular fatty change and Kupffer cell hyperplasia are typically seen in the liver and extensive follicular necrosis and necrotic debris in the spleen and lymph nodes. Diffuse alveolar damage, interstitial oedema and focal haemorrhage may be seen in the lung and myocardial oedema and focal necrosis in the heart. Filovirus antigen can be found in the skin and sweat glands by immunohistochemistry, but the implications of this finding with regard to the potential for virus transmission through skin contact are uncertain.

Pro-inflammatory cytokines, including TNFα and various interleukins, are thought to play a central role in the pathogenesis of filovirus infection, with high levels of IL-10 and IL-1 receptor antagonist correlating with a poor prognosis, as well as neopterin, a marker of cellular immune system activation.[39] This pro-inflammatory state is facilitated by virus-induced suppression of the host adaptive immune response, including the actions of IFN and antiviral RNA interference, by various filovirus proteins, including a secreted glycoprotein. DIC is frequently noted.

CLINICAL FEATURES

Although mild or even asymptomatic cases have been reported, the vast majority of filovirus infections are thought to result in

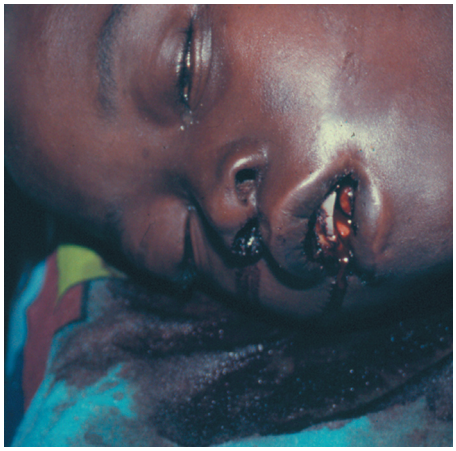

Figure 16.6 Oral bleeding in Ebola haemorrhagic fever. *(From Bausch DG. Viral Hemorrhagic Fevers. In: Schlossberg D, editor. Clinical Infectious Disease. New York, NY: Cambridge University Press; 2008. Used with permission. Photo by D. Bausch.)*

severe disease.[40–42] A fleeting maculopapular rash on the torso or face may be one early and relatively specific, although insensitive, indicator of infection. Abdominal tenderness over the liver is frequently seen and may represent stretching of the liver capsule. External bleeding, especially from the gastrointestinal tract, may be profuse and most fatal cases will manifest oozing from the mucus membranes and skin puncture sites in the late stages (Figures 16.6 and 16.7). Central nervous system manifestations and renal failure are also frequent in end-stage disease. In one unusual case, uveitis with isolation of *Ebolavirus* from the eye was noted 2 months after resolution of acute viral HF.[10]

DIAGNOSIS

Contact with bats or non-human primates and entry into mines, caves or forests in sub-Saharan Africa should enhance suspicion. Advances have been made in recent decades to establish mobile field laboratories that can provide ELISA or PCR-based diagnostics at or near the site of outbreaks.[43,44]

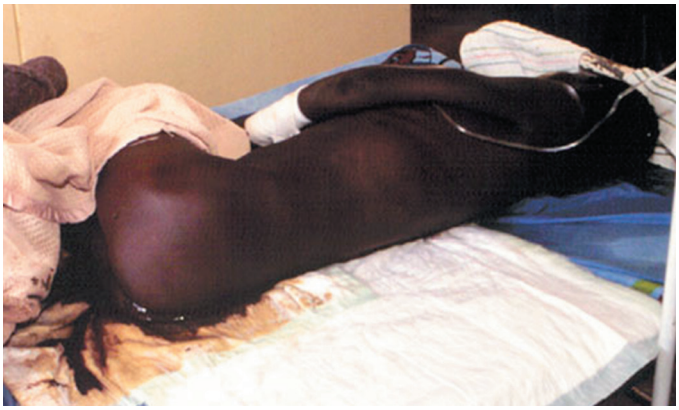

Figure 16.7 Rectal bleeding in Ebola haemorrhagic fever. *(From Bausch DG. Viral Hemorrhagic Fevers. In: Schlossberg D, editor. Clinical Infectious Disease. New York, NY: Cambridge University Press; 2008. Used with permission. Photo by D. Bausch.)*

MANAGEMENT AND TREATMENT

There is presently no specific antiviral therapy for filovirus infection.[45] Nor has the use of convalescent plasma shown convincing efficacy; although 8 of 10 persons treated with convalescent plasma during an Ebola HF outbreak in the Democratic Republic of the Congo survived, in most cases treatment started after the mean time to death for this disease, indicating that the patients were likely to survive anyway.[46] Human-mouse chimeric monoclonal antibodies have recently shown efficacy in animal models of Ebola HF.[47,48] Activated protein C reduces mortality in *Ebolavirus*-infected monkeys but has not been tried in humans with Ebola HF.[49] *Ebolavirus* induces overexpression of the procoagulant tissue factor in nonhuman primate monocytes/macrophages, suggesting that inhibition of the tissue factor pathway could ameliorate filovirus infection. Accordingly, rNAPc2 decreased mortality by 67% in *Ebolavirus*-infected monkeys.[50] A Phase I trial of the drug in humans was recently completed with no safety concerns arising.[51]

PREVENTION

Post-exposure Prophylaxis. Although no post-exposure prophylaxis is available for filovirus infection, a live recombinant vesicular stomatitis virus vector engineered to express the key immunogenic proteins of *Ebolavirus* was administered on a compassionate use basis to a laboratory worker after a needle stick injury, with no apparent detrimental effect.[52] Efficacy could not be assessed because it was not clear that the accident resulted in *Ebolavirus* infection. rNAPc2, small interfering RNAs and monoclonal antibodies have also shown efficacy as post-exposure prophylactics in monkey models.[45,53–55]

Vaccines

A number of experimental approaches for filovirus infection have shown promise;[56] the aforementioned vesicular stomatitis virus vectored vaccine for viral HFs has shown protective immunity in animal models. In addition, a DNA plasmid vaccine for Ebola HF has been shown to be safe and immunogenic in a Phase I trial.[57,58]

Reservoir Control

Avoiding contact with bats, primarily by avoiding entry into caves and mines in endemic areas, is a key prevention measure for the filoviruses. Personal protective equipment may be indicated for miners and other persons who work in these environments. Humans should also avoid exposure to fresh blood, bodily fluids or meat of wild animals, especially non-human primates, in filovirus-endemic areas.

