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Comments

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Hemorrhagic Fever Viruses

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Viral hemorrhagic fever (VHF) viruses are diverse and include arenaviruses, bunyaviruses, filoviruses, and flaviviruses. Lassa fever, South American hemorrhagic fever (HF), Rift Valley HF, Crimean-Congo HF, Ebola, Marburg, yellow fever, and dengue fever are well known examples of the hemorrhagic fever viruses. They are often difficult to diagnose and treat resulting in significant morbidity and mortality. Transmission varies from vector borne to person-to-person. The common clinical presentation includes fever, myalgia, microvascular damage, and hemorrhage as well as a history of travel to the tropics. If VHF is suspected, strict infection control procedures must be implemented to prevent the spread of these agents within the emergency department. Management of VHF is largely supportive, but ribavirin has been useful for certain viruses. **Key words:** *arenavirus, bioterrorism, bunyavirus, filovirus, flavivirus, hemorrhagic fever, ribavirin*

“COMMON things occur commonly. Uncommon things don't. Therefore, when you hear hoofbeats, think horses, not zebras. What if the hoofbeats, this time, aren't horses?”¹ The risk of exposure to a variety of tropical viral diseases has increased due to continued extension of human inhabitants into tropical rain forests and shifting ecological environments around equatorial regions of the world. The potential to spread viral illnesses worldwide has become a reality with the expansion of international trade in combination with improved access to remote areas with global transportation. Physicians in endemic regions need to be alert to the potential threat of viral hemorrhagic fevers (VHF). In addition, physicians in nonendemic areas need to be able to identify hemorrhagic viral illness in international travelers from tropical regions.

The key for physicians in nonendemic areas to identify a VHF is to know the travel history of the patient, incubation period, and common clinical signs and symptoms of hemorrhagic disease.² Although hemorrhagic fever

clinical presentation varies by virus, some common features include fever, myalgias, and petechiae, which may progress to prostration, microvascular damage, and shock.³ Involvement of the vascular system can manifest as hypotension (vascular dysregulation), organ dysfunction (vascular damage), and hemorrhage, which occurs mainly in patients with thrombocytopenia or platelet dysfunction.² When there is no significant travel history, but clinical features of VHF are present, the clinician might also consider bioterrorism.^{3,4} It is key that physicians be conscious of the potential risk of tropical viral hemorrhagic fevers for a number of reasons: (1) to ensure proper diagnosis and rapid management of index cases; (2) to provide counseling and possible prophylaxis to close contacts; and (3) to minimize the chances of nosocomial transmission among health care staff caring for such patients. All cases of VHF should be reported to state and local health departments as well as the Centers for Disease Control and Prevention.

Viral hemorrhagic fever syndrome refers to a clinical illness caused by a virus belonging to 1 of 4 distinct families: Arenaviridae (eg Lassa and South American HF), Bunyaviridae (eg Rift Valley fever and Crimean-Congo HF), Filoviridae (eg Ebola and Marburg), and Flaviviridae (eg yellow fever and dengue). They are all RNA viruses transmitted to humans via contact with infected animal

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reservoirs or arthropod vectors. Human cases of HF caused by these viruses are geographically restricted to the areas where their host species live or were transported.⁵

Few treatments are available for VHFs. Although there are no FDA approved drugs for the treatment of VHF, ribavirin, a synthetic guanosine analog with antiviral activity against DNA and RNA viruses, has been used clinically against Bunyaviridae and Arenaviridae. Ribavirin is available in both oral and intravenous (IV) dosage forms as well as an oral form in combination with injectable interferon alpha-2b. Ribavirin has poor Central Nervous System penetration, making it relatively ineffective against neurologic effects of VHF viruses. A major adverse effect of ribavirin is dose-related, reversible, hemolytic anemia. Intramuscular injections, aspirin, nonsteroidal anti-inflammatory agents, and anticoagulant therapies are generally contraindicated for VHF and steroids are not effective.⁴

The following is an overview of VHF, clinical features, and medical management available to clinicians.

ARENAVIRUS

Overview

The arenaviruses have been separated on the basis of immunologic and geographic features into New and Old World sets. At least 19 individual viruses have been recognized. Four members of the New World family, Junin (Argentine HF), Machupo (Bolivian HF), Guanarito (Venezuelan HF), and Sabia (Brazilian HF) cause human HF (also referred to collectively as South American hemorrhagic fevers), while Lassa is an Old World virus that causes HF in West Africa (Sierra Leone, Guinea, Liberia, and Nigeria).⁶ All of the arenaviruses causing HF have a specific rodent host with humans being the accidental host. Patients will usually give a history of travel within the last 21 days (maximum incubation period) to West Africa or South America in areas where the rodent host is known to inhabit and contact with

rodent urine and feces, either by aerosolization, ingestion, or direct contact.⁶ Nosocomial person-to-person transmission occurs with Lassa fever, but person-to-person spread of South American HF is unlikely.³ The case-fatality rate ranges from 2% to 15% in Lassa fever and 15% to 30% in the South American HFs.²

