

Chapter 29

VIRAL HEMORRHAGIC FEVERS

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INTRODUCTION

The concept of a viral hemorrhagic fever (VHF) syndrome is useful in clinical medicine. VHF syndrome can be described as an acute febrile illness characterized by malaise, prostration, generalized signs of increased vascular permeability, and abnormalities of circulatory regulation. Bleeding manifestations often occur, especially in the more severely ill patients, but this does not result in a life-threatening loss of blood volume. Rather, these signs are the result of damage to the vascular endothelium and are an index of how severe the disease is in specific target organs.

The viral agents that cause VHFs are taxonomically diverse; they are all ribonucleic acid (RNA) viruses and are transmitted to humans through contact with infected animal reservoirs or arthropod vectors. They are all natural infectious disease threats although their geographical ranges may be tightly circumscribed. The recent advent of jet travel coupled with human demographics increase the

opportunity for humans to contract these infections.

The VHF agents are all highly infectious via the aerosol route, and most are quite stable as respirable aerosols. This means that they satisfy at least one criterion for being weaponized, and some clearly have the potential to be biological warfare threats. Most of these agents replicate in cell culture to concentrations sufficiently high to produce a small terrorist weapon, one suitable for introducing lethal doses of virus into the air intake of an airplane or office building. Some replicate to even higher concentrations, with obvious potential ramifications. Since the VHF agents cause serious diseases with high morbidity and mortality, their existence as endemic disease threats and as potential biological warfare weapons suggests a formidable potential impact on unit readiness. Further, returning troops may well be carrying exotic viral diseases to which the civilian population is not immune, a major public health concern.

EPIDEMIOLOGICAL OVERVIEW

The VHF agents are a taxonomically diverse group of RNA viruses whose major characteristics are summarized in Table 29-1. Four virus families contribute pathogens to the group of VHF agents: the *Arenaviridae*, *Bunyaviridae*, *Filoviridae*, and *Flaviviridae*. Despite their diverse taxonomy, all these viruses share some common characteristics. They are all relatively simple RNA viruses, and they all have lipid envelopes. This renders them relatively susceptible to detergents, as well as to low-pH environments and household bleach. Conversely, they are quite stable at neutral pH, especially when protein is present. Thus, these viruses are stable in blood for long periods, and can be isolated from a patient's blood after weeks of storage at refrigerator or even at ambient temperatures.

These viruses tend to be stable and highly infectious as fine-particle aerosols. These characteristics have great significance in not only the natural transmission cycle for arenaviruses and bunyaviruses (from rodents to man) but also make nosocomial transmission a concern. As a group, the viruses are also linked to the ecology of their vectors or reservoirs, whether rodents or arthropods. In that regard, most of these reservoirs tend to be rural, and a patient's history of being in a rural

locale is an important factor to consider when reaching a diagnosis. Human-to-human spread is possible, but pandemics are unlikely.

The *Arenaviridae*

The arenaviruses are classified into the Old World and New World groups. All the arenaviruses are maintained in nature by a life-long association with a rodent reservoir. Rodents spread the virus to humans, and outbreaks can usually be related to some perturbation in the ecosystem that brings man into contact with the rodents.

Lassa virus causes Lassa fever, a major febrile disease of West Africa, where it is associated with 10% to 15% of adult febrile admissions to the hospital and perhaps 40% of nonsurgical deaths.¹ In addition, Lassa fever is a pediatric disease and the cause of high mortality in pregnant women. While nosocomial infections do occur, most Lassa virus infections can be traced to contact with the carrier rodent, *Mastomys natalensis*.