Old World Arenavirus Diseases: Lassa Fever and Lujo Haemorrhagic Fever

Lassa and Lujo viruses are members of the Arenaviridae family, which derives its name from the Latin *arenosus* for 'sandy', referring to the grainy appearance of internal electron-dense particles seen on electron microscopy. Arenaviridae are serologically, phylogenetically and geographically divided into Old World (i.e. Africa) and New World (i.e. the Americas) complexes (Figures 16.2 and 16.3).[59] Although almost 15 Old World arenaviruses have been recognized only two, Lassa and Lujo viruses, have been associated with viral HF.

Lassa virus was first isolated from Nigeria in 1969 and named after the town from which the first case came. Lassa fever is endemic exclusively in West Africa (Figure 16.2).[60] The risk of exposure to Lassa virus varies significantly in a given country and often among regions or even villages within endemic areas. The highest incidence of disease appears to be in areas of eastern Sierra Leone, northern Liberia, south-eastern Guinea and central and southern Nigeria.[61] The reasons for the extreme heterogeneity in incidence across West Africa are not clear, especially considering that the rodent reservoir is often readily found in areas where little or no human Lassa fever has been recognized. Varied intensity of surveillance may contribute to the heterogeneous distribution but cannot completely explain it.

An annual incidence of 300 000–500 000 Lassa virus infections with up to 5000 deaths is often quoted in the scientific literature but these figures are extrapolations from surveillance in the 1970s and 1980s in eastern Sierra Leone where Lassa fever is clearly hyperendemic. Estimating the true incidence and mortality is challenging due to the nonspecific clinical presentation and the civil unrest, unstable governments with underdeveloped surveillance systems, extensive human migration and perturbation of the physical landscape and paucity of laboratories with the capacity to perform the diagnosis in West Africa. The incidence of Lassa fever is consistently highest during the dry season, although cases may be seen throughout the year.

Lujo virus was first identified in 2008 after an outbreak of five cases (four fatal).[15,62] The first case was infected in Zambia and subsequently medically evacuated to Johannesburg, initiating a chain of four nosocomial infections in South Africa (Figure 16.2). The disease has not been seen since.

EPIDEMIOLOGY

Arenaviruses causing viral HF are maintained by chronic infection of rodents with a tight reservoir species-virus pairing, thought to be the result of long-term rodent-virus co-evolution.[1] Rodent populations are usually not uniformly infected across their entire geographic range. There are generally few human cases relative to the frequency of infected rodents. The reservoir for Lassa virus is *Mastomys natalensis*, commonly called the 'multimammate rat', which is almost always found in close association with humans in rural villages and surrounding cultivated fields and, less commonly, in grasslands and at the forest edge.[63] Consumption of rodents and poor-quality housing, which may allow rodents easy entry, have been shown to be risk factors for Lassa fever. Foreign military personnel, peacekeepers and aid workers in rural settings are occasionally infected, sometimes importing Lassa virus back to their countries of origin.[64] Multimammate rats are not typically found in large urban centres, so the risk of rodent transmission of Lassa virus to humans in these environments is negligible. Despite the occurrence of *Mastomys* species throughout sub-Saharan Africa, Lassa virus has not been found outside of West Africa. The reasons for this are unclear, but may relate to evolutionary bottlenecks in dispersal of the virus, reservoir or both. On rare occasions, Lassa virus has been isolated from other rodent species, a finding which is usually considered to be due to spillover infection (i.e. incidental transient infection of a non-reservoir host) or difficulty identifying the rodent species. These animals are not thought to play a role in Lassa virus maintenance.

Transmission of Lassa virus to humans occurs via exposure to rodent excreta, either from direct inoculation to the mucous membranes or from inhalation of aerosols produced when rodents urinate.[1] The relative frequency of these modes of transmission is unknown. Experimental data illustrate that arenavirus infection may also occur by the oral route. Lassa virus may also be contracted when rodents are trapped and prepared for consumption, a common practice in some parts of West Africa. Since HF viruses are easily inactivated by heating, eating cooked rodent meat should pose no danger.[1] It is not known whether Lassa virus can be transmitted through a rodent bite, although the virus has been found in rodent saliva. Transmission of Lassa virus through aerosolized rodent urine or virus-contaminated dust particles is often referred to in the scientific literature, but there are few data to support or refute this mode of transmission. The reservoir for Lujo virus is unknown, but is presumed to be a rodent.

PATHOGENESIS AND PATHOLOGY

The pathogenesis of arenaviral HF is thought to relate more to disruption of cellular function, as opposed to extensive cell death; patients often die without significant bleeding and histopathological lesions (on the few cases in which autopsies have been performed) are usually not severe enough to account for death. Lassa virus can be found in virtually all organs, which is not surprising considering that one of the primary receptors, α-dystroglycan, is expressed on most tissues. The liver is usually the most affected organ, which is consistent with the finding of elevated hepatic transaminases in severe cases. The lowest titres are in the central nervous system, presumably due to protection afforded by the blood–brain barrier. Infection of mesothelial cells can explain the serous effusions sometimes seen in Lassa fever. Lassa virus infection of hormone-secreting cells may relate to the more severe pathophysiology of the disease noted in pregnant women. Gross pathological findings include pulmonary oedema, pleural effusion, ascites and haemorrhage from the gastrointestinal mucosa. Microscopic lesions include hepatocellular and splenic necrosis, renal tubular injury with interstitial nephritis, interstitial pneumonitis and myocarditis.

Although the data are mixed, severe Lassa fever appears to result from an insufficient or suppressed immune response[65]; most studies show that Lassa virus infection of dendritic and peripheral blood mononuclear cells does not result in significant secretion of proinflammatory cytokines, upregulation of costimulatory molecules or significant T-cell proliferation. Absent or diminished inflammatory cytokine responses (including TNFα, IL-8 and IFN IP-10) are often noted in both in vitro and in vivo experiments and have been correlated with a poor outcome in humans. In contrast, early and strong cytokine and cellular immune responses correlated with survival in monkey models and in case reports on humans. The lack of an immune response may reflect active Lassa virus-induced downregulation induced, at least in part, by counter-action of the type I IFN response by Lassa virus. Based on data from guinea pig models, cardiac inotropy may be directly or indirectly inhibited from a yet-to-be-identified soluble mediator in the serum. Disseminated intravascular coagulopathy does not appear to be part of the pathogenesis of Lassa fever, although this finding bears confirmation.

