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A Current Review of Ebola Virus: Pathogenesis, Clinical Presentation, and Diagnostic Assessment

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Ebola hemorrhagic fever (EHF) is an acute viral syndrome that presents with fever and an ensuing bleeding diathesis that is marked by high mortality in human and nonhuman primates. Fatality rates are between 50% and 100%. Due to its lethal nature, this filovirus is classified as a biological class 4 pathogen. The natural reservoir of the virus is unknown. As a result, little is understood about how Ebola virus is transmitted or how it replicates in its host. Although the primary source of infection is unknown, the epidemiologic mode of transmission is well defined. A variety of tests have proven to be specific and useful for Ebola virus identification. There is no FDA-approved antiviral treatment for EHF. Incubation ranges from 2 to 21 days. Patients who are able to mount an immune response to the virus will begin to recover in 7 to 10 days and start a period of prolonged convalescence. Supportive management of infected patients is the primary method of treatment, with particular attention to maintenance of hydration, circulatory volume, blood pressure, and the provision of supplemental oxygen. Since there is no specific treatment outside of supportive management and palliative care, containment of this potentially lethal virus is paramount. In almost all outbreaks of EHF, the fatality rate among health care workers with documented infections was higher than that of non-health care workers.

Key words: *Ebola virus, Ebola hemorrhagic fever, immunity, T cell, bioterrorism*

Ebola hemorrhagic fever (EHF) is an acute viral syndrome that presents with fever and an ensuing bleeding diathesis that is marked by high mortality in human and nonhuman primates. It is caused by Ebola virus, a lipid-enveloped, negatively stranded RNA virus that belongs to the viral family Filoviridae (World Health Organization 1997). In 1976, the first reported cases of Ebola fever surfaced during 2 simultaneous outbreaks in southern Sudan and the Democratic Republic of

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As this article goes to press, a total of 61 cases (48 deaths) of acute hemorrhagic fever syndrome have been reported in the Cuvette West region of the Republic of Congo. Ebola hemorrhagic fever (EHF) is suspected due to the presence of Ebola virus collected from dead gorillas in the same region. Confirmation of EHF in humans has not been possible due to the refusal by the local inhabitants to give blood samples. However, officials believe that the cause of the current outbreak may have been the villagers eating infected primates.

Congo (formerly Zaire). Fatality rates reached 53% and 88%, respectively (Klenk and others 1995; Centers for Disease Control and Prevention [CDC] Special Pathogens Branch 2002a). From that time until January 2003, 10 significant Ebola fever outbreaks have occurred in Africa involving more than 1600 cases of infection and 1100 fatalities (Figure 1). In addition, there have been a small number of subclinical infections in the United States and the Philippines from the Reston strain of the virus, which is harmless to humans but lethal for monkeys (CDC Special Pathogens Branch 2002b). Despite concerted investigative efforts, the natural reservoir of the virus is unknown. As a result, little is understood about how Ebola virus is transmitted or how it replicates in its host. However, based on evidence from similar viruses, it is theorized that the virus is zoonotic and therefore is maintained by an unidentified animal host (Peters and LeDuc 1999; World Health Organization 2000; CDC Special Pathogens Branch 2002b). The fact that outbreaks of EHF have coincided with the end of the African rainy season may provide a clue to the natural ecology of Ebola virus and to the host, which may be influenced by this weather cycle (Carballal 1996).

Pathogenesis and Transmission

Due to its lethal nature, this filovirus is classified as a biological class 4 pathogen. Three subtypes of the virus have been identified as pathogenic for humans: Ebola Zaire, Ebola Sudan, and Ebola (Côte d'Ivoire) Tai (World Health Organization 1997) (Figure 1). The infection generally involves necrosis of the liver, spleen, kidney, lymph nodes, testes, and ovaries due to viral replication within parenchymal cells (Klenk and others 1995; Collier and others 1998; Feldmann and others 1999; Klenk and Feldmann 2001; Borio and others 2002). More significant effects are microvascular damage, changes in vascular permeability, and activation of the clotting cascade (Jahrling and others 1990; Feldmann and others 1999). Damage to platelets and endothelial cells results in the disruption of fluid balance and homeostasis (Klenk and others 1995; Feldmann and others 1999; Chen and Cosgriff 2000; Borio and others 2002). In addition, the virus is believed to compromise and suppress immu-

nological function (Collier and others 1998; Baize and others 1999; Connolly and others 1999; Feldmann and others 1999; Klenk and Feldmann 2001; Baize and others 2002; Borio and others 2002).

