

Care of the Child With Ebola Virus Disease*

Carl O. Eriksson, MD, MPH¹; Timothy M. Uyeki, MD, MPH, MPP²; Michael D. Christian, MD, MSc³; Mary A. King, MD, MPH⁴; Dana A. V. Braner, MD¹; Robert K. Kanter, MD^{5,6}; Niranjana Kissoon, MD⁷

Objectives: To provide clinicians with practical considerations for care of children with Ebola virus disease in resource-rich settings.

Data Sources: Review of the published medical literature, World Health Organization and government documents, and expert opinion.

Data Synthesis: There are limited data regarding Ebola virus disease in children; however, reported case-fatality proportions in children are high. Ebola virus may affect immune regulation and endothelial function differently in children than adults. Considerations for care of children with Ebola virus disease are presented.

Conclusions: Ebola virus disease is a severe multisystem disease with high mortality in children and adults. Hospitals and clinicians must prepare to provide care for patients with Ebola virus disease before such patients present for care, with particular attention to rigorous infection control to limit secondary cases. Although there is no proven specific treatment for Ebola virus disease, meticulous supportive care offers patients the best chance of survival. (*Pediatr Crit Care Med* 2015; 16:97–103)

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¹Division of Pediatric Critical Care, Department of Pediatrics, Oregon Health & Science University, Portland, OR.

²Influenza Division, National Center for Immunization and Respiratory Diseases, U.S. Centers for Disease Control and Prevention, Atlanta, GA.

³Department of Critical Care, Mount Sinai Hospital, Toronto, ON, Canada.

⁴Pediatric Critical Care Medicine, Seattle Children's Hospital and Harborview Medical Center, Seattle, WA.

⁵Pediatric Critical Care Medicine, Virginia Tech Carilion School of Medicine, Roanoke, VA.

⁶National Center for Disaster Preparedness, Columbia University, New York, NY.

⁷Departments of Pediatrics and Emergency Medicine, British Columbia's Children's Hospital, Vancouver, BC, Canada.

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For information regarding this article, E-mail: eriksson@ohsu.edu

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Ebola virus infection causes a severe disease characterized by multisystem involvement and high mortality. Since the first recognized epidemics of Ebola virus in 1976, the virus has been responsible for sporadic outbreaks in sub-Saharan Africa. In March 2014, the World Health Organization was notified of an outbreak of Ebola virus disease (EVD) in southwestern Guinea, subsequently attributed to *Zaire ebolavirus* (EBOV). This ongoing outbreak likely began in Guinea in December 2013 (1) and constitutes the largest Ebola virus epidemic to date with further spread to Liberia, Sierra Leone, Nigeria, Senegal, Mali, Spain, the United Kingdom, and the United States through December 2014.

Most patients with EVD have been treated in very resource-poor settings, with interventions limited to basic supportive care; therefore, it is difficult to estimate the potential benefit of modern critical care. To date, a small number of adult patients have been treated in the United States and several European countries. Most published clinical data are derived from adult patients. There is limited knowledge about EVD in children; however, reported case-fatality proportions in children are high (2, 3).

The objective of this report is to provide clinicians with practical considerations for care of children with EVD in resource-rich settings.

TRANSMISSION OF EBOLA VIRUS

The natural reservoir for Ebola viruses is believed to be fruit bats, with infected mammals such as duiker antelopes and nonhuman primates having high mortality (4–6). Ebola virus particles or viral RNA have been detected in skin and body fluids of humans or nonhuman primates. Ebola viruses can enter the body through mucosal surfaces, skin breaks, or parenteral introduction and appear to initially infect monocytes, macrophages, and dendritic cells, which then disseminate the infection (7). Direct contact with infected animals can result in zoonotic transmission with subsequent spread among humans who had direct contact with blood or bodily fluids of infected persons. To date, five species of Ebola virus have been identified (*Zaire*, *Sudan*, *Bundibugyo*, *Reston*, and *Tai Forest*) with variable virulence; case-fatality proportions during outbreaks for EBOV infection range from 59% to 88% (8, 9), whereas there

are no known fatalities from *Tai Forest ebolavirus* infection, and *Reston ebolavirus* is not known to cause human disease.