There is considerable sequence heterogeneity of Lassa viruses across West Africa, with four recognized lineages: three in Nigeria and one in the area comprising Sierra Leone, Liberia, Guinea and the Ivory Coast. There is also considerable genetic heterogeneity within lineages, especially in Nigeria. Field and laboratory data suggest variation in virulence among the various lineages and strains of Lassa virus, although systematic strain classifications based on virulence have not been possible. Interestingly, strains isolated from pregnant women and infants were benign in guinea pigs, suggesting that host factors such as immunosuppression play a significant role in human disease. There is evidence that three human genes, including *LARGE*, *DMD* and *IL-21*, have undergone positive selection in populations in endemic areas for Lassa fever in Nigeria, suggesting a protective effect.[66]

Based on the few cases noted to date, the pathogenesis of Lujo HF appears to be very similar to that of Lassa fever.

CLINICAL FEATURES

A long-standing mystery of Lassa fever is the apparent extreme range of clinical severity. Up to 80% of Lassa virus infections are mild or asymptomatic, although this finding bears repeating with newer more sensitive and specific diagnostic assays. Case fatality in symptomatic persons is often in the range of 25%. The reasons for the considerable variation of clinical severity are unknown, but may relate to heterogeneity in the virulence of infecting Lassa virus strains, route and dose of inoculation, genetic predisposition, underlying co-infections and/or premorbid conditions (such as malaria, malnutrition and diabetes) or misclassification of reinfection as new infection due to waning of antibody.

Pharyngitis is common and may be particularly severe in Lassa fever, sometimes with an exudate that has led to misdiagnosis of streptococcal pharyngitis. A morbilliform or maculopapular skin rash almost always occurs in fair-skinned persons but, for unclear reasons, rarely in persons with black skin. Swelling in the face and neck and bleeding and to a lesser degree conjunctival injection, are particularly specific signs but are not very sensitive – seen in less than 20% of cases (Figures 16.8 and 16.9). Lassa fever is one of the viral HFs with the lowest likelihood of clinically discernible haemorrhage – less than 20%, most often consisting of mild epistaxis and oozing from the oral mucous membranes and, in the late stages, venepuncture sites. Central nervous system manifestations may also be seen in the late phases, with virus isolated from the cerebrospinal fluid of some but not all patients and without apparent correlation between disease severity and virus or antibody titre. The cellular and chemistry profile in cerebrospinal fluid is usually normal.

Fatal disease is occasionally seen in persons who have already cleared Lassa virus from the blood and produced a strong IgM antibody response. The pathogenesis of these unusual cases is poorly understood but may relate to persistent Lassa virus sequestered in the central nervous system, perhaps facilitated by an immunocompromised state in some patients with HIV/AIDS, severe malnutrition or diabetes. In one unusual case, Lassa virus was isolated from the CSF, but not the blood, of a patient with encephalopathy after the febrile stage of disease. Other cases with sudden deterioration after apparent stabilization may involve acute complicating events, such as pericardial tamponade.

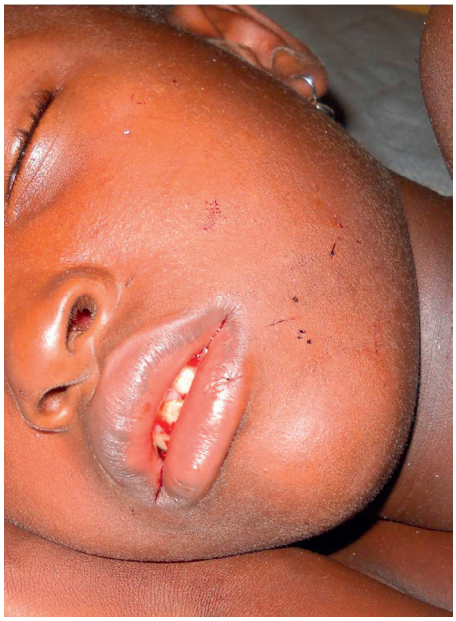

Figure 16.8 Facial swelling and mild gum bleeding in Lassa fever. *(Photo by Donald Grant.)*

Lassa fever is particularly severe in pregnancy, with Lassa virus found at high concentrations in placenta and fetal tissues. Anasarca has been described in a single report of children with Lassa fever (termed the 'swollen baby syndrome') but may have been related to aggressive rehydration. One instance of polyserositis with pleural and pericardial effusions and ascites 6 months after infection was reported. Lassa virus could not be recovered from the effusion fluid, but lymphocytes and high levels of antibody were noted, suggesting an immune-mediated mechanism.

Sensorineural deafness is the only recognized permanent sequela of Lassa fever. It is reported to occur in as many as 25% of cases, although this seems like a significant overestimate from our experience in West Africa over the last 15 years. Deafness typically presents during convalescence and is unassociated with the severity of the acute illness or level of viremia, suggesting an immune-mediated pathogenesis. Deafness may be uni- or bilateral and is permanent in approximately two