Although the primary source of infection is unknown, the epidemiologic mode of transmission is well defined. Ebola fever outbreaks among humans begin with an index case that is subsequently transmitted to secondary individuals by close, intimate contact with blood, body secretions, excretions, organ tissue, or semen; nosocomial infection precipitated by the reuse of unsterilized syringes and failure to follow the universal precautions of barrier nursing; or unhygienic practices, such as unsterile burial customs involving the rigorous external and internal cleansing of an infected corpse (Jahrling and others 1990; World Health Organization 1997; Dowell and others 1999; Roels and others 1999; Zaki and others 1999; Schou and Hansen 2000; CDC Special Pathogens Branch 2002b). The main routes of infection are through mucous membranes, the conjunctiva, and small skin breaks (Peters and others 1996; Peters and LeDuc 1999). Case reports of hospital personnel acquiring the disease that are not attributable to the percutaneous route suggest that rubbing one's eye after caring for a patient with acute illness transmits enough inoculum to produce clinical infection. Aerosol dissemination of Ebola virus has not been established as a mode of transmission in humans. However, in nonhuman primates, this mode of transmission has been associated with disease (Peters and others 1996; World Health Organization 1997; Peters and LeDuc 1999; Schou and Hansen 2000; CDC Special Pathogens Branch 2002b). There is no evidence of communicability during the viral incubation period with nonfebrile, asymptomatic individuals (World Health Organization 1997). Isolated cases of transmission between individuals convalescing from EHF and close household contacts have been found and are primarily attributed to sexual contact. Rowe's (1999) cohort prospective study described a case involving a male convalescent who had Ebola viral antigen still present in seminal fluid almost 3 months after the initial diagnosis. Transmission risk does increase significantly with direct patient contact during the acute disease phase (Dowell and others 1999).

Figure 1. Ebola hemorrhagic fever diagnosed cases and fatalities by country in Africa, 1976-2002.

Clinical Presentation and Diagnosis

Incubation ranges from 2 to 21 days (World Health Organization 1997; Borio and others 2002). The variable clinical presentation of Ebola fever can make differential diagnosis difficult. Early symptoms may resemble influenza, malaria, typhoid fever, fulminant hepatitis, sepsis, nontyphoidal salmonellosis, various forms of encephalitis, dengue fever, yellow fever, Lassa fever, Marburg, and other hemorrhagic diseases. Confounding noninfectious syndromes with hemorrhage such as acute leukemia, lupus erythematosus, idiopathic or thrombotic thrombocytopenia purpura, and hemolytic uremic syndrome also fall into the differential diagnosis (Jahrling and others 1990; Schou and Hansen 2000; Borio and others 2002). Thus, clinical diagnosis is presumptive until there is laboratory confirmation of Ebola virus (Zaki and others 1999). Typically, the onset of Ebola fever is sudden, with most cases presenting in 5 to 12 days. The clinical symptoms begin with a nonspecific prodrome. Early symptoms can include acute fever, chills, myalgia, headache, arthralgia, and anorexia. Nausea, vomiting, abdominal pain, hypotension, tachypnea, relative bradycardia, conjunctivitis, conjunctival injection, pharyngitis, and diarrhea, which may be bloody, are other evolving signs. Cutaneous flushing or prominent, nonpruritic, maculopapular centripetal rash are common (World Health Organization 1997; Villinger and others 1999). Infected women who are pregnant frequently abort (Collier and others 1998). Dehydration and wasting are present as the disease advances (World Health Organization 1997). Later, the illness may develop into a progressive hemorrhagic diathesis that features epistaxis, hematuria, hematemesis, petechiae, melena, and mucous membrane and conjunctival hemorrhage (World Health Organization 1997; Borio and others 2002). Hemorrhaging usually occurs from the gastrointestinal tract, lungs, and gingiva (Klenk and others 1995). As the vascular bed is the main target of Ebola virus, disseminated intravascular coagulation (DIC) becomes the dominant clinical feature (Jahrling and others 1990). Abnormal laboratory findings typically indicate leukopenia with a left shift, atypical lymphocytes, thrombocytopenia, elevated transaminase levels, hyperproteinemia, proteinuria, hematuria, and prolonged bleeding time, prothombin time, and activated