PATHOPHYSIOLOGY OF EVD

Ebola virus has tropism for multiple tissues, including the liver and adrenal gland, causing hepatocellular and adrenocortical necrosis (7). In addition, infection triggers a dysregulated immune response that includes expression of several inflammatory mediators and inhibition of type I interferon response (10–12). Recovery from ebolavirus infection is associated with a well-regulated inflammatory response characterized by early Ebola-specific IgM and IgG production; in contrast, fatal cases are associated with an impaired response characterized by increased expression of several proinflammatory cytokines, lymphocyte apoptosis, marked CD8(+) lymphopenia, and lack of neutralizing antibody production (13–16). Fatal cases are also associated with high levels of ferritin, nitric oxide, and thrombomodulin, and higher levels of viremia are associated with elevated tissue factor and tissue plasminogen activator (13, 16, 17). Immune dysregulation has led to concern about bacterial superinfection (18).

Ebola virus may affect immune regulation and endothelial function differently in children than in adults, and markers associated with survival differ between children and adults. Children infected with *Sudan ebolavirus* have greater elevation of interleukin (IL)-10 and the chemokine regulated on activation, normal T-cell expressed and secreted (RANTES) marker. Fatal *Sudan ebolavirus* cases in childhood were associated with higher IL-10 and lower RANTES levels than children who survived, while levels of IL-10 and RANTES had no association with outcomes in adults (2). Children also had higher levels of several markers of endothelial overactivation, and elevations in these markers were associated with fatal cases in children but not in adults (2). This combination of immune dysregulation and endothelial damage shares several features with severe sepsis (19).

CLINICAL FEATURES OF EVD

Although EVD is classically divided into early, late, and terminal or recovery phases, considerable overlap between these phases may occur. After an incubation period of 2–21 days (mean, 11 d), an acute febrile illness develops in patients; nonspecific signs and symptoms of this early phase of disease commonly include fever, headache, chills, malaise, myalgias, asthenia, vomiting, and diarrhea (3, 7, 20).

Diarrhea can be profuse and may mimic cholera. Hiccups, conjunctivitis, and pharyngeal erythema may also develop in patients, and a nonpruritic maculopapular rash on the face and upper body may be present during early or late phases of the disease (7, 18). Early laboratory abnormalities are not specific to Ebola and can include leukopenia, lymphopenia, thrombocytopenia, serum aminotransferase elevation, hyperlipasemia, hyperproteinemia, elevated prothrombin and partial thromboplastin times, fibrin split products, and elevated creatinine kinase (7, 21).

Patients with severe disease may develop shock from hypovolemia or sepsis, multiple organ failure, and disseminated intravascular coagulation; one patient with fatal disease cared

for in a tertiary care center developed significant left ventricular systolic dysfunction (21). Fewer than half of patients develop hemorrhagic manifestations, which are often in the gastrointestinal tract and may be life threatening (3, 7, 21). Late neurologic sequelae include confusion, delirium, seizures, and coma. Patients with fatal disease typically die between day 6 and 16 of symptoms from multisystem failure, while nonfatal cases show improvement by days 6–11 (11). Viral load has been reported to be substantially higher in fatal cases compared with survivors (17, 22), although this difference may be less pronounced in children (2). In surviving patients, there is a prolonged convalescent period lasting up to 8 weeks (23), characterized by arthralgia, myalgia, abdominal pain, fatigue, and weakness (18, 24). Ebola virus has been cultured from the breast milk of an infected patient at illness day 15 (25). The duration of infectivity after resolution of viremia for other bodily fluids is not completely understood, but infectious virus has been recovered from survivor semen up to 82 days after symptom onset (26).