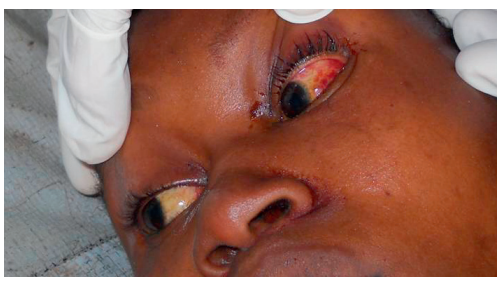

Figure 16.9 Conjunctival infection in Lassa fever. *(Photo by Donald Grant.)*

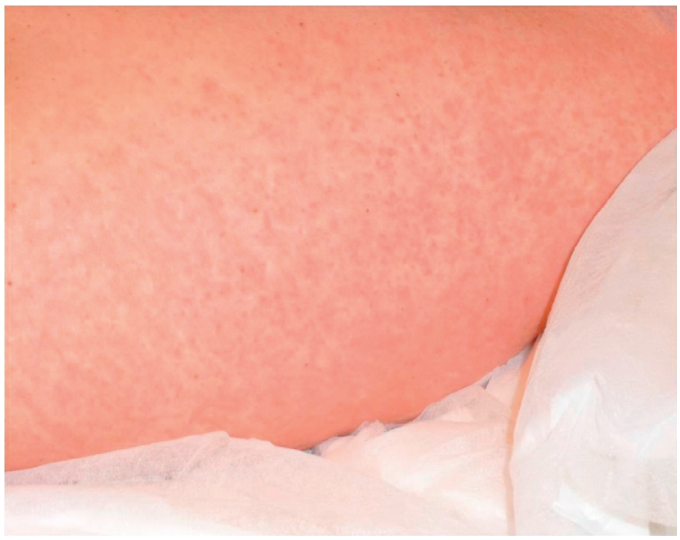

Figure 16.10 Maculopapular rash in Lujo haemorrhagic fever. *(Photo by TH Dinh.)*

thirds of cases. Auditory patterns resemble idiopathic nerve deafness.

The clinical features of Lujo HF are similar to Lassa fever. In the limited series of five cases reported to date, key features included prominent facial oedema, pharyngitis and diffuse macular rash with shock, depressed consciousness and convulsions in fatal cases (Figure 16.10). Bleeding was not a prominent feature.

DIAGNOSIS

Although ELISA has been the traditional mainstay of diagnosis, RT-PCR is becoming an increasingly valuable tool and can detect Lassa virus in over 80% in the first 10 days of illness.[67] Sequence heterogeneity of Lassa virus across West Africa has traditionally posed a challenge to PCR-based diagnostics due to primer–target mismatch but recent development of assays targeting conserved portions of the genome may have resolved this problem. Post-mortem diagnosis through immunohistochemistry does not appear to be as reliable for Lassa fever as for some of the other viral HFs, although it was helpful in the diagnosis of Lujo HF..

MANAGEMENT AND TREATMENT

Intravenous ribavirin has been shown to decrease mortality in severe Lassa fever from 55% to 5% when begun within the first 6 days of illness and should be given to all patients with this disease.[20] There is still benefit, albeit less, after 6 days. Convalescent plasma has been used in Lassa fever with apparent benefit, but is only efficacious if it contains a high titre of neutralizing antibody, which is not uniformly the case even in survivors. Furthermore, animal studies suggest that a close antigenic match between the infecting Lassa virus of the donor and recipient is required for the treatment to be effective. The infrequency of bleeding in Lassa fever relative to most other viral HFs might make it a logical candidate for trials with activated protein C. Statin drugs, which appear to have immunomodulatory, anti-inflammatory, antimicrobial and vasculature-stabilizing properties, were included in the successful treatment of a case of Lujo HF along with the antioxidant and free radical scavenger N-acetylcysteine.

PREVENTION

Post-exposure Prophylaxis

Post-exposure prophylaxis with oral ribavirin should be considered for persons with high-risk exposures following the guidelines described above.[21,22]

Vaccines

A number of experimental vaccine platforms are being explored. The recombinant vesicular stomatitis virus platform is perhaps the most promising, providing 100% protection after a single dose in a monkey model.[68]

Reservoir Control

Measures to prevent contact with rodents are important in control of Lassa fever. Since multimammate rats often colonize human dwellings, prevention is best achieved by improving 'village hygiene', including eliminating unprotected storage of garbage, foodstuffs and water and, when possible, plugging holes that allow rodents entry into homes.[1] Rodent trapping or poisoning is generally not thought to be an effective long-term control strategy because animals from surrounding fields will likely soon recolonize the area.

New World Arenavirus Diseases: South American Haemorrhagic Fevers

The New World Arenavirus Complex is divided into three major clades: A, B and C.[69] Five arenaviruses are known to cause natural infection and viral HF, all belonging to clade B. Although there may be subtle differences among the syndromes produced by these five viruses, they are usually grouped and referred to simply as the 'South American HFs'. Each virus is named after its place of first finding, with the disease name generally named after the country (Figure 16.3). Junin virus, the aetiological agent of Argentine HF, was identified in 1958 after a new disease emerged in the Argentine pampas. Annual outbreaks have been noted since then, with progressive extension of the endemic area and increase in the population at risk. Bolivian HF was first described in 1959 in Bolivia's Beni Department and the aetiological agent, Machupo virus, identified in 1964. Community outbreaks of Bolivian HF continued during the 1960s and were brought under control, in part, by rodent trapping. There were then no reported cases for decades, followed by sporadic cases and small outbreaks reported again in the 1990s and continuing through the time of this writing. An outbreak of viral HF in the Portuguesa State, Venezuela, in 1989 originally thought to be dengue HF, eventually was attributed to a new arenavirus named Guanarito. Outbreaks of Venezuelan HF have been reported every 4–5 years since then, suggesting some cyclic climatic or social influence. Sabiá virus was isolated from a fatal case of viral HF in Sao Paulo State, Brazil, in 1990. Since then, only two cases have been identified, both from laboratory infection. A second arenavirus, named Chapare, was discovered in Bolivia in 2003 after a small outbreak of viral HF

near Cochabamba. Cases have not been noted since but surveillance is limited.

EPIDEMIOLOGY

Like Old World arenaviruses, New World arenaviruses are maintained in rodents and spread to humans via exposure to rodent excreta.[1,59] The reservoirs of Junin and Guanarito viruses are generally found in rural areas, often in agricultural lands. Consequently, the highest risk of Argentine and Venezuelan HFs is among agricultural workers. Incidence may vary considerably with variations in rodent population densities that may relate to both climatic changes and human-induced habitat perturbation. Although cases can be seen throughout the year, incidence is usually highest at times of peak agricultural activity: March–June in Argentina and November–January in Venezuela. The reservoir for Machupo virus is primarily a household pest. Although Bolivian HF may be seen throughout the year, incidence is usually increased during the dry season (June–August), sometimes with family and community clusters. The reservoirs for Sabiá and Chapare viruses are unknown, but are presumed to be rodents.

New World arenaviruses appear to be less transmissible between humans than their Old World counterparts, although human-to-human transmission of Machupo virus has been reported in both community and nosocomial settings. Only one family cluster of Argentine HF is described, with the index case presenting with atypical skin lesions that may have facilitated transmission.