The Junin virus that causes Argentine hemorrhagic fever is carried by a field mouse, *Calomys colosus*, and is associated with agricultural activities in the pampas of Argentina, where 300 to 600 cases have occurred every year since 1955.² In Bo-

TABLE 29-1
RECOGNIZED VIRAL HEMORRHAGIC FEVERS OF HUMANS

Virus Family			Source of Human Infection		Incubation
Genus	Disease (Virus)	Natural Distribution	Usual	Less Likely	(Days)
Arenaviridae					
Arenavirus	Lassa fever	Africa	Rodent	Nosocomial	5–16
	Argentine HF (Junin)	South America	Rodent	Nosocomial	7–14
	Bolivian HF (Machupo)	South America	Rodent	Nosocomial	9–15
	Brazilian HF (Sabia)	South America	Rodent	Nosocomial	7–14
	Venezuelan HF (Guanarito)	South America	Rodent	Nosocomial	7–14
Bunyaviridae					
Phlebovirus	Rift Valley fever	Africa	Mosquito	Slaughter of domestic animal	2–5
Nairovirus	Crimean-Congo HF	Europe, Asia, Africa	Tick	Slaughter of domestic animal; nosocomial	3–12
Hantavirus	HFRS (Hantaan and related viruses)	Asia, Europe; possibly worldwide	Rodent		9–35
Filoviridae					
Filovirus	Marburg and Ebola HF	Africa	Unknown	Nosocomial	3–16
Flaviviridae					
Flavivirus (Mosquito-borne)	Yellow fever	Tropical Africa, South America	Mosquito		3–6
	Dengue HF	Asia, Americas, Africa	Mosquito		Unknown for dengue HF, but 3–5 for uncomplicated dengue
(Tick-borne)	Kyasanur Forest disease	India	Tick		3–8
	Omsk HF	Soviet Union	Tick	Muskrat-contaminated water	3–8

HF: hemorrhagic fever; HFRS: hemorrhagic fever with renal syndrome

livia, Machupo virus is the agent associated with Bolivian hemorrhagic fever,³ a disease that was associated with outbreaks in the 1960s but only with sporadic disease subsequently. Guanarito virus is a newly described arenavirus, first recognized in association with an outbreak of VHF involving several hundred patients in Venezuela beginning in 1989.⁴ More recently, yet another VHF arenavirus has been recognized: Sabia virus was associated with a fatal VHF infection in Brazil in 1990, followed by a severe laboratory infection in Brazil in 1992 and another laboratory infection in the United States in 1994.⁵

The *Bunyaviridae*

Among the bunyaviruses, the significant human pathogens include the phlebovirus Rift Valley fever (RVF) virus, which causes Rift Valley fever. This major African disease is frequently associated with unusual increases in mosquito populations.⁶ Rift Valley fever is also a disease of domestic livestock, and human infections have resulted from contact with infected blood, especially around slaughter houses.

A nairovirus, Crimean-Congo hemorrhagic fever (C-CHF) virus is carried by ticks, and has been

associated with sporadic, yet particularly severe, VHF in Europe, Africa, and Asia.⁷ Crimean-Congo hemorrhagic fever has frequently occurred as small, hospital-centered outbreaks, owing to the copious hemorrhage and highly infective nature of this virus via the aerosol route.

Hantaviruses, unlike the other bunyaviruses, are not transmitted via infected arthropods; rather, they infect man via contact with infected rodents and their excreta. Hantavirus disease was described prior to World War II in Manchuria along the Amur River, and later among United Nations troops during the Korean War, where it became known as Korean hemorrhagic fever.⁸ The prototype virus from this group, Hantaan, is the cause of Korean hemorrhagic fever as well as the severe form of hemorrhagic fever with renal syndrome (HFRS). Hantaan virus is borne in nature by the striped field mouse, *Apodemus agrarius*.

Hantaan virus is still active in Korea, Japan, and China. Seoul virus causes a milder form of HFRS, and may be distributed worldwide. There are a number of other hantaviruses that are associated with HFRS, including Puumala virus, which is associated with chronically infected bank voles (*Clethrionomys glareolus*). Recently in the United States, a new hantavirus (Sin nombre virus) has been associated with the hantavirus pulmonary syndrome (HPS).⁹

The *Filoviridae*

The *Filoviridae* includes the causative agents of Ebola and Marburg hemorrhagic fevers. These filoviruses have an exotic, threadlike appearance when observed via electron microscopy. Marburg virus was first recognized in 1967 when a lethal epidemic of VHF occurred in Marburg, Germany, among laboratory workers exposed to the blood and tissues of African green monkeys that had been imported from Uganda; secondary transmission to medical personnel and family members also occurred.¹⁰ In all, 31 patients became infected, 9 of whom died. Subsequently, Marburg virus has been associated with sporadic, isolated, usually fatal cases among residents and travelers in southeast Africa.¹¹