CARE OF CHILDREN WITH EVD

Diagnosis of EVD

Since early identification of potential Ebola cases is essential for implementing proper infection control measures and the early symptoms of EVD are nonspecific, clinicians should maintain a high index of suspicion for patients with both clinical findings consistent with EVD (fever and symptoms such as headache, myalgia, abdominal pain, vomiting, diarrhea, and hemorrhage) and an epidemiologic risk factor within 21 days before symptoms onset. Such risk factors include having been in a country with widespread ebolavirus transmission or having contact with a symptomatic person with EVD (27, 28).

Suspected cases of EVD should be reported to public health officials immediately. National public health agencies can provide guidance regarding diagnosis and infection control (29, 30), as well as the level-4 biosafety containment laboratories required for safely diagnosing infection with high-risk organisms such as ebolavirus.

The standard method to identify acute ebolavirus infection is by real-time reverse transcription-polymerase chain reaction testing of blood specimens (22). Other methods such as antigen-detection enzyme-linked immunosorbent assay (ELISA) have been used in the past. Antibodies to Ebola virus may be detected using direct IgG and IgM ELISAs or IgM capture ELISA starting 2 days after symptom onset, although patients with fatal disease may not develop detectable antibody responses (7).

Even during Ebola outbreaks, the likelihood of EVD in a febrile returned traveler is generally much lower than the likelihood of more common imported febrile illnesses. In particular, malaria is endemic in all regions where Ebola has been identified and remains the most likely diagnosis in febrile patients from these regions. Delay in the diagnosis and treatment of malaria can lead to severe or lethal disease in a short period of time. Thus, urgent malaria testing should be performed in all children suspected of having EVD (**Table 1**).

TABLE 1. Care of Patients With Ebola Virus Disease: Summary of Key Pediatric Considerations

Advance planning
Institutions should plan and practice for the care of children with suspected EVD before such patients present for care
Diagnosis
Urgent malaria testing should be performed in children suspected of having EVD
Notify local public health officials immediately regarding suspected cases of EVD
Patient placement and infection control
If transport can be safely undertaken, patients may benefit from early transfer to high-volume pediatric centers or biocontainment units
Consider initial admission to PICU or an Ebola treatment unit led by PICU providers even for patients not yet critically ill
Meticulous attention to infection control is essential to limiting secondary cases
Only essential staff should participate in the care of patients with suspected EVD
Ebola-specific treatment
There are no data regarding the use of anti-Ebola virus treatment in children; use of experimental therapy must occur within an acceptable ethical framework and should include case reporting to facilitate assessment of effectiveness
Monitoring and supportive care
Closely monitor and replace fluid and electrolyte losses
Consider placement of central venous or peripherally inserted central catheters to minimize venipuncture
Avoid emergent and high-risk procedures (such as extracorporeal life support), which may present an unacceptable risk of healthcare worker exposure
Case reporting and documentation
Strongly consider prospective, systematic case reporting to increase knowledge of EVD in children

EVD = Ebola virus disease.

Infection Control

As with any emerging infectious illness, appropriate hospital infection control for Ebola virus is essential. Institutions should plan for the care of patients with emerging infectious illnesses before potentially infected patients present for care (29, 31); lessons and preparedness protocols from institutions that have cared for patients with EVD can provide practical guidance (32, 33). Hospitals should train clinical staff to identify signs and symptoms of EVD and ensure that emergency department screening includes questions regarding travel within 21 days from an affected country and possible exposure to Ebola virus for patients

with symptoms compatible with EVD (29, 31, 34). Potential Ebola cases should be isolated immediately. Risk of Ebola virus transmission to healthcare workers in resource-rich settings is expected to be much lower than in African field hospitals, where inadequate medical supplies, no running water, and no floors likely contribute to greater exposure to Ebola virus (21, 35). However, due to the high case fatality of EVD, lack of proven antiviral therapy, and healthcare worker infection in Spain and the United States, meticulous attention must be paid to infection control practices.