CLINICAL FEATURES

The clinical syndrome of South American HF is generally similar to that of the Old World arenaviruses, although bleeding and central nervous system manifestations are thought to occur more frequently, especially in Argentine HF. Characteristic signs and symptoms included flushing of the face, neck and upper chest; enanthem over the soft palate with petechiae and small vesicles; gum bleeding; petechiae in the axillae, upper chest and arms; enlarged cervical lymph nodes; fine tremor of the hands and tongue; moderate ataxia; cutaneous hyperesthesia; and decreased deep tendon reflexes and muscle tone (Figures 16.11 and 16.12). Sore throat is frequently reported in Venezuelan HF.

PATHOGENESIS AND PATHOLOGY

The pathogenesis of the New World arenavirus infection is thought to be similar to that of their Old World counterparts. A notable exception is the increased frequency of bleeding in South American HF. An acute transitory immunodeficiency after illness has also been noted.

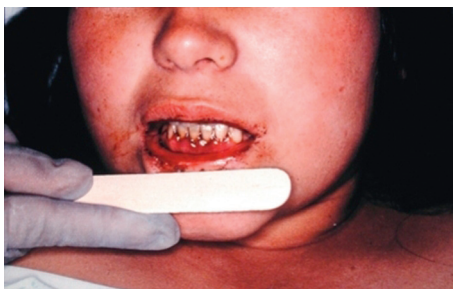

Figure 16.11 Gum bleeding in Argentine haemorrhagic fever.

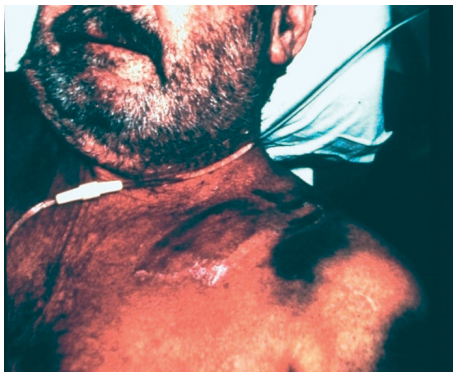

Figure 16.12 Petechial rash in Argentine haemorrhagic fever.

DIAGNOSIS

South American HF should be suspected in persons with a compatible clinical syndrome in endemic areas, especially in those with rural agricultural exposures. Laboratory diagnostic assays employed are similar to those used for the other arenaviruses.

MANAGEMENT AND TREATMENT

Transfusion of appropriately titred immune plasma within the first 8 days of illness reduces the mortality of Argentine HF from 15–30% to less than 1%.[70] Treatment after this time is not effective. However, this therapy has been associated with a convalescent-phase neurologic syndrome characterized by fever, cerebellar signs and cranial nerve palsies in 10% of those treated. Ribavirin appears to be efficacious in the treatment of the South American HFs although randomized trials have not been performed.

PREVENTION

Post-exposure Prophylaxis

Immune plasma is indicated as post-exposure prophylaxis for high-risk exposures to Junin virus, substituting oral ribavirin following the guidelines described above when immune plasma is not available or when the exposure was to one of the other New World arenaviruses.[21,70]

Vaccine

A live attenuated vaccine called Candid No.1 decreases the morbidity and mortality of Argentine HF and may also protect against Bolivian HF, although it does not appear to cross-protect against other arenaviruses.[71] The vaccine is generally not available or approved, however, outside of Argentina and even within Argentina supplies are insufficient to cover the population at risk.

Reservoir Control

Trapping and other rodent control measures in and around houses have contributed to stemming epidemics of Bolivian HF in villages. This approach is not feasible for control of Argentine

HF and Venezuelan HF, however, for which the reservoirs are widespread in fields.[1]

Bunyavirus Diseases: Haemorrhagic Fever with Renal Syndrome and Hantavirus Pulmonary Syndrome

Hantaviruses comprise a genus of the Bunyaviridae family.[59,72] Over 20 pathogenic hantaviruses are currently recognized (Table 16.6). Hantaviruses are taxonomically and clinically divided into Old World (i.e. Asia, Europe and Africa) and New World (i.e. the Americas) groups akin to the Arenaviruses described above. One Old World *Hantavirus*, Seoul, is now found virtually worldwide because its reservoir, the common Norway rat, has spread globally through transport on ships.

EPIDEMIOLOGY

Hantaviruses have been identified on every continent except Antarctica. The pathogenic hantaviruses are maintained in rodents, again with a tight reservoir–virus pairing like arenaviruses (Table 16.6). Transmission between rodents is horizontal through biting. Transmission to humans is through exposure to infected excreta. With the exception of Seoul virus, for which the rodent host is common in urban settings, Hantavirus reservoirs are rural rodents and disease is highest in persons exposed in rural areas, usually during outdoor occupational or recreational activities. Prevalence of exposure in humans varies greatly from region to region, from zero (0) to as high as 40% among some rural indigenous populations in South America. Although there appears to be a relationship between outbreaks in humans, rodent population density, proportion of infected rodents and climatic factors, such as El Niño effects, the precise nature of the relationship is complex and remains to be fully elucidated. Person-to-person transmission has been documented only for Andes virus, a New World hantavirus found in South America (Tables 16.1 and 16.6).

CLINICAL FEATURES

Hantaviruses have the longest incubation periods of any of the viral HFs, ranging up to 7 weeks, although 2–4 weeks is typical. Two distinct syndromes are recognized: Old World hantaviruses cause HF with renal syndrome, a term coined in 1983 to integrate various previously recognized febrile syndromes entailing haemostatic and renal disturbances, including 'Korean HF', 'nephropathia epidemica' and others. New World hantaviruses cause HPS, a disease first recognized in the USA in 1993 and across the Americas since. While these clinical distinctions generally hold true, elements of both syndromes may occasionally be seen and the pathogenicity and degree to which the classic syndromes manifest themselves may vary considerably depending upon the specific infecting virus.