Ebola viruses are taxonomically related to Marburg viruses; they were first recognized in association with explosive outbreaks that occurred almost simultaneously in 1976 in small communities in Zaire¹² and Sudan.¹³ Significant secondary transmission occurred through reuse of unsterilized needles and syringes and nosocomial contacts. These independent outbreaks involved serologically distinct viral strains. The Ebola–Zaire outbreak involved 277 cases and 257 deaths (92% mortality), while the Ebola–Sudan outbreak involved 280 cases and 148 deaths (53% mortality). Sporadic cases occurred subsequently. In 1989, a third strain of Ebola virus appeared in Reston, Virginia, in association with an outbreak of VHF among cynomolgus monkeys imported to the United States from the Philippines.¹⁴ Hundreds of monkeys were infected (with high mortality) but no human cases occurred, although four animal caretakers seroconverted without overt disease. Recently, small outbreaks involving new strains of Ebola virus occurred in human populations in Côte d’Ivoire in 1994 and Gabon in 1995; a larger outbreak involving the Ebola–Zaire strain involved more than 300 people, with 75% mortality, in Zaire in 1995.¹⁵

Very little is known about the natural history of any of the filoviruses. Animal reservoirs and arthropod vectors have been aggressively sought without success.

The *Flaviviridae*

Finally, the flaviviruses include the agents of yellow fever, found throughout tropical Africa and South America; and dengue, found throughout the Americas, Asia, and Africa, both transmitted by mosquitoes.¹⁶ Both yellow fever and dengue have had major impact on military campaigns and military medicine. The tick-borne flaviviruses include the agents of Kyasanur Forest disease, which occurs in India,¹⁷ and Omsk hemorrhagic fever, which occurs in the former Soviet Union.¹⁸ Both diseases have a biphasic course; the initial phase includes a prominent pulmonary component, followed by a neurological phase with central nervous system manifestations.

CLINICAL FEATURES OF THE VIRAL HEMORRHAGIC FEVER SYNDROME

The VHF syndrome develops to varying degrees in patients infected with these viruses. The exact nature of the disease depends on viral virulence and strain characteristics, routes of exposure, dose, and

host factors. For example, dengue hemorrhagic fever is typically seen only in patients previously exposed to heterologous dengue serotypes.¹⁹ The target organ in the VHF syndrome is the vascular bed;

correspondingly, the dominant clinical features are usually a consequence of microvascular damage and changes in vascular permeability.²⁰ Common presenting complaints are fever, myalgia, and prostration; clinical examination may reveal only conjunctival injection, mild hypotension, flushing, and petechial hemorrhages. Full-blown VHF typically evolves to shock and generalized bleeding from the mucous membranes, and often is accompanied by evidence of neurological, hematopoietic, or pulmonary involvement. Hepatic involvement is common, but a clinical picture dominated by jaundice and other evidence of hepatic failure is seen in only a small percentage patients with Rift Valley fever, Crimean-Congo hemorrhagic fever, Marburg hemorrhagic fever, Ebola hemorrhagic fever, and yellow fever. Renal failure is proportional to cardiovascular compromise, except in HFRS caused by hantaviruses, where it is an integral part of the disease process; oliguria is a prominent feature of the acutely ill patient.⁸ VHF mortality may be substantial, ranging from 5% to 20% or higher in recognized cases. Ebola outbreaks in Africa have had particularly high case fatality rates, from 50% up to 90%.^{12,13}

The clinical characteristics of the various VHFs are somewhat variable. For Lassa fever patients, hemorrhagic manifestations are not pronounced, and neurological complications are infrequent, occurring only late and in only the most severely ill group. Deafness is a frequent sequela of severe Lassa fever. For the South American arenaviruses, (Argentine and Bolivian hemorrhagic fevers), neurological and hemorrhagic manifestations are much more prominent. RVF virus is primarily hepatotropic; hemorrhagic disease is seen in only a small proportion of cases. In recent outbreaks in Egypt, retinitis was a frequently reported component of Rift Valley fever.²¹

Unlike Rift Valley fever, where hemorrhage is not prominent, Crimean-Congo hemorrhagic fever infection is usually associated with profound disseminated intravascular coagulation (DIC) (Figure 29-1). Patients with Crimean-Congo hemorrhagic fever may bleed profusely; and since this occurs during the acute, viremic phase, contact with the blood of an infected patient is a special concern: a number of nosocomial outbreaks have been associated with C-CHV virus.