Early planning for care of patients with EVD includes taking inventory of existing resources and identifying potential areas for managing highly infectious patients. Important factors to consider include the ability to provide negative pressure isolation as aerosol-generating procedures may be necessary, the presence of a private bathroom, the ability to restrict access to the room, sufficient space to don and remove personal protective equipment safely, the ability to perform laboratory studies while minimizing healthcare provider exposure risk, and the ability to provide critical care if necessary without having to move the patient. Hospitals should consider initially admitting children with suspected EVD to the PICU even if they do not otherwise meet PICU admission criteria. Admitting patients with EVD to the more controlled and highly monitored PICU environment may allow more effective limitation of foot traffic, decrease the number of staff that must be educated in proper infection control measures, facilitate lower nurse-to-patient ratios to ensure that infection control measures are strictly followed, and minimize risky in-hospital transfers if patients deteriorate. Alternatively, hospitals may consider establishing a geographically separate Ebola treatment unit staffed by PICU nurses and physicians, as this may further limit potential exposure of other patients and healthcare workers.

Table 2 describes recommended infection control measures for patients with EVD. Guidelines from national public health agencies have changed with increased experience treating EVD in resource-rich settings and may continue to evolve. Regardless of the equipment chosen, staff must be thoroughly trained and meticulously monitored in the appropriate use of personal protective equipment, especially its removal (36). To decrease exposure risk, only essential staff should participate in the care of patients with EVD. Given the profound importance of limiting secondary cases, children with confirmed EVD may need to be separated from their caregivers. Such separation may cause significant emotional distress, which can be somewhat mitigated by frequent videoconferencing and additional psychological support.

To decrease opportunities for healthcare personnel exposure to Ebola virus, phlebotomy, procedures, laboratory testing, and the use of needles and sharps should be minimized as much as possible (31, 37, 38). Strict adherence to recommendations for body fluid specimen collection, transport, and testing (39), as well as for environmental infection control (40), is advisable. Hospital laboratories should be notified as early as possible of the need to perform laboratory testing for a patient suspected of having EVD so that appropriate packaging and transport can be ensured. Specimens should not be sent by pneumatic tube systems. Hospitals may consider using dedicated laboratory equipment for patients with suspected EVD and keeping this equipment at the bedside

TABLE 2. Recommended Isolation Measures for Patients Suspected of Having Ebola Virus Disease, Based on U.S. and Canadian Government and World Health Organization Recommendations (31, 36–38, 40, 65)

<p>Patient placement</p> <p>Patients should be placed in single-patient rooms with private bathrooms</p> <p>Consider initial placement in an airborne isolation room for any patients with suspected EVD who may need aerosol-generating procedures</p> <p>Consider initial placement in PICU or geographically separate Ebola treatment unit to facilitate close monitoring, limit the pool of healthcare providers, and avoid potentially risky transfers if patients deteriorate</p> <p>Facilities should establish separate spaces for donning and removing PPE; space where PPE is removed must be sufficiently large to allow ideal practices without risk of surface contamination</p> <p>Nonessential contact with the patient or body fluids should be avoided</p>
<p>Transmission-based precautions</p> <p>In addition to universal precautions, contact and droplet precautions should be used</p> <p>All healthcare personnel and caregivers entering the patient room must be thoroughly trained in proper technique when donning and removing PPE; equipment must be removed without contaminating the healthcare worker or environment</p> <p>All persons entering the patient room should wear at least:</p> <p>Respiratory protection with either:</p> <ul style="list-style-type: none"> A fit-tested N95 filtering mask and a full face shield or A powered air-purifying respirator with a full face shield, helmet, or headpiece <p>Single-use surgical hood that extends to shoulders and fully covers neck</p> <p>Single-use fluid resistant or impermeable gown and boot covers</p> <p>Two pairs of single-use nitrile gloves with extended cuffs</p> <p>Single-use fluid resistant or impermeable apron if patient has vomiting or diarrhea</p> <p>Institutions may consider enhanced PPE beyond national guidelines</p> <p>Hospitals should assist and monitor healthcare workers to ensure close adherence to appropriate PPE donning and removal procedures and practices</p> <p>Once removed, disposable PPE should be discarded in biohazard waste containers, and reusable equipment must be appropriately disinfected before reuse</p> <p>Hospitals should identify appropriate mechanisms to safely and legally manage and dispose waste suspected to be contaminated with Ebola virus</p>
<p>Healthcare workers with significant exposures</p> <p>Healthcare workers with skin or mucocutaneous exposure to body fluids from a patient with suspected EVD should immediately wash affected skin surfaces with soap and water, irrigate mucous membranes copiously, and contact appropriate institutional personnel to report a potential exposure</p>
<p>Additional measures</p> <p>Aerosol-generating procedures, such as noninvasive ventilation, intubation or extubation, and open airway suctioning, should be avoided unless essential and should be conducted in an airborne infection isolation room</p> <p>Facilities should maintain a log of all persons entering the patient's room</p> <p>All visitors who have had contact with the patient before hospital admission should be actively monitored for fever and other possible symptoms of EVD</p> <p>Local public health officials should lead efforts to monitor people exposed to EVD</p>