Clinical manifestations

Untreated, arenaviral infections are potentially fatal diseases with focal hemorrhagic manifestations and hypovolemic shock. Fever is typically insidious in onset and is accompanied by headache and significant myalgia and malaise. Relative bradycardia is common, as is dysesthesia, particularly hyperesthesia of the skin. Lassa fever, however, usually has less neurologic involvement, thrombocytopenia, leukopenia, and bleeding.⁶ However, when bleeding is present, there is a high viremia or an elevated aspartate aminotransferase; a poor prognosis is more likely.⁷ Most infected individuals defervesce by 10 days, but a small percentage progress rapidly to shock, delirium, respiratory distress, coma, and death.⁶

Infection with South American hemorrhagic viruses typically results in symptomatic illness, the clinical features of which are remarkably similar to those to Lassa fever 3 to 4 days after the onset of fever, malaise, and myalgia. Patients manifest severe prostration, headache, dizziness, back pain, and gastrointestinal disturbances. Conjunctival injection, flushing of the face, orthostatic hypotension, petechiae on the palate and axillae, and bleeding of the gums reflect damage to the vascular bed. Hemorrhage along the gingival margin is a characteristic finding. Neurologic manifestations are common. Laboratory findings early in the course of disease nearly always include thrombocytopenia (platelet count $<100\,000/\text{mm}^3$) and leukopenia (white blood cell count $<4000/\text{mm}^3$). By the second week of the disease, 70% to 80% improve, while the remaining 20% progress over the next week or so with severe hemorrhagic or neurologic manifestations.⁶



Fig 1.

Management

General supportive therapy involves adequate hydration, management of neurologic conditions, blood transfusions, and other supportive measures. Platelet transfusions are probably not useful due to the complex nature of hemorrhage. If initiated within 8 days, transfusion of immune plasma for Argentine HF has reduced mortality to less than 1%.⁸ There is limited human experience with ribavirin for the treatment of South American HFs, but at least 1 study demonstrated a significant drop in viremia for the Junin virus even in the later stages of the disease.⁹ Ribavirin can be used for treatment or prophylaxis of Lassa fever. A 10-day IV course of ribavirin is effective at all stages of illness and oral dosing is effective for postexposure prophylaxis.¹⁰ Alternatively, ribavirin may be given IV for the first 4 days followed by oral dosing to complete the 10-day course.¹¹ Starting ribavirin before day 7 of illness was associated with a higher survival rate.¹⁰ An effective live attenuated Junin virus vaccine is available in South America to prevent Argentine HF in high-risk populations.¹²

BUNYAVIRUS

Overview

The family Bunyaviridae contains at least 41 different tropical viruses, including those that cause Crimean-Congo hemorrhagic fever

(CCHF), Rift Valley fever (RVF), HF with renal syndrome, and hantavirus pulmonary syndrome. A tick-borne viral illness, CCHF causes severe hemorrhagic manifestations and occurs mainly in tropical Africa, temperate Europe, and as far east as China.¹³ The disease is generally rural in distribution and arises mainly among farm workers, many of whom recount a history of tick bite or of squeezing ticks with their fingers. Nosocomial transmission of CCHF is common.^{14,15} The case-to-infection ratio approaches 100%, with a case-fatality rate of 15% to 30%.²

Rift Valley fever is primarily a mosquito-borne (*Aedes* sp.) viral disease of sheep and cattle but humans can acquire the infection from aerosols generated from body fluids and tissues of diseased animals or from bites of infected mosquitoes. Person-to-person transmission has not been reported. Based on virus isolations, RVF occurs endemically during the rainy season throughout most of sub-Saharan Africa and more recently, in the Middle East.^{16,17} In 1977, an epidemic of RVF occurred in Egypt, infecting over 200 000 and killing 600.¹⁸ The case-to-infection ratio is only about 1%, but the case-fatality rate is over 50% and nearly 100% for animals it infects.²

Clinical features

Crimean-Congo hemorrhagic fever is a severe hemorrhagic fever with shock, disseminated intravascular coagulation, and severe

thrombocytopenia. In about 80% of cases, CCHF is subclinical.¹³ After an incubation period of 3 to 9 days, CCHF begins swiftly with fever, headache, nausea, myalgia, vomiting, abdominal pain, and conjunctival injection.¹⁹ In about half of the cases, hepatomegaly is evident. Hemorrhagic manifestations do not generally appear before the third or fourth day of the illness. The onset of the hemorrhagic phase is marked by the appearance of purpura on the skin and mucous membranes, which lasts 3 to 6 days. Hemorrhages also develop from the nose, gums, and buccal cavity. In severe cases of CCHF, gastric, uterine, intestinal, genitourinary, and pulmonary hemorrhages occur. In patients with profuse hemorrhage, tachycardia, shock, and death may occur. If the patient survives the hemorrhagic phase of the disease, by the ninth or tenth day recovery begins and a 2- to 6-week period of slow convalescence follows. Viremia is intense and prolonged in CCHF, especially in fatal cases. Blood from these patients should be treated with extreme care.¹³