TABLE 16.6 Hantaviruses Known to be Human Pathogens

Hantavirus	Reservoir Common Name (Scientific Name)	Disease	Geographic Distribution
Old World Viruses			
Amur	Korean field mouse (*Apodemus peninsulae*)	HFRS	Far eastern Russia
Dobrava-Belgrade	Yellow-necked field mouse (*Apodemus flavicollis*)	HFRS	Balkans, European Russia
Hantaan	Striped field mouse (*Apodemus agrarius*)	HFRS	China, Korea, Russia
Puumala	Bank vole (*Myodes glareolus*)	HFRS	Europe, European Russia
Saaremaa	Striped field mouse (*Apodemus agrarius*)	HFRS	Northern Europe
Seoul	Norway or Brown rat (*Rattus norvegicus*)	HFRS	Worldwide
New World Viruses			
Anajatuba	Fornes colilargo (*Oligoryzomys fornesi*)	HPS	Northern Brazil
Andes	Long-tailed colilargo (*Oligoryzomys longicaudatus*)	HPS	Southwestern Argentina, Chile
Araraquara	Hoary-tailed akodont (*Bolomys lasiurus*)	HPS	Southern Brazil
Bayou	Marsh oryzomys (*Oryzomys palustris*)	HPS	Southeastern United States
Bermejo	Chacoan colilargo (*Oligoryzomys chacoensis*)	HPS	Northern Argentina, southern Bolivia
Black Creek Canal	Hispid cotton rat (*Sigmodon hispidus*)	HPS	Southeastern United States (Florida)
Castelo dos Sonhos	Brazilian pygmy rice rat (*Oligoryzomys utiaritensis*)	HPS	Central Brazil
Central Plata	Yellow Pygmy rice rat or Flavescent colilargo (*Oligoryzomys flavescens*)	HPS	Uruguay
Choclo	Fulvous colilargo (*Oligoryzomys fulvescens*)	HPS	Panamá
Hu39694	Yellow Pygmy rice rat or Flavescent colilargo (*Oligoryzomys flavescens*)	HPS	Argentina
Juquitiba	Black-footed Pygmy rice rat or Black-footed colilargo (*Oligoryzomys nigripes*)	HPS	Southeastern Brazil
Laguna Negra	Little laucha or small vesper mouse (*Calomys laucha*)	HPS	Paraguay, Bolivia
Lechiguanas	Yellow Pygmy rice rat or Flavescent colilargo (*Oligoryzomys flavescens*)	HPS	Central Argentina
New York	White-footed deer mouse (*Peromyscus leucopus*)	HPS	Northeastern United States
Orán	Long-tailed colilargo (*Oligoryzomys longicaudatus*)	HPS	Northwestern Argentina
Río Mamoré	Small-eared Pygmy rice rat (*Oligoryzomys microtis*)	HPS	Amazon Basin of Brazil and contiguous lowlands of Peru, Bolivia and Paraguay
Sin Nombre	North American deer mouse (*Peromyscus maniculatus*)	HPS	Canada, United States

HFRS, haemorrhagic fever with renal syndrome; HPS, hantavirus pulmonary syndrome.
Controversy exists for some viruses regarding whether they constitute distinct species and whether the rodent listed above is the definitive reservoir.

Haemorrhagic Fever with Renal Syndrome. HF with renal syndrome caused by the prototype virus, Hantaan, is classically divided into five progressive phases: prodrome, hypotension, oliguria/renal failure, diuresis and convalescence. However, in clinical practice, phases may overlap or be completely absent, especially when other viruses such as Seoul and Puumala are the culprits, in which bleeding is much less common and mortality much lower. Liver involvement is frequent in Seoul virus infection.

Disease starts with a prodrome of abrupt onset of high fever and constitutional symptoms lasting 3–7 days. The fever then begins to abate and the patient enters the hypotensive phase, often with accompanying confusion, nausea, vomiting and worsening back pain. Around 15% of patients progress to severe shock with some fatalities at this stage. Plasma extravasation usually results in haemoconcentration and urinary concentration (Table 16.4). The platelet count reaches its nadir and the WBC count increases markedly, often above 30 000/μl. Radiological exams of the abdomen may show retroperitoneal oedema and haemorrhage.

A period of oliguria and renal failure follows the hypotensive phase, with the usual complications of uraemia and electrolyte abnormalities. Although platelets begin to rise, bleeding may be troublesome during this stage. Gastrointestinal bleeding and haematuria are characteristic. Low-grade DIC is common. Fluid resorption from third spaces may lead to high-output cardiac failure and pulmonary oedema, especially if the patient is overhydrated. Dialysis is often needed. Finally, after 2–7 days of oliguria, a period of diuresis ensues, sometimes reaching several litres of daily urine output that may cause electrolyte abnormalities and dehydration.

Complications include kidney rupture, right atrial haemorrhage and arrhythmias and retroperitoneal and intracranial haemorrhage, which may cause acute and chronic abnormalities of pituitary hormone secretion if the bleeding involves the pituitary gland. A urine-concentrating defect may persist for as long as 3 months. Recovery is usually complete, although an association between hypertensive chronic renal failure and antibodies to Seoul virus has been reported.

Hantavirus Pulmonary Syndrome. HPS typically begins with the gradual onset of fever and constitutional symptoms lasting 3–5 days, sometimes with prominent gastrointestinal complaints. Pharyngitis, rhinorrhea, cough, tachypnea and rash are usually absent and may help distinguish HPS from influenza and other upper respiratory illnesses. Pulmonary symptoms then abruptly ensue, with worsening shortness of breath, tachypnea and cough, which may be productive. Arterial desaturation may be noted on oximetry or blood gas analysis. Rales are typically noted but objective signs of pulmonary oedema may still be absent. The chest X-ray may be normal, show subtle signs of increased pulmonary vascular permeability, such as peribronchial oedema and Kerley B lines or show marked alveolar infiltrates and pleural effusions. Findings may be asymmetrical.

Deterioration in the patient's pulmonary status may then rapidly occur, with progressive hypoxia culminating in severe pulmonary oedema requiring intubation in two-thirds of patients. The high degree of pulmonary capillary permeability may result in copious, highly proteinaceous endotracheal secretions, the content of which resembles serum. Impaired cardiac inotropy is a key and dangerous component of the disease. Systemic vascular resistance is typically elevated, cardiac index decreased and pulmonary wedge pressure normal or even low. The cardiogenic shock is often refractory to fluid administration, inotropic and pressure support and independent of the management of the pulmonary component of the disease, death often coming in the form of electromechanical dissociation. Severe metabolic acidosis and lactate levels above 4 mmol/L confer a poor prognosis. Bleeding signs and DIC have been reported, but are uncommon. HPS is generally a very acute disease, with most deaths occurring within 48 hours of admission. Survivors usually have no long-term sequelae.