EVD = Ebola virus disease, PPE = personal protective equipment.

to decrease potential transmission (32). The decision whether to transport a potentially infectious patient to a tertiary care facility is controversial, and risks and benefits of either approach must be

weighed; if transport can be safely undertaken (41, 42), children may benefit from transport to an institution with a dedicated bio-containment unit or greater pediatric expertise.

Treatment of Ebola Virus Infection

There is currently no approved or available treatment with proven efficacy against Ebola virus infection in humans. Several promising investigational drugs are in development with limited data from nonhuman primate studies. Postexposure prophylaxis regimens consisting of monoclonal antibodies against virus glycoproteins or small-interfering RNA targeting viral proteins have shown promising results in macaques (43, 44), and monoclonal antibody cocktails have demonstrated efficacy treating nonhuman primates after development of symptoms (45, 46). Clinicians may decide to offer patients treatment with an Ebola investigational therapeutic on a compassionate use basis as long as appropriate ethical criteria are met and scientifically relevant data are shared to establish the safety and effectiveness of the treatment (47); in those cases, Ebola antiviral medications may be supplied by manufacturers if supply is adequate (48–52) and use must be approved by the appropriate regulatory body (53, 54). There is limited experience with the use of convalescent plasma to treat EVD in humans (55, 56). The World Health Organization has prioritized investigation of convalescent plasma and whole blood therapy for EVD and issued guidance for appropriate use of these products, recommending transfusion of 10 mL/kg whole blood or plasma in children with confirmed EVD with standardized data collection to allow assessment of efficacy (57, 58). No Ebola vaccines have been approved for clinical use, although human safety testing of investigational vaccines has been expedited in response to the 2014 West African Ebola virus outbreak (59). Ideally, investigational therapies for patients with EVD, including convalescent plasma, should be used in the context of randomized clinical trials.

Monitoring

Due to extremely high gastrointestinal and insensible fluid losses, fluid intake and output must be closely monitored. A nasogastric tube may be placed in patients without hemorrhagic manifestations. Serum electrolytes should be measured at least daily to avoid development of life-threatening hyponatremia, hypokalemia, hypocalcemia, hypomagnesemia, and metabolic acidosis, which may occur in patients with severe diarrhea. Patients should be monitored for development of liver failure and for renal failure or cerebral edema in severe cases of EVD. Coagulopathy due to disseminated intravascular coagulation and hepatic dysfunction can occur. Thus, clinicians should assess for coagulopathy and clinical bleeding. Children with severe sepsis or septic shock should be monitored closely for development of cardiac compromise, especially ventricular dysfunction.

Clinicians should consider early placement of a central venous catheter or peripherally inserted central catheter to decrease the risk of exposure to blood from multiple phlebotomies and IV catheter placements. Arterial catheters may present unacceptably high risk of bleeding and healthcare worker exposure; hence, consideration of other forms of monitoring and access for blood sampling is advised.

