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Major article

Ebola virus disease: What clinicians in the United States need to know

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In March 2014 the World Health Organization was notified of an outbreak of Ebola virus disease (EVD) in the forest region of Guinea. As of May 2015, the outbreak had become the most devastating EVD epidemic in history with more than 27,000 cases and more than 11,000 deaths. The introduction of EVD into noncontiguous countries, including the United States, from infected travelers highlights the importance of preparedness of all health care providers. Early identification and rapid isolation of patients suspected with EVD is critical to limiting the spread of Ebola virus. Additionally, enhanced understanding of EVD case definitions, clinical presentation, treatment procedures, and infection control strategies will improve the ability of health care workers to provide safe care for patients with EVD.

The Ebola virus disease (EVD) epidemic currently in West Africa has evolved into a full-scale humanitarian crisis. As of May 24, 2015, 27,013 cases of EVD with 11,134 deaths had been reported to the World Health Organization from Guinea, Liberia, and Sierra Leone.[1] This includes 869 cases and 507 deaths of health care personnel.[1] An additional 32 cases and 15 deaths linked to this outbreak have been reported from Nigeria, Senegal, Mali, Spain, and the United States.[1] It is likely that cases reported to World Health Organization are substantial underestimates.[2] Due to heroic efforts by public health and health care personnel on the front lines, the number of EVD cases has declined substantially in affected West African countries, and although EVD cases are continuing to occur as of May 2015, the number of EVD cases has been far less than modeling projections.[3,4]

The long incubation period (typically 8-10 days, but up to 21 days) and an increasingly interconnected global community increases the likelihood that other individuals from West Africa with EVD infection will travel to the United States and other countries. Indeed, the first imported case of EVD in the United States was identified in a traveler from Liberia resulting in 2 secondary cases in health care personnel who cared for the index case.[5] Early recognition of suspect cases of EVD is critical to prevention of secondary EVD transmission. In addition to vigilance, health care providers can benefit from increased preparedness, including a working knowledge of EVD case definitions, clinical presentation, treatment, and strategies to protect themselves and others while caring for patients with suspected or confirmed EVD. The Centers for Disease Control and Prevention (CDC) website regularly posts updated information and guidance related to the care of patients with EVD (www.cdc.gov/vhf/ebola/).

The genus *Ebolavirus*, first discovered in 1976 during simultaneous outbreaks in Yambuku, Zaire, and Nzara, Sudan, causes a severe acute viral illness with a case fatality ratio of 45%-88%.[6] In nearly 40 years since, there have been 25 outbreaks with more than 2,600 cases and more than 1,500 deaths before the current outbreak. The current West African EVD outbreak has now infected and killed more people than all previous outbreaks combined. There are 5 known species that comprise the genus *Ebolavirus*. The etiologic species of the current outbreak is *Zaire ebolavirus* (EBOV). Ebola virus is nonsegmented negative sense, single-stranded RNA-enveloped virus that is detected

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Table 1
Signs and symptoms associated with Ebola virus disease[4,12,16]

Presenting signs and symptoms	All patients (%)
Fever (measured)*	84-89
Fatigue	65-76
Headache	53-80
Aching muscles or joints	39
Vomiting	43-68
Diarrhea	61-67
Abdominal pain	44-46
Unexplained hemorrhage (including miscarriage)	18-19
Weakness	79

*Fever was reported in 84%-89% of patients; thus fever is not always present.[4]

in a number of body fluids of infected patients, including blood, diarrhea, vomit, sweat, breastmilk, vaginal secretions, and semen.[7,8] Transmission occurs through direct contact between infectious body fluids of a symptomatic patient with EVD and breaks in the skin and/or mucous membranes of an uninfected person, and thus can be interrupted with barrier precautions and disinfection. Despite this knowledge, EBOV transmission continues unabated was widespread during 2014-2015 in some countries in West Africa.