partial thromboplastin time (Collier and others 1998; Borio and others 2002). There may be central nervous system involvement that results in delirium, somnolence, or convulsions (World Health Organization 1997; Borio and others 2002). These symptoms, in addition to DIC, are indicative of poor prognosis. Patients who are able to mount an immune response to the virus will begin to recover in 7 to 10 days and start a period of slow, prolonged convalescence involving complications such as weakness, fatigue, hepatitis, uveitis, and other clinical sequelae (Borio and others 2002). Patients who do not improve by the 1st week usually experience multiorgan failure and die from hypovolemic shock, with or without blood loss (Klenk and others 1995; World Health Organization 1997).

Laboratory Diagnosis

The virologic and immunologic consequences of EHF are different in acute, early fatal cases of disease than in less severe cases that eventually recover. Identification of Ebola virus should not be required for the initial diagnosis of EHF. Given the early nonspecific symptoms, however, a high index of suspicion is needed in making this diagnosis. The presentation of abrupt illness, high fevers ($>101^{\circ}\text{F}$) of less than 3 weeks' duration, no predisposing factors for hemorrhagic manifestations, and at least 2 hemorrhagic symptoms (e.g., epistaxis, bloody stools, or hemoptysis) generally constitutes ample evidence to at least consider EHF and begin supportive treatment until such time that laboratory confirmation is available (Borio and others 2002). Nevertheless, specific diagnosis of EHF requires laboratory evidence of viral antigens and/or the presence of specific IgM or IgG antibodies, in addition to clinical symptoms (Rowe and others 1999).

A variety of tests have proven to be specific and useful for Ebola virus identification. Antigen-capture enzyme-linked immunosorbent assay (ELISA) for IgM and IgG antibodies can prove a useful diagnostic tool. IgM antibodies to Ebola virus appear between 2 and 9 days after symptoms begin and disappear between 30 and 168 days after. IgG antibodies appear between days 6 and 18 after symptom onset. IgG antibodies persist for many months.

Viral antigen detection by ELISA and reverse transcriptase polymerase chain reaction (RT-PCR) are particularly useful tests that are rapid and sensitive. Ebola

viral antigen is detectable in the blood by 3 to 6 days after symptom onset, but antigen positivity disappears 7 to 16 days after symptoms have begun. Antigen disappearance reflects effective immune response and viral containment. Currently, there are only 2 laboratories in the United States that are capable of appropriate biosafety containment procedures for safe isolation of Ebola virus (Ksiazek, Rollin, and others 1999; Ksiazek, West, and others 1999; Rodriguez and others 1999). Consequently, this method of diagnosis has limited clinical value. Indirect fluorescent antibody tests are easily performed but have demonstrated a lack of specificity and a tendency to produce false positives (Ksiazek, Rollin, and others 1999). In summary, definitive laboratory diagnosis of Ebola virus requires ELISA and RT-PCR capability, which is presently not practical in the field or other settings where outbreaks are likely to occur (Jahrling and others 1990).

In 1995, Dr. Sherif Zaki of the CDC developed a colorimetric test that can identify Ebola virus in formalin-preserved skin biopsies from fatal cases of suspected EHF infection. The formalin inactivates the virus, rendering the specimen safe for transport and obviating the need for a special lab. Results can be available within 24 h. Although the samples must be taken posthumously, this diagnostic immunohistochemical test could prove to be a reliable surveillance device in the field when EHF is suspected (Zaki and others 1999). The CDC has made this skin biopsy kit available but requires all specimens to be sent to the United States for analysis. Current literature has not documented the widespread use of this test in the field as a tool to determine when to initiate infection control procedures.

