Analyzing The Ebola ViruAnalyzing The Impact That The Ebola Virus Disease Has on Children

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Abstract

Ebola virus is one of the most deadly pathogens known to infect humans. The current Ebola outbreak in West Africa is unprecedented in magnitude and duration and, as of November 30, 2014, shows no signs of abating. For the first time, cases of Ebola virus disease have been diagnosed in the US, originating from patients who traveled during the incubation period. The outbreak has generated worldwide concern. It is clear that U.S. physicians need to be aware of this disease, know when to consider Ebola and how to care for the patient as well as protect themselves. Children comprise a small percentage of all cases globally, likely because of their lower risk of exposure given social and cultural practices. Limited evidence is available on pediatric disease course and prognosis. In this article, we present an overview of the pathogen, its epidemiology and transmission, clinical and laboratory manifestations, treatment and infection control procedures, with an emphasis on what is known about Ebola virus disease in the pediatric population.

Ebola virus is one of the most virulent pathogens known to infect humans.1 The first recognized Ebola outbreak occurred in 1976, near the Ebola River in Zaire (now Democratic Republic of Congo, DRC). Over the past 40 years, more than 20 outbreaks have occurred in Africa, with most of the known outbreaks occurring in the past 20 years.2,3 Before the 2014 epidemic, over 2300 cases with greater than 1500 deaths had been documented from this disease.2 The current outbreak in West Africa has so far affected more people than all previous Ebola outbreaks combined4 : as of January 20, 2015, the cumulative number of probable, suspect and laboratory-confirmed cases attributed to Ebola virus was more than 21,000, with greater than 8500 deaths.5 These numbers likely represent underestimates of the outbreak's true size because of poor local health system infrastructure, with many patients being cared for outside hospital settings, or not reported.6 The unprecedented size and scale of this outbreak have generated worldwide concern, not only in part because it can destabilize the fragile social and economic milieu and healthcare systems of the involved countries, but also because it has raised fears of spread beyond the African continent. It has thus become a massive focus of international public health action.7

The first few cases of this disease have now occurred in the US. Given that this epidemic will likely last for at least several more months,8 additional patients with Ebola virus disease (EVD) may present to health care settings in the US. Therefore, an improved understanding of EVD among U.S. healthcare providers, especially infectious diseases specialists, is warranted. This article summarizes current knowledge on EVD, its epidemiology and clinical presentation as well as treatment and infection control procedures, with a focus on summarizing the limited available understanding of the effects of EVD in infants and children.

EBOLA VIRUS: EPIDEMIOLOGICAL AND CLINICAL FEATURES

Epidemiology

The genus Ebolavirus is composed of single-stranded, enveloped, filamentous RNA viruses, that, together with the Marburgvirus genus, comprise the family Filoviridae.3,9 Ebola and Marburg viruses are antigenically distinct but cause similar illnesses.10 These viruses have classically been referred to as hemorrhagic fever viruses because of their clinical manifestations, which can include coagulation defects, capillary leak and shock; however, the disease caused by infection with viruses in the Ebolavirus genus is now referred to as EVD.

There are currently 5 species in the Ebolavirus genus; Tai Forest ebolavirus, Sudan ebolavirus (SUDV), Zaire ebolavirus (Ebola virus, EBOV), Bundibugyo ebolavirus (Bundibugyo virus) and Reston ebolavirus (Reston virus, RESTV). These viruses differ in their virulence for humans. Tai Forest ebolavirus has only been clearly documented in one individual, and the case was not fatal. Mortality with SUDV (41–65%) and Bundibugyo virus (40%) is lower than the mortality seen with EBOV (57–88%). RESTV is named after Reston, Virginia, where it was first described in 1989 in cynomolgus macaques imported from the Philippines and has been reported to cause illness in primates but not in humans. Although serologic conversion was detected among scientists working with the infected monkeys, RESTV has not caused symptomatic disease in humans.1,3,9

Some studies of seroprevalence during EVD outbreaks have shown a small percentage (<2%) of the population having IgG antibodies to Zaire and SUDV, suggesting that subclinical infection may occur but is not common.11–13 With the exception of an outbreak of Marburg virus among vaccine manufacturing plant workers in Europe who came in contact with infected monkeys from Uganda in 1967,1 all filovirus human outbreaks before 2014 have occurred in Africa, with the frequency of recognized outbreaks increasing since 1990.3 EVD was first recognized in 1976, when 2 unrelated epidemics occurred in northern Zaire and southern Sudan; disease recurred in the same area of the Sudan in 1979, but EVD was not recognized again until 1994. The current outbreak, caused by EBOV, started in Guinea in late 2013, subsequently spread to Liberia, Sierra Leone, Nigeria, Senegal and Mali and continues unabated in the first 3 countries above.7,14 EBOV may have also been spreading among primates3,8 ; the great apes are likely dead-end hosts like humans. EVD is a zoonotic disease, but its natural animal reservoir remains unknown. Several species of small animals have been implicated as reservoirs; bats seem to be the most likely culprit based on epidemiologic evidence.15 Evidence that fruit bats are naturally infected by EBOV has been documented,16 but virus isolation has not been successful from bats or any other animal species to date. Sequence analysis of viruses indicates that the 2014 epidemic in West Africa has resulted from sustained person to person transmission, without additional introduction from animal reservoirs.3