The picture for diseases caused by hantaviruses is evolving, especially now in the context of HPS syndrome. The pathogenesis of HFRS may be somewhat different; immunopathological events seem to be a major factor. When patients present with HFRS,



Fig. 29-1. Massive cutaneous ecchymosis associated with late-stage Crimean-Congo hemorrhagic fever virus infection, 7 to 10 days after clinical onset. Ecchymosis is indicative of multiple abnormalities in the coagulation system, coupled with loss of vascular integrity. Epistaxis and profuse bleeding from puncture sites, hematemesis, melena, and hematuria often accompany spreading ecchymosis, which may occur anywhere on the body as a result of needlesticks or other minor trauma. The sharply demarcated proximal border of this patient's lesion is not explained. Photograph: Courtesy of Robert Swanepoel, PhD, DTVM, MRCVS, National Institute of Virology, Sandringham, South Africa.

they are typically oliguric. Surprisingly, the oliguria occurs while the patient's viremia is resolving and they are mounting a demonstrable antibody response. This has practical significance in that renal dialysis can be started with relative safety.

For the diseases caused by filoviruses, little clinical data from human outbreaks exist. Although mortality is high, outbreaks are rare and sporadic. Marburg and Ebola viruses produce prominent maculopapular rashes, and DIC is a major factor in their pathogenesis. Therefore, treatment of the DIC should be considered, if practicable, for these patients.

Among the flaviviruses, yellow fever virus is, of course, hepatotropic: black vomit caused by hematemesis has been associated with this disease. Patients with yellow fever develop clinical jaundice and die with something comparable to hepatorenal syndrome. Dengue hemorrhagic fever and shock are uncommon, life-threatening complications of dengue, and are thought—especially in children—to result from an immunopathological mechanism triggered by sequential infections with different dengue viral serotypes.¹⁹ Although this is the general epidemiological pattern, dengue virus may also rarely cause hemorrhagic fever in adults and in primary infections.²²

DIAGNOSIS

The natural distribution and circulation of VHF agents are geographically restricted and mechanistically linked with the ecology of the reservoir species and vectors. Therefore, a high index of suspicion and elicitation of a detailed travel history are critical in making the diagnosis of VHF. Patients with arenaviral or hantaviral infections often recall having seen rodents during the presumed incubation period, but, since the viruses are spread to humans by aerosolized excreta or environmental contamination, actual contact with the reservoir is not necessary. Large mosquito populations are common during the seasons when RVF virus and the flaviviruses are transmitted, but a history of mosquito bite is sufficiently common to be of little assistance in making a diagnosis, whereas tick bites or nosocomial exposure are of some significance when Crimean-Congo hemorrhagic fever is suspected. History of exposure to animals in slaughterhouses should raise suspicions of Rift Valley fever and Crimean-Congo hemorrhagic fever in a patient with VHF. When large numbers of military personnel present with VHF manifestations in the same geographical area over a short period of time, medical personnel should suspect either a natural outbreak (in an endemic setting) or possibly a biowarfare attack (particularly if the virus causing the VHF is not endemic to the area).

VHF should be suspected in any patient presenting with a severe febrile illness and evidence of vascular involvement (subnormal blood pressure, postural hypotension, petechiae, hemorrhagic diathesis, flushing of the face and chest, nondependent edema) who has traveled to an area where the etiologic virus is known to occur, or where intelligence suggests a biological warfare threat. Signs and symptoms suggesting additional organ system involvement are common (headache, photophobia, pharyngitis, cough, nausea or vomiting, diarrhea, constipation, abdominal pain, hyperesthesia, dizziness, confusion, tremor), but they rarely dominate the picture. A macular eruption occurs in most patients who have Marburg and Ebola hemorrhagic fevers; this clinical manifestation is of diagnostic importance.