Management Guidelines

There is no FDA-approved antiviral treatment for EHF (Borio and others 2002; CDC Special Pathogens Branch 2002b). Ribavirin is not effective against any of the filoviruses and has no clinical utility (CDC Special Pathogens Branch 2002a). All patients require close supervision and/or intensive care support. Supportive management of infected patients is the primary method of treatment, with particular attention to maintenance of hydration, circulatory volume, and blood pressure and the provision of supplemental oxygen.

Injectors, catheters, and parenteral interventions must be minimized to avoid trauma and the increased risk of transmission (CDC Special Pathogens Branch 2002a). Aspirin, nonsteroidal anti-inflammatory drugs, anticoagulant therapies, and steroids are contraindicated (Borio and others 2002).

Patients with Ebola fever presenting with hypotension and shock are difficult to manage. The administration of intravenous fluids can easily evolve into pulmonary edema. Thus, asanguineous fluids should be used judiciously (Jahrling and others 1990; Franz and others 1997; Borio and others 2002). In addition, the management of bleeding is controversial given the development of DIC in severe disease. Mild bleeding should not be treated when there is no evidence of DIC. Conversely, it has been advocated that DIC should be treated prophylactically through the replacement of coagulation factors and platelets; when DIC is confirmed by definitive laboratory findings, heparin therapy should commence (Jahrling and others 1990).

A significant management issue also entails appropriate considerations for close contacts of individuals diagnosed with the disease. Long-term observation of healthy household contacts (HHCs) revealed episodes of symptoms that were consistent with the outbreak clinical definition of EHF (fever and 3 accompanying symptoms or unexplained bleeding), but these individuals did not test positive for IgM or IgG antibodies (Rowe and others 1999). Indeed, there are many possible causes for fevers, constitutional symptoms, and bleeding episodes. The fact that antibody-negative HHCs frequently met the clinical criteria for EHF underscores the point that the "outbreak case" clinical definition should not be used alone for endemic disease detection, and it points to the need for laboratory diagnosis. Initial testing of at-risk individuals discovered some contacts who were seropositive and had a history either of mild symptoms or of being asymptomatic (Rowe and others 1999). The reasonable presumption would be that milder and asymptomatic forms of infection do occur.

Nursing Implications

Since there is no specific treatment outside of supportive management and palliative care, containment of this potentially lethal virus is paramount. During the 1995 Ebola fever outbreak in the Democratic Republic

Table 1. Human Pathogenic Ebola Outbreaks since 1976

Year	Subtype	Country	Region	Total Cases ^a	Fatalities ^b		HCW ^c Cases ^d		HCW Fatalities ^e	
					<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
1976	Sudan	Sudan	Nzara, Maridi, and surrounding area	284	141	50	76	27	41	54
1976	Zaire	Zaire	Yambuko and surrounding area	318	280	88	13	4	11	85
1976	Sudan	England	Porton Down, Salisbury	1	0	0	1	100	0	0
1977	Zaire	Zaire	Tandala	1	1	100	0	0	0	NA
1979	Sudan	Sudan	Nzara	34	22	65	No data ^f		No data ^f	
1994	Zaire	Gabon	Mékouka and other encampments, Makokou area	49	32	65	No data ^f		No data ^f	
1994	Taï	Côte d'Ivoire	Taï National Forest	1	0	0	1	100	0	0
1995	Taï	Liberia	Plibo Village, Maryland County	1	0	0	0	0	0	NA
1995	Zaire	Democratic Republic of Congo	Kikwit and surrounding area	315	245	78	80	25	63	79
1996	Zaire	Gabon	Mayibout II area	31	21	68	No data ^f		No data ^f	
1996/1997	Zaire	Gabon	Libreville, Booué area, Lambarene	60	45	75	No data ^f		No data ^f	
1996	Zaire	South Africa	Johannesburg (via Libreville, Gabon)	2	1	50	2	100	1	50
2000/2001	Sudan	Uganda	Gulu, Masindi, and Mbarara districts	425	224	53	29	7	17	59
2001/2002	Zaire	Gabon	Mekembo district	65	53	82	1	2	1	100
2001/2002	Zaire	Republic of Congo	Mbomo district and Kellé district	58	44	76	No data ^f		No data ^f	

a. Total number of individuals diagnosed with Ebola hemorrhagic fever (EHF).