The incubation period of RVF is 3 to 7 days; onset is sudden, with chills, myalgia, joint pains, headache, and a biphasic fever that lasts about 1 week. The patient often complains of nausea, vomiting, and abdominal fullness and pain. There is bradycardia, and there may be slight tenderness over the liver, which may be enlarged. Many patients become delirious, and some have hallucinations. Three main complications of RVF include encephalitis, optic neuropathy, and hepatitis. About 10% of patients experience optic neuritis, which manifests as cotton-wool exudates on the macula.²⁰ Death usually follows massive gastrointestinal hemorrhage, oliguria, anuria, and acute renal failure after 3 to 6 days.¹³

Management

An inactivated vaccine is available from the US military for RVF and outside the United States there is a vaccine for CCHF. For RVF, interferon alpha has been used in doses of 5×10^5 units/kg for 5 days for primates.¹³ When ribavirin was used in Rhesus monkeys with experimental RFV, a significant decline in viremia was noted, but human trials have

not been done.²¹ The combination of ribavirin and interferon, RebetronTM, is not approved for RVF and published experience is absent. For CCHF, immune serum appears useful when given early in infection and at a dose of 250 mL IV over 1 to 2 days.¹³ Ribavirin has in-vitro activity against CCHF, but controlled clinical trials are lacking. A published report suggests that ribavirin given for postexposure prophylaxis at an IV or PO dose of 2 g to load, then 4 g/day in 4 divided doses for 4 days, finally dropping to 2 g/day for 6 days for a total of 10 days was beneficial at preventing death.²²

FILOVIRUS

Overview

The family Filoviridae is composed of 2 distinctive species, Marburg and Ebola, with specific subtypes for each named after the country where the virus was isolated in relation to an outbreak (eg Ebola, Zaire). Ebola was first described in 1976 in the Sudan and Zaire. Twice Ebola has surfaced in the United States as a result of infected primates, in Reston Virginia in 1989 and in Texas in 1996, but neither event resulted in spread beyond lab workers, who remained asymptomatic, or the infected primates.²³ Both Ebola and Marburg are rare infections, making it difficult to study them in a controlled manner. The natural reservoir for Ebola is unknown, but it appears to be effectively transmitted person-to-person via contaminated blood and bodily fluids or reused needles and from animal to human.²⁴ Filoviruses are exceedingly virulent in humans, with case-fatality rates up to 100%.²⁵

Clinical features

Both Ebola and Marburg virus infections have a similar course of illness. Following a 5- to 10-day incubation period there is an abrupt onset of fever usually associated with myalgia and severe frontal headache. Disease progression is characterized by nausea, pharyngitis, photophobia, severe vomiting of blood, and diarrhea. Hemorrhagic symptoms include

epistaxis, bleeding gums, hematemesis, and bleeding from sites of needle insertion.²⁶ After 5 to 7 days, a nonpruritic maculopapular rash develops. Neurologic symptoms include somnolence, delirium, or coma. A poor prognosis is marked by hemorrhagic signs, as well as oliguria or anuria, chest pain, shock, tachypnea, and neurologic symptoms. If fatal, death occurs 6 to 9 days after onset of the clinical disease and results from severe blood loss and shock. Clinical laboratory findings show an early lymphopenia and a thrombocytopenia. Liver function enzyme levels (aspartate aminotransferase and alanine aminotransferase) are elevated. Viral isolation is not practical since it requires a biosafety level 4 laboratory; thus samples must be sent to the Centers for Disease Control and Prevention for confirmation.

Management

Ribavirin does not have good in-vitro activity against Ebola and Marburg and has not been shown to be effective in animals.²⁷ Therapy centers around supportive care, primarily volume replacement, correcting electrolyte imbalances, pressure support, and transfusions and heparin for disseminated intravascular coagulation. Convalescent immune serum and human interferon probably have limited utility as clinical experience is lacking and in-vitro data suggests IV fluids have not reversed hypotension and may have contributed to pulmonary edema.