Laboratory findings can be helpful, although they vary from disease to disease and summarization is difficult. Leukopenia may be suggestive, but in some patients, white blood cell counts may be normal or even elevated. Thrombocytopenia is a component of most VHF diseases, but to a varying extent. In some, platelet counts may be near nor-

mal, and platelet function tests are required to explain the bleeding diathesis. A positive tourniquet test has been particularly useful in diagnosing dengue hemorrhagic fever, but this sign may be associated with other hemorrhagic fevers as well. Proteinuria or hematuria or both are common in VHF, and their absence virtually rules out Argentine hemorrhagic fever, Bolivian hemorrhagic fever, and hantaviral infections. Hematocrits are usually normal, and if there is sufficient loss of vascular integrity perhaps mixed with dehydration, hematocrits may be increased. Liver enzymes such as aspartate aminotransferase (AST) are frequently elevated. VHF viruses are not primarily hepatotropic, but livers are involved and an elevated AST may help to distinguish VHF from a simple febrile disease.

For much of the world, the major differential diagnosis is malaria. It must be borne in mind that parasitemia in patients partially immune to malaria does not prove that symptoms are due to malaria. Typhoid fever and rickettsial and leptospiral diseases are major confounding infections; nontyphoidal salmonellosis, shigellosis, relapsing fever, fulminant hepatitis, and meningococcemia are some of the other important diagnoses to exclude. Ascertaining the etiology of DIC is usually surrounded by confusion. Any condition leading to DIC could be mistaken for diseases such as acute leukemia, lupus erythematosus, idiopathic or thrombotic thrombocytopenic purpura, and hemolytic uremic syndrome.

Definitive diagnosis in an individual case rests on specific virological diagnosis. Most patients have readily detectable viremia at presentation (the exception is those with hantaviral infections). Infectious virus and viral antigens can be detected and identified by a number of assays using fresh or frozen serum or plasma samples. Likewise, early immunoglobulin (Ig) M antibody responses to the VHF-causing agents can be detected by enzyme-linked immunosorbent assays (ELISA), often during the acute illness. Diagnosis by viral cultivation and identification requires 3 to 10 days for most (longer for the hantaviruses); and, with the exception of dengue, specialized microbiologic containment is required for safe handling of these viruses.²³ Appropriate precautions should be observed in collection, handling, shipping, and processing of diagnostic samples.²⁴ Both the Centers for Disease Control and Prevention (CDC, Atlanta, Georgia.) and the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID, Fort Detrick,

Frederick, Maryland.) have diagnostic laboratories operating at the maximum Biosafety Level (BL-4; see Chapter 19, The U.S. Biological Warfare and Biological Defense Programs, for further discussion of BLs). Viral isolation should not be attempted without BL-4 containment.

In contrast, most antigen-capture and antibody-detection ELISAs for these agents can be performed with samples that have been inactivated by treatment with β -propiolactone (BPL).²⁵ Likewise, diagnostic tests based on reverse transcriptase polymerase chain reaction (RT-PCR) technology are safely performed on samples following RNA extraction using chloroform and methanol. RT-PCR has been successfully applied to the real-time diagnosis of most of the VHF agents.^{26,27} When isolation of the infectious virus is difficult or impractical, RT-PCR has proven to be extremely valuable; for example, with HPS, where the agent was recog-

nized by PCR months before it was finally isolated in culture.⁹

When the identity of a VHF agent is totally unknown, isolation in cell culture and direct visualization by electron microscopy, followed by immunological identification by immunohistochemical techniques is often successful.¹⁴ Immunohistochemical techniques are also useful for retrospective diagnosis using formalin-fixed tissues, where viral antigens can be detected and identified using batteries of specific immune sera and monoclonal antibodies.

Although intensive efforts are being directed toward the development of simple, qualitative tests for rapid diagnosis in the field, definitive diagnosis for these diseases today requires, at a minimum, an ELISA capability coupled with specialized immunological reagents, supplemented (ideally) with an RT-PCR capability.

MEDICAL MANAGEMENT

Patients with VHF syndrome require close supervision, and some will require intensive care. Since the pathogenesis of VHF is not entirely understood and availability of specific antiviral drugs is limited, treatment is largely supportive. This care is essentially the same as the conventional care provided to patients with other causes of multisystem failure. The challenge is to provide this support while minimizing the risk of infection to other patients and medical personnel.