b. Total number of EHF fatalities and percentage of EHF fatalities.

c. Health care workers (HCW) include physicians, nurses, laboratory workers, scientists, hospital aides, and missionary workers involved with direct patient contact.

d. Total number of HCWs diagnosed with EHF and percentage.

e. Total number of HCW EHF fatalities and the percentage of HCW EHF fatalities.

f. No data denote insufficient information on numbers regarding HCWs diagnosed with EHF.

of the Congo, it is worth noting that 25% of the cases were among health care workers who provided direct care to patients with this infection (Table 1). After the implementation of barrier nursing techniques, only 1 new case among 80 health care workers was reported (Arthur 2002). During the 2000 EHF outbreak in the Gulu district of Uganda, 14 of 22 (64%) health care workers were infected after establishing isolation wards ("Outbreak of Ebola Hemorrhagic Fever" 2001). It is unclear if these situations were an exception and if these health care workers were diligent in following the barrier nursing protocol. The Gulu outbreak emphasizes the importance of strict infection control measures. In all other outbreaks in which barrier nursing procedures have been followed, the infection of health care workers has been significantly reduced.

As with other illnesses requiring the level and duration of contact associated with hospitalization, nurses are on the front lines in the care of patients with Ebola virus. Hence, important nursing implications such as barrier/infection control nursing techniques are critical if person-to-person transmission is to be avoided. Along those lines, the CDC and the World Health Organization have developed a manual detailing procedures that reduce the risk of transmission, which can be accessed at www.cdc.gov/ncidod/dvrd/spb/mnpages/vhfmanual.htm. These guidelines also make use of common and easily accessible supplies such as household bleach, water, plastic sheeting, and so on, which patients can be educated to use in their homes. The observance of strict infection control by bedside nurses and all levels of health care providers who eval-

uate or treat these patients is critical. Infection control techniques should include

- use of protective clothing featuring masks, gowns, and double gloves;
- hand washing with disinfectant rinse followed by soap and water;
- patient isolation;
- autoclaving or disinfecting of all contaminated materials with bleach;
- needle precautions;
- proper containment, disinfection, and disposal of biohazardous materials;
- appropriate labeling of specimens; and
- strictly limited access to patients (World Health Organization 1997; Borio and others 2002; CDC Special Pathogens Branch 2002b).

It should also be noted that in almost all outbreaks of EHF, the fatality rate of healthcare workers (physicians, nurses, laboratory workers, scientists, hospital aides, and missionary workers involved with direct patient contact) with documented infections was higher than that of non-healthcare workers (Table 1). Thus, barrier nursing and other protocols are crucial, not only for containing the virus but also for protecting healthcare workers.

Summary

Since its discovery in 1976, Ebola fever has emerged as one of the deadliest known forms of hemorrhagic fever. Ebola virus is a class 4 pathogen belonging to the family Filoviridae, which causes fever and severe hemorrhaging and for which there is no specific treatment. Transmission among humans occurs through the exchange of blood and body secretions. Nosocomial infection and improper hygiene practices are also prominent means of transmission. Containment of Ebola virus greatly depends on the isolation of infected patients along with the strict observance of barrier nursing techniques and adherence to universal precautions for the handling of infectious material. Survival of infection depends on the ability of an individual to mount an effective immune response. Reports that histologic inflammatory responses are conspicuously absent in Ebola viral infec-

tion may reflect the overwhelming acute infection and the predilection the virus has for endothelial cells and platelets. Effective containment of Ebola fever greatly depends on the isolation of the infected patients, and the careful adherence to barrier nursing techniques and universal precautions for the handling of infectious materials. The future awaits development of an effective Ebola virus vaccine.

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