Anecdotal observations suggest some variation in clinical manifestations depending on the specific infecting hantavirus. Persons infected with some South American hantaviruses may more commonly manifest conjunctival congestion, head and neck suffusion, haemorrhage and renal impairment, the latter especially seen with infection with *Andes* and *Lechiguanas* viruses in Argentina.

PATHOGENESIS AND PATHOBIOLOGY

The pathogenesis of hantavirus infection is thought to be similar to that of other viral HFs, with particularly severe involvement of the renal and pulmonary vasculature in HF with renal syndrome and HPS, respectively.[59] In HPS, viral antigen is primarily detected in pulmonary capillary endothelial cells. Pathological findings include serous pleural effusions and severe oedema of the lung with mild-to-moderate numbers of hyaline membranes, normal pneumocytes and, in contrast to infectious pneumonias, absence of acute inflammatory cells. Myocarditis, hepatic necrosis, renal medullary lesions and thrombosis of small vessels may be noted. In contrast to other viral HFs, the immune response may play a detrimental role in HPS, indicated by the frequent clearance of viremia prior to onset of the most severe phases of disease.

DIAGNOSIS

Hantavirus infection should be suspected in persons with a compatible clinical syndrome who are at risk of exposure to rodent excreta, especially in rural areas where hantaviruses are known to be endemic. Detection of IgM antibody by ELISA and/or nucleic acid by RT-PCR are the typical diagnostic means, with sequencing of PCR products to identify the specific infecting virus. Hantaviruses are difficult to isolate in cell culture.

MANAGEMENT AND TREATMENT

Ribavirin has been shown to reduce mortality in HF with renal syndrome if administered within 4 days of onset.[73] Two clinical trials of ribavirin for HPS were inconclusive due to limitations in the studies' design and statistical power, although the trends did not suggest benefit.[74] One problem is that the nonspecific early presentation of HPS often results in delayed diagnosis, precluding early administration of ribavirin when it might logically be assumed to be most effective. To circumvent this problem, a protocol has been approved in Argentina, where cases are often seen in clusters, for early administration of ribavirin to high-risk contacts of confirmed HPS cases who develop a febrile syndrome. The use of adjunctive steroids is also being examined in South America.

PREVENTION

Patient Isolation, Personal Protective Equipment and Nursing Precautions

Patient isolation and viral HF precautions should be implemented in patients with exposures in Argentina and Chile if Andes virus infection is suspected.

Vaccines

A vaccine for HF with renal syndrome is available in parts of Asia but the efficacy has not been extensively evaluated and the vaccine is not generally licensed or available outside these regions.[75] The vaccine is based on hantaviruses found in Asia and is unlikely to protect against those found in Europe or the Americas.

Reservoir Control

Because almost all hantavirus reservoirs are rural sylvatic rodents which cannot and should not be exterminated, control measures focus on avoiding human exposure to rodent excreta through rodent-proofing houses and avoiding sites of occupational or recreational exposure such as abandoned cabins or wood piles.

Bunyavirus Diseases: Rift Valley Fever

Rift Valley fever virus belongs to the *Phlebovirus* genus of the family Bunyaviridae. The virus was first isolated in Kenya in 1930 following an outbreak of 'enzootic hepatitis' in sheep in the East Africa's Rift Valley. Sporadic disease is seen throughout Africa and the Arabian Peninsula, but large outbreaks are most common in Africa, especially in east Africa, sometimes resulting in tens of thousands of infections in humans and hundreds of thousands of infections, spontaneous abortions and deaths in livestock.

EPIDEMIOLOGY

Rift Valley fever virus is maintained in a cycle between domestic ruminants (i.e. livestock, such as cattle, buffalo, sheep, goats and camels) and zoophilic flood-water breeding *Aedes* mosquitoes, with *Culex* mosquitoes sometimes serving as vectors during epizootics.[76] The virus may provoke abortions in pregnant animals with heavy mortality in newborns and is thus a major agricultural concern. Epizootics generally occur in 5–15-year cycles and follow droughts broken by heavy rains. Transovarial transmission in *Aedes* is thought to be responsible for virus maintenance during interepidemic periods.

Transmission of Rift Valley fever virus to humans occurs through direct contact with the blood and tissues of infected animals, especially during parturition, by mosquito bite and rarely through ingestion of unpasteurized infected milk. Farmers, abattoir workers and veterinarians are at particular risk. With the exception of needle stick injuries, human-to-human transmission has not been documented. Patient isolation is therefore not warranted, although patients should be protected from mosquito bites to curtail transmission.

PATHOGENESIS AND PATHOLOGY

The liver is a major target organ in HF, with histopathological examination showing moderate focal or midzonal coagulative necrosis.[77] Necrosis in the ventricular myocardium, fibrin thrombi in the glomeruli and small intertubular vessels of renal medulla in the kidneys and mild depletion of lymphocytes from white pulp and the deposition of eosinophilic amorphous fibrin-like material in red pulp cords in the spleen may be seen. An IFN-α response may play a significant role in mitigating disease.

CLINICAL FEATURES

Most human Rift Valley fever virus infections are asymptomatic or cause a mild and nonspecific illness with fever, headache, myalgia and sometimes photophobia. Severe disease occurs in a minority of infected persons and may include hepatitis, encephalitis and HF. Mortality though is high in persons with hepatitis and HF. Retinitis is a late complication of Rift Valley fever infection. Illness may be biphasic, with a brief amelioration before worsening symptoms. There are generally no sequelae in survivors, with the exception of occasional optic retinopathy resulting in vision loss.

DIAGNOSIS

Rift Valley fever should be suspected in persons with a compatible clinical syndrome, especially those with exposures to livestock in Africa. Disease in livestock, especially abortions, is usually a clue that Rift Valley fever virus is circulating. Single human cases are rarely detected.

MANAGEMENT AND TREATMENT

Although ribavirin has in vitro activity against Rift Valley fever virus, the drug is considered contraindicated after some patients treated in Saudi Arabia in 2000 succumbed to late-onset encephalitis, although the association with ribavirin is not clear. There are no controlled studies for the use of immune plasma for Rift Valley fever patients.