Supportive Care

Patients with VHF syndrome generally benefit from rapid, nontraumatic hospitalization to prevent unnecessary damage to the fragile capillary bed. Transportation of these patients, especially by air, is usually contraindicated because of the effects of drastic changes in ambient pressure on lung water balance. Restlessness, confusion, myalgia, and hyperesthesia occur frequently and should be managed by reassurance and other supportive measures, including the judicious use of sedative, pain-relieving, and amnestic medications. Aspirin and other antiplatelet or anticlotting-factor drugs should be avoided.

Secondary infections are common and should be sought and aggressively treated. Concomitant malaria should be treated aggressively with a regimen known to be effective against the geographical strain of the parasite; however, the presence of malaria, particularly in immune individuals, should not preclude management of the patient for VHF

syndrome if such is clinically indicated.

Intravenous lines, catheters, and other invasive techniques should be avoided unless they are clearly indicated for appropriate management of the patient. Attention should be given to pulmonary toilet, the usual measures to prevent superinfection, and the provision of supplemental oxygen. Immunosuppression with steroids or other agents has no empirical and little theoretical basis, and is contraindicated except possibly for HFRS.

The diffuse nature of the vascular pathological process may lead to a requirement for support of several organ systems. Myocardial lesions detected at autopsy reflect cardiac insufficiency antemortem. Pulmonary insufficiency may develop, and, particularly with yellow fever, hepatorenal syndrome is prominent.¹⁶

Treatment of Bleeding

The management of bleeding is controversial. Uncontrolled clinical observations support vigorous administration of fresh frozen plasma, clotting factor concentrates, and platelets, as well as early use of heparin for prophylaxis of DIC. In the absence of definitive evidence, mild bleeding manifestations should not be treated at all. More-severe hemorrhage indicates that appropriate replacement therapy is needed. When definite laboratory evidence of DIC becomes available, heparin therapy should be employed if appropriate laboratory support is available.

Treatment of Hypotension and Shock

Management of hypotension and shock is difficult. Patients often are modestly dehydrated from heat, fever, anorexia, vomiting, and diarrhea, in any combination. There are covert losses of intravascular volume through hemorrhage and increased vascular permeability.²⁸ Nevertheless, these patients often respond poorly to fluid infusions and readily develop pulmonary edema, possibly due to myocardial impairment and increased pulmonary vascular permeability. Asanguineous fluids—either colloid or crystalloid solutions—should be given, but cautiously. Although it has never been evaluated critically for VHFs, dopamine would seem to be the agent of choice for patients with shock who are unresponsive to fluid replacement. α -Adrenergic vasoconstricting agents have not been clinically helpful except when emergent intervention to treat profound hypotension is necessary. Vasodilators have never been systematically evaluated. Pharmacological doses of corticosteroids (eg, methylprednisolone 30 mg/kg) provide another possible but untested therapeutic modality in treating shock.

Particular Problems With Dengue and Hantaviral Infections

Two hemorrhagic fevers should be clearly separated from the other VHF diseases. Severe consequences of dengue infection are largely due to systemic capillary leakage syndrome and should be managed initially by brisk infusion of crystalloid, followed by albumin or other colloid if there is no response.²⁹

Severe hantaviral infections have many of the management problems of the other hemorrhagic fevers but will culminate in acute renal failure with a subsequent polyuria during the patient's recovery. Careful fluid and electrolyte management, and often renal dialysis, are necessary for optimal treatment.

Isolation and Containment

Patients with VHF syndrome generally have significant quantities of virus in their blood, and perhaps in other secretions as well (with the exceptions of dengue and classic hantaviral disease). Well-documented secondary infections among contacts and medical personnel not parenterally exposed have occurred. Thus, caution should be

exercised in evaluating and treating patients with suspected VHF syndrome. Over-reaction on the part of medical personnel is inappropriate and detrimental to both patient and staff, but it is prudent to provide isolation measures as rigorous as feasible.³⁰ At a minimum, these should include the following:

- stringent barrier nursing;
- mask, gown, glove, and needle precautions;
- hazard-labeling of specimens submitted to the clinical laboratory;
- restricted access to the patient; and
- autoclaving or liberal disinfection of contaminated materials, using hypochlorite or phenolic disinfectants.