Supportive Care

Patients with EVD may present with hypovolemia requiring aggressive initial volume resuscitation. Oral fluid replacement is preferred in patients who are able to drink without vomiting, but administration of IV fluids may be necessary. Hypovolemia from profound vomiting and diarrhea may be exacerbated by capillary leak associated with immune dysregulation, and ongoing significant volume resuscitation to maintain normovolemia may be necessary. Patients may benefit from volume resuscitation with balanced fluids rather than saline (60). Patients who develop severe sepsis or septic shock should be managed according to international sepsis treatment guidelines (61). This includes early goal-directed therapy, vasopressor and inotropic support as needed, glucose control, and enteral nutrition as tolerated. Coagulopathy should be corrected if severe or associated with significant bleeding (61). Given the prominence of immune dysregulation in severe and fatal EVD, clinicians may consider employing sepsis treatment guidelines in any patient with severe EVD.

Although pulmonary involvement of EVD is not common, respiratory failure may occur due to pulmonary edema, circulatory overload, or acute lung injury related to blood transfusion or sepsis. Noninvasive ventilation may not be advisable due to significant droplet dispersion and associated risk to healthcare workers. Furthermore, elective tracheal intubation will likely result in lower risk to the patient and healthcare team than urgent intubation in the setting of aspiration or frank respiratory failure. In addition, airway protection may be required for patients with severe neurologic or bleeding sequelae. Noninvasive ventilation and tracheal intubation are aerosol-generating procedures requiring airborne precautions. Patients should be intubated by an experienced, skilled provider in order to minimize the risk of airway trauma and healthcare provider exposure.

Corticosteroids should generally not be administered to patients with EVD. However, as EVD can cause adrenocortical infection and necrosis (7), clinicians may consider stress-dose glucocorticoid administration in patients with persistent shock who require escalating or persistent vasoactive support or replacement mineralocorticoids in patients with inappropriate urine sodium losses.

Due to the risk of secondary bacterial infections and the difficulty of clinical detection in the setting of a severe systemic viral infection, broad-spectrum antibiotics may be administered initially for patients with manifestations of possible sepsis. Antipyresis, analgesia, and antiemetic treatment may provide symptomatic relief; nonsteroidal anti-inflammatory drugs should be avoided due to bleeding risk. Psychosocial support of children and their caregivers are essential components of high-quality care for patients infected with highly virulent emerging pathogens such as Ebola virus; video conferencing and other technology may facilitate such support without increasing risk of virus transmission.

The potential benefits of each treatment must be weighed against both the risks to the patient and healthcare providers. Testing and procedures with unclear benefit should be avoided. Clinicians may decide to limit the use of plasmapheresis,

extracorporeal life support, cardiopulmonary resuscitation in patients with multiple organ failure, and other high-risk procedures to situations where they show clear evidence of benefit for patients with EVD. In addition, emergent procedures may be inadvisable given the long time required to properly don personal protective equipment, and loss of a controlled environment during emergency procedures will likely create unacceptable risk of transmission to healthcare workers. Institutional bioethics experts may help guide decision making in situations where clinicians are considering resource restriction or nonstandard allocation. As new data become available regarding the efficacy and exposure risk of such procedures in the patient with EVD, recommendations regarding avoiding certain procedures may evolve.

Case Reporting and Documentation

Little is known about EVD in children in resource-rich settings, and clinicians should strongly consider prospective, systematic detailed case documentation to increase our collective knowledge about EVD (62). The World Health Organization and the International Severe Acute Respiratory and Emerging Infection Consortium have developed a case reporting and biological sampling protocol for emerging severe respiratory pathogens, including informed consent documents and case record forms (63, 64); this protocol can serve as a template for efforts to efficiently and systematically gather information about EVD. Careful case reporting can improve knowledge of not only EVD and its clinical manifestations but also of the effects of treatment strategies.

CONCLUSION

EVD is a severe multisystem disease with high mortality in children and adults. Hospitals and clinicians must prepare to provide care for patients with EVD before such patients present for care, with particular attention to rigorous infection control in order to limit secondary cases. Although there is no proven specific treatment for EVD, meticulous supportive care offers patients the best chance of survival.

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