PREVENTION

Vaccine

A live-attenuated virus vaccine based on the Smithburn strain of Rift Valley fever virus leads to long-term immunity in sheep and goats, but not cattle.[78,79] This vaccine is associated with abortion in a small proportion of pregnant animals, which often creates significant resistance to its use among farmers. A killed vaccine was developed for use in cattle, but repeated doses are required, again discouraging use by farmers. A formalin inactivated cell culture-derived vaccine (TSI-GSD-200) is efficacious in humans but is not widely available and requires yearly boosters.

Bunyavirus Diseases: Crimean-Congo Haemorrhagic Fever

Crimean-Congo HF virus is a member of the genus *Nairovirus* within the family Bunyaviridae.[80] The virus was first discovered in 1944 in Crimea on the southern coast of Ukraine and recognized in 1969 as the same virus that caused an outbreak of illness in the Democratic Republic of the Congo.

Crimean-Congo HF virus is found across Africa, the Balkans, the Middle East and western Asia (Figure 16.4).

EPIDEMIOLOGY

Crimean-Congo HF virus is maintained in small mammals such as hares, between which the virus is spread by ticks, primarily of the *Hyalomma* species. Humans are infected either by tick bites or by exposure to contaminated blood or excreta of the reservoir animals. Ticks also spread Crimean-Congo HF virus to large mammals, including cattle, sheep and ostriches, whose transient and asymptomatic viraemia puts farmers, abattoir workers and veterinarians at risk. Nosocomial human-to-human transmission occurs frequently if universal precautions are not maintained.

PATHOGENESIS AND PATHOLOGY

Hepatocellular necrosis is present in all cases, frequently associated with haemorrhage, cell loss and eosinophilic changes of hepatocytes with formation of Councilman bodies.[81] Histological changes are not pathognomonic. Disseminated intravascular coagulopathy is an early and central event in the pathogenesis.

CLINICAL FEATURES

The incubation period may vary from as short as 1 day following tick bite transmission up to 11 days after other modes of inoculation.[82] Symptom onset is typically abrupt. Patients may undergo sharp changes of mood over the first two days, with feelings of confusion and aggression. Neck pain and stiffness, sore eyes and photophobia may be noted. By day 2–4, patients may exhibit lassitude, depression and somnolence and have a flushed appearance with infected conjunctivae or chemosis. Hepatomegaly with right upper quadrant tenderness may be discernible, as well as lymphadenopathy and enanthema and petechiae of the throat, tonsils and buccal mucosa. A petechial rash appears on the trunk and limbs by days 3–6 of illness and may be followed rapidly by the appearance of large bruises and ecchymoses, especially in the antecubital fossae, upper arms, axillae and groin (Figure 16.13). Internal bleeding, including retroperitoneal and intracranial haemorrhage, may occur. Severely ill patients develop hepatorenal and pulmonary failure from about day 5 onwards, with progressive drowsiness, stupor and coma. Jaundice may be seen during the 2nd week of illness. During the first 5 days of illness any of the following clinical laboratory values are highly predictive of a fatal outcome: leucocyte count $\geq 10 \times 10^9$/L; platelet count $\leq 20 \times 10^9$/L; AST ≥200 U/L; ALT ≥150 U/L; APTT ≥60 seconds; and fibrinogen ≤110 mg/dL. Leucopenia does not have the same poor prognostic connotation as leucocytosis at this early stage and all clinical laboratory values may be grossly abnormal after day 5 of illness without necessarily being indicative of a poor prognosis. Asthenia, conjunctivitis, slight confusion and amnesia may persist for months after acute disease.

DIAGNOSIS

Crimean-Congo HF should be suspected in persons with a compatible clinical syndrome (especially if bleeding is present) and likely exposure to ticks, animals or patients in endemic areas. African tick bite fever and other rickettsial infections are major considerations in the differential diagnosis (Table 16.3). Thrombocytopenia and elevated aspartate and alanine transferases are consistent findings in Crimean-Congo HF and the absence of these on successive blood draws should suggest an alternative diagnoses.

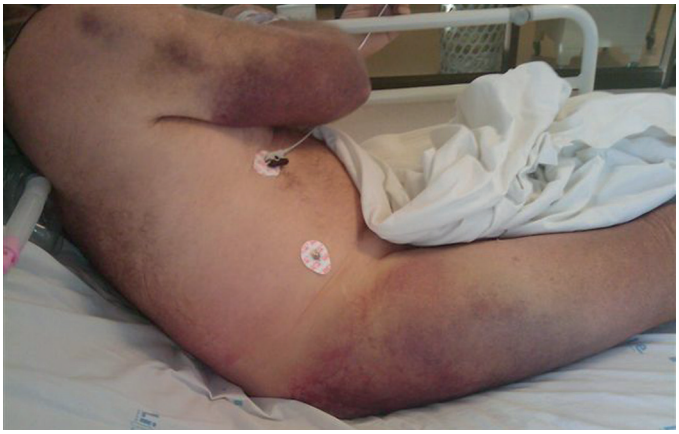

Figure 16.13 Extensive ecchymosis in Crimean-Congo haemorrhagic fever. *(Photo by Freak Bester.)*

MANAGEMENT AND TREATMENT

Ribavirin has in vivo activity against Crimean-Congo HF and is often administered in both IV and oral forms to patients with the disease with apparent benefit. However, randomized controlled trials have not been performed.[79,83,84] Limited studies, but no placebo controlled trials, have suggested that immune plasma administered early in the course of illness may be efficacious. Platelet transfusion is often beneficial in patients with platelets counts of <50 000 and bleeding. Empiric doxycycline treatment for rickettsial infection should be considered until the diagnosis of Crimean-Congo HF can be confirmed.

PREVENTION

Post-exposure Prophylaxis

Post-exposure prophylaxis with oral ribavirin should be considered for persons with high-risk exposures following the guidelines described above.[21]

Vaccine

There is presently no vaccine for Crimean-Congo HF.[85]

Reservoir and Vector Control

Prevention of Crimean-Congo HF is achieved by controlling ticks through acaricides treatment of livestock and use of protective materials by abattoir workers and other animal workers to prevent contact with blood of viraemic animals.

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