Patients with EVD initially present with nonspecific symptoms, including fever, chills, fatigue, malaise, anorexia, asthenia, weakness, maculopapular rash, and myalgia (Table 1).[4,7] After several days, abdominal pain and pronounced gastrointestinal symptoms occur. Vomiting and especially profuse watery diarrhea can result in intravascular volume depletion and electrolyte abnormalities, including hypo- and hypernatremia, hypokalemia, hypomagnesaemia, and hypocalcemia.[9-12] In most cases the profound volume loss from diarrhea leads to a decrease in effective circulating volume, poor organ perfusion, and eventually multiorgan failure and shock. Conjunctival injection, chest pain, headache, and joint pain have also been noted. Respiratory symptoms, including shortness of breath and a nonproductive cough occur in a minority of patients but may be more frequently observed in resource-rich countries where the possibility of more aggressive volume resuscitation may lead to a comprise in oxygenation.[4] Neurologic signs may occur, including seizures, confusion, delirium, and coma. Hiccups may also occur later in the clinical course. Hemorrhagic manifestations, including petechiae, ecchymosis, oozing from venipuncture sites, mucosal hemorrhage, hematemesis, melena, or frank hemorrhage occur in 30%-50% of cases but blood loss is rarely sufficient to be the cause of death.[7,13,14] Pregnant women often experience spontaneous miscarriages and significant bleeding.[15] There are no approved antiviral therapeutics or vaccines.

IDENTIFICATION OF PATIENTS SUSPECTED OF EVD INFECTION: PERSONS UNDER INVESTIGATION (PUI)

Early identification and isolation of patients suspected of having EVD infection is critical to controlling the spread of EBOV.[16,17] A patient who has both signs and symptoms consistent with EVD and an epidemiologic risk factor, including a history of travel in a country with widespread EBOV transmission or contact with a symptomatic EVD patient within the preceding 21 days, is referred to as a PUI (Table 2).[18] The epidemiology link is further stratified into high, some, low (but not 0), and no identifiable risk (Table 2). Although travelers returning from affected West African countries may have fever from a number of different infectious diseases, EVD should be considered immediately to protect health care workers, and interventions should be implemented to prevent ongoing transmission. Once identified as a PUI case of EVD, patients must be quickly triaged into the categories of confirmed cases or those without EVD.[17]

Evaluation of PUIs is dependent on 3 components:

1. Epidemiologic risk factors (Table 2),
2. Clinical findings (Table 1), and
3. Laboratory confirmation.

Laboratory confirmation

As soon as a PUI is identified, the patient should be isolated and recommended infection control precautions should be implemented immediately (see below). The local and state health departments should be notified, and arrangements made to collect blood for plasma to be tested by reverse transcription polymerase chain reaction (RT-PCR) assay at a qualified laboratory. On August 6, 2014, the Food and Drug Administration issued an Emergency Use Authorization to allow use of a RT-PCR assay in the diagnosis of EVD.[19] This specimen should be obtained following recommended precautions because of the potential for EBOV transmission associated with percutaneous exposure (see below).[20] Blood can be tested by the Laboratory Response Network (http://www.bt.cdc.gov/lrn/) as directed by the state public health department. If the sample is obtained at least 72 hours after the onset of symptoms and is negative this can be considered a final result.[21] However a positive test result for EBOV in a patient in the U.S. must be confirmed at the CDC.

Patients with confirmed EBOV infection will need to remain isolated in a single room (with a private bathroom) with rigorous adherence to recommended infection control precautions.[18] This should be at a facility with dedicated isolation rooms and appropriately trained staff. Additionally, local and state health departments can also provide guidance on which hospital(s) in the area are equipped and trained to care for patients with EVD. All persons who have had close or direct contact with a patient with EVD during their illness (either suspect or confirmed) must be actively monitored by public health authorities for 21 days after that contact to ensure that they do not develop EVD throughout the duration of the incubation period. A confirmed case may be discharged once clinical recovery and clearance of EBOV viremia has been documented with a negative result from a validated RT-PCR test, in consultation with the CDC.

Exclusion of EVD

In a PUI, Ebola virus disease is excluded when a patient with fever and symptoms for >3 days has a plasma specimen that is negative for EBOV RNA by a validated RT-PCR assays at an approved laboratory in consultation with the CDC. These patients may be safely discharged if clinically stable, but still must be followed as part of contact tracing for 21 days if their history includes contact with a PUI or confirmed EVD case in collaboration with state public health departments and the CDC. If testing is done on plasma collected earlier than 3 days after symptom onset, a negative result does not exclude EBVO infection; therefore, if symptoms persist, repeat testing should be performed on a specimen collected after the third day of illness.

PROTECTING HEALTH CARE WORKERS WHILE CARING FOR PATIENTS WITH EVD

Protection of health care workers is critical and requires the knowledge and understanding of EBOV transmission, proper use of personal protective equipment (PPE), and strict adherence to guidelines for donning and doffing. Interruption of EVD transmission through the institution of barrier precautions, including the use of PPE, is a cornerstone of health care worker protection.