FLAVIVIRIDAE

Overview

Flaviviridae are a diverse group of RNA viruses containing *Hepacivirus* (Hepatitis C) and the genus *flavivirus*, which causes yellow fever (YF), dengue hemorrhagic fever (DHF), Japanese encephalitis, and tick-borne encephalitis. Yellow fever is a mosquito-borne (*Aedes aegypti*) infection endemic to nonurban areas of tropical South America and sub-Saharan Africa. Up to 50% of hemorrhagic-fever-related mortality worldwide can be attributed to YF.²⁸ The World Health Organi-

zation estimates that there are over 200 000 cases annually of YF and over 6400 deaths, with more than 90% acquired in Africa.²⁹ The case-fatality rate varies from 20% to 50%.² A highly effective live attenuated vaccine is available in the United States and abroad for the prevention of YF. Since 1996, 3 deaths have occurred in unvaccinated people, most recently in a returned traveler from the Amazon.³⁰ Dengue fever (DF) virus is fast on its way to becoming the world's major emerging infection. Transmitted by mosquito bites (*A. aegypti* and *A. albopictus*) during the day in about 101 countries, DF infects about 50 to 100 million people worldwide and DHF affects about 250 000 to 500 000.³¹ More than half of the world's population lives in a DF-infected area, including the United States. In the United States, Texas and Hawaii have recently experienced DF outbreaks, adding to the approximate 20 cases per year of laboratory confirmed imported DF cases.³² Case-fatality rates for DHF vary from <1% to 5% up to 12% to 44% for dengue shock syndrome, a variant of DF.³³

Clinical features

Yellow fever

After a 3- to 6-day incubation period, there is an abrupt onset of flu-like symptoms including fever, chills, malaise, headache, myalgia, nausea, and dizziness. Classic YF displays 3 clinical periods: infection (sudden onset of flu-like symptoms with bradycardia), remission (lasting about 24 hours before the return of symptoms), and intoxication (jaundice, albuminuria, oliguria, cardiovascular instability, hemorrhagic manifestations).²⁸ When death occurs, it usually happens around day 7 to 10 as a result of ongoing liver failure and metabolic acidosis.

Dengue hemorrhagic fever

Dengue fever manifests with a sudden onset of fever and flu-like symptoms that spontaneously resolve after 3 to 7 days. Circulating antibodies from a previously acquired DF infection appear to be a strong indicator of progression to DHF.³¹ Classically, DHF is a

disease of children, characterized by a sudden onset of fever with other non-specific symptoms. Unfortunately, there is no pathognomonic sign or symptom to help clinicians differentiate DHF from other childhood illnesses and many infections are asymptomatic. The World Health Organization provides a classification of DF from grade 1 to 4 based on severity of illness. As the illness progresses through the stages of infection, the patient begins to experience hemorrhagic symptoms (skin, gums, and gastrointestinal tract) with thrombocytopenia, circulatory failure, shock, and finally death.

Management

Prevention through vaccination and mosquito bite avoidance are the mainstays of minimizing the risk of YF. A single dose of the 17D live attenuated vaccine after 10 days provides nearly complete protection for at least 10 years.³⁴ A combination of DEET insect repellent (at least 30%) applied to the skin and permethrin insecticide applied to the clothing, both worn during the day, is an important means of preventing bites from mosquitoes carrying DF or YF. Although ribavirin may be effective in the treatment of arenaviruses and bunyaviruses, it does not appear to be effective in the treatment of flavivirus infections, including DHF and YF.²⁷ Experience is limited with severe YF infection, but symptomatic management of fluids, electrolytes, and circulatory support appears warranted. Dengue hemorrhagic fever often responds to early fluid replacement, often with reversal of disseminated intravascular coagulation.³⁵ Early intervention for shock re-

quires knowing how much time has elapsed since the onset of infection (DHF usually occurs around day 3 to 7) and monitoring for a rapidly decreasing platelet count with a rising hematocrit.³¹ There is no vaccine or drug available for the prevention or treatment of DF.

RECOMMENDATIONS

Viral hemorrhagic fevers are primarily imported diseases from the tropics. Emergency Department personnel should be aware of the clinical presentation, management, and infection control procedures for VHF. When a VHF is highly suspected, it is important to institute strict infection control procedures (ie personal protective measures, contact, and respiratory isolation) for arenaviruses, such as that causing Lassa fever, bunyaviruses, such as that causing Crimean-Congo hemorrhagic fever, and filoviruses, such as Marburg and Ebola, due to their potential for person-to-person transmission. Local and state health department and the Centers for Disease Control and Prevention should be notified immediately when a case of VHF is suspected. In the event of a VHF related to bioterrorism, the Working Group on Civilian Biodefense has issued guidelines for isolation precautions, personal protective equipment, laboratory testing, postmortem practices, and environmental decontamination.⁴ In the words of one of the world's foremost virus hunters, "I don't pretend to be able to predict what the next great disease will be . . . [however] I believe it is possible to identify some of the most dangerous pieces of the puzzle beforehand."¹

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