For more intensive care, however, increased precautions are advisable. Members of the patient care team should be limited to a small number of selected, trained individuals, and special care should be directed toward eliminating all parenteral exposures. Use of endoscopy, respirators, arterial catheters, routine blood sampling, and extensive laboratory analysis increase opportunities for aerosol dissemination of infectious blood and body fluids. For medical personnel, the wearing of flexible plastic hoods equipped with battery-powered blowers provides excellent protection of the mucous membranes and airways.

Specific Antiviral Therapy

Ribavirin is a nonimmunosuppressive nucleoside analogue with broad antiviral properties,³¹ and is of proven value for some of the VHF agents. Ribavirin reduces mortality from Lassa fever in high-risk patients,³² and presumably decreases morbidity in all patients with Lassa fever, for whom current recommendations are to treat initially with ribavirin 30 mg/kg, administered intravenously, followed by 15 mg/kg every 6 hours for 4 days, and then 7.5 mg/kg every 8 hours for an additional 6 days.³⁰ Treatment is most effective if begun within 7 days of onset; lower intravenous doses or oral administration of 2 g followed by 1 g/d for 10 days also may be useful.

The only significant side effects have been anemia and hyperbilirubinemia related to a mild hemolysis and reversible block of erythropoiesis. The anemia did not require transfusions or cessation of therapy in the published Sierra Leone study³² or in subsequent unpublished limited trials in West

Africa. Ribavirin is contraindicated in pregnant women, but, in the case of definite Lassa fever, the predictability of fetal death and the need to evacuate the uterus justify its use. Safety of ribavirin in infants and children has not been established.

A similar dose of ribavirin begun within 4 days of disease is efficacious in patients with HFRS.³³ In Argentina, ribavirin has been shown to reduce virological parameters of Junin virus infection (ie, Argentine hemorrhagic fever), and is now used routinely as an adjunct to immune plasma. However, ribavirin does not penetrate the brain and is expected to protect only against the visceral, not the neurological phase of Junin infection.

Small studies investigating the use of ribavirin

in the treatment of Bolivian hemorrhagic fever and Crimean-Congo hemorrhagic fever have been promising, as have preclinical studies for Rift Valley fever.³³ Conversely, ongoing studies conducted at USAMRMC predict that ribavirin will be ineffective against both the filoviruses and the flaviviruses. No other antiviral compounds are currently available for the VHF agents.

Interferon alpha has no role in therapy, with the possible exception of Rift Valley fever,³⁴ where fatal hemorrhagic fever has been associated with low interferon responses in experimental animals. However, as an adjunct to ribavirin, exogenous interferon gamma holds promise in treatment of arenaviral infections.

IMMUNOPROPHYLAXIS AND IMMUNOTHERAPY

Passive immunization has been attempted for treatment of most VHF infections. This approach has often been taken in desperation, owing to the limited availability of effective antiviral drugs. Anecdotal case reports describing miraculous successes are frequently tempered by more systematic studies, where efficacy is less obvious. For all VHF viruses, the benefit of passive immunization seems to be correlated with the concentration of neutralizing antibodies, which are readily induced by some—but not all—of these viruses.

Passive Immunization

Antibody therapy (ie, passive immunization) also has a place in the treatment of some VHFs. Argentine hemorrhagic fever responds to therapy with two or more units of convalescent plasma that contain adequate amounts of neutralizing antibody (or an equivalent quantity of immune globulin), provided that treatment is initiated within 8 days of onset.³⁵ Antibody therapy is also beneficial in the treatment of Bolivian hemorrhagic fever. Efficacy of immune plasma in treatment of Lassa fever³⁶ and Crimean-Congo hemorrhagic fever³⁷ is limited by low neutralizing antibody titers and the consequent need for careful donor selection.

In the future, engineered human monoclonal antibodies may be available for specific, passive immunization against the VHF agents. In HFRS, a passive immunization approach is contraindicated for treatment, since an active immune response is usually already evolving in most patients when they are first recognized, although plasma containing neutralizing antibodies has been used empirically in prophylaxis of high-risk exposures.

Active Immunization

The only established and licensed virus-specific vaccine available against any of the hemorrhagic fever viruses is yellow fever vaccine, which is mandatory for travelers to endemic areas of Africa and South America. For prophylaxis against Argentine hemorrhagic fever (AHF) virus, a live-attenuated Junin vaccine strain (Candid #1) was developed at USAMRMC and is available as an Investigational New Drug (IND). Candid #1 was proven to be effective in Phase III studies in Argentina, and plans are proceeding to obtain a New Drug license. This vaccine also provides some cross-protection against Bolivian hemorrhagic fever in experimentally infected primates. Two IND vaccines were developed at USAMRMC against Rift Valley fever; an inactivated vaccine that requires three boosters, which has been in use for 20 years; and a live-attenuated RVF virus strain (MP-12), which is presently in Phase II clinical trials.

For Hantaan virus, a formalin-inactivated rodent brain vaccine is available in Korea, but is not generally considered acceptable by U.S. standards. Another USAMRMC product, a genetically engineered vaccinia construct, expressing hantaviral structural proteins, is in Phase II safety testing in U.S. volunteers. For dengue, a number of live attenuated strains for all four serotypes are entering Phase II efficacy testing. However, none of these vaccines in Phase I or II IND status will be available as licensed products in the near term. For the remaining VHF agents, availability of effective vaccines is more distant.

SUMMARY

The VHF agents are a taxonomically diverse group of RNA viruses that cause serious diseases with high morbidity and mortality. Their existence as endemic disease threats or their use in biological warfare could have a formidable impact on unit readiness. Significant human pathogens include the arenaviruses (Lassa, Junin, and Machupo viruses, the agents of Lassa fever and Argentinean and Bolivian hemorrhagic fevers, respectively). Bunyavirus pathogens include RVF virus, the agent of Rift Valley fever; C-CHF virus, the agent of Crimean-Congo hemorrhagic fever; and the hantaviruses. Filovirus pathogens include Marburg and Ebola viruses. The flaviviruses are arthropod-borne viruses and include the agents of yellow fever, dengue, Kyasanur Forest disease, and Omsk hemorrhagic fever.

The dominant clinical features of VHF are a consequence of microvascular damage and changes in vascular permeability. Patients commonly present with fever, myalgia, and prostration. Full-blown VHF syndrome typically evolves to shock and generalized mucous membrane hemorrhage, and often is accompanied by evidence of neurological, hematopoietic, or pulmonary involvement. A viral hemorrhagic fever should be suspected in any patient who presents with a severe febrile illness and evidence of vascular involvement (subnormal blood pressure, postural hypotension, petechiae, easy bleeding, flushing of the face and chest, nondependent edema), and who has traveled to an area where the virus is known to occur, or

where intelligence suggests a biological warfare threat.

Definitive diagnosis rests on specific virological diagnosis, including detection of viremia or IgM by ELISA at presentation. Diagnosis by viral cultivation and identification requires 3 to 10 days or longer and specialized microbiologic containment. Appropriate precautions should be observed in collection, handling, shipping, and processing of diagnostic samples. It is prudent to provide isolation measures that are as rigorous as feasible.

Patients with viral hemorrhagic fevers generally benefit from rapid, nontraumatic hospitalization to prevent unnecessary damage to the fragile capillary bed. Aspirin and other antiplatelet or anticlotting-factor drugs should be avoided. Secondary and concomitant infections including malaria should be sought and aggressively treated. The management of bleeding includes administration of fresh frozen plasma, clotting factor concentrates and platelets, and early use of heparin to control DIC. Fluids should be given cautiously, and asanguineous colloid or crystalloid solutions should be used. Multiple organ system support may be required.

Ribavirin is an antiviral drug with efficacy for treatment of the arenaviruses and bunyaviruses. Passively administered antibody is also effective in therapy of some viral hemorrhagic fevers. The only licensed vaccine available for VHF agents is for yellow fever. Experimental vaccines exist for Junin, RVF, hantaan, and dengue viruses, but these will not be licensed in the near future.

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