Modes of Transmission

The main routes of Ebola virus transmission are direct contact with a symptomatic Ebola patient's blood and body fluids (including but not limited to urine, feces, vomitus, saliva and sweat) through breaks in the skin or through inoculation into the mouth, nose or eyes.3 Human infection can also occur through contact with wild animals, such as by hunting, butchering or preparing meat from infected animals. Ritual washing of Ebola victims at funerals is a type of direct contact that plays an important role in Ebola transmission among humans.9 Transmission to household contacts is associated with close contact with sick patients, their body fluids or their remains.9 Unsafe medical procedures, such as injections employing reused syringes and improperly sterilized needles, have also played a role in some Ebola outbreaks; accidental needle stick injuries have led to isolated cases among laboratory personnel working in research laboratories.3,9 A

nosocomial outbreak occurred in DRC in 1995 when a patient hospitalized with abdominal pain underwent an exploratory laparotomy; the entire surgical team became infected.17 Ebola virus spread from these workers to other hospital staff, patients and family members through direct physical contact. Healthcare workers are at risk for infection if they care for a patient with EVD without appropriate protective measures, and this has been a major route of transmission in some outbreaks.9 As of January 20, 2015, 828 health care workers are known to have become infected as a result of the current outbreak in West Africa, and 499 have died.18 The typical pattern of transmission of EVD to health care workers is from an infected patient to his or her primary caretaker while symptomatic, with subsequent spread from the caretaker to his or her primary caretaker. Household members who did not share nursing duties have remained unaffected, even if they slept in the same room. This pattern further suggests that transmission without direct contact with the patient is an unlikely route.17

Clinical Manifestations

The incubation period is typically 8–10 days (range, 2–21 days, though it may be shorter when transmission has occurred through contaminated injection needles).19 Following the incubation period, there is usually an abrupt onset of fever, chills, malaise, anorexia, severe Kourtis et al. Page 3 Pediatr Infect Dis J. Author manuscript; available in PMC 2016 August 01. Author Manuscript Author Manuscript Author Manuscript Author Manuscript headache and myalgias of the trunk and lower back. Some patients may develop a diffuse maculopapular rash by days 5–7 of illness, mainly on the trunk. These initial symptoms are nonspecific and can easily be mistaken for other, endemic infectious diseases, such as malaria, typhoid fever, yellow fever or, particularly in the case of children, for other infections with exanthems, such as measles or meningococcemia. Gastrointestinal symptoms, including vomiting, nausea, watery diarrhea and abdominal pain, usually develop several days after the initial nonspecific presentation and become the predominant clinical feature. Bleeding is not universally present (less than 50% of patients)20,21 but can occur later in the course of the disease (usually around day 5–7), manifesting as petechia, bruising, oozing from venipuncture sites and/or mucosal hemorrhage. Conjunctival injection and dark red discoloration of the soft palate are common physical findings. Central nervous system involvement is often manifested by somnolence, delirium, seizures or coma.9 Pregnant women may experience spontaneous miscarriages, and they also seem to be at higher risk for severe illness and death.22 In addition to extensive tissue damage of some organs, filoviruses also induce a systemic inflammatory syndrome by causing the release of cytokines, chemokines and other proinflammatory mediators.23 In nonfatal cases, patients improve typically 6–11 days from onset of symptoms.10 Fatal disease is associated with more severe clinical signs early in infection, with progression to disseminated intravascular coagulation, septic shock and multiorgan failure. Death usually occurs between 6 and 16 days (mostly around the 9th day) after symptom onset.10

Laboratory findings in EVD patients include leukopenia, thrombocytopenia, electrolyte abnormalities, transaminase elevations and renal and coagulation abnormalities.9,10 Other findings include a marked decrease in albumin (reflective of a capillary leak syndrome) and elevated amylase levels. Patients with evidence of severe intravascular volume depletion, metabolic abnormalities, tachypnea, anuria, delirium, coma and shock have a poor prognosis.9,10 Elevated levels of several cytokines and chemokines are also associated with a worse clinical outcome.23,24 Convalescence is prolonged, marked by weakness, fatigue, arthralgia and failure to regain weight lost during the illness. Extensive skin sloughing and hair loss are also commonly observed, as are neuropsychiatric symptoms.3,10

Presence of thrombocytopenia and leukopenia with elevated transaminase levels is characteristic of filovirus disease as well as some other viral hemorrhagic fevers, but a severe progressive course with abdominal pain and diarrhea should lead to suspicion of a filovirus.

Diagnosis and Care of the Infected Patient

Laboratory diagnosis of Ebola virus infection can be made by detection of RNA or viral antigens in blood or other body fluids, using reverse transcription-polymerase chain reaction (RT-PCR), antigen capture enzyme immunoassay or virus isolation.[9,10] These tests are generally performed only in specialized laboratories. Most acute infections are identified through RT-PCR; virus is generally detectable between 3 and 10 days from the onset of symptoms.[25] In survivors, viremia usually resolves during the second week, in association with the appearance of virus-specific antibodies.[9,10] However, virus can persist for weeks in particular body fluids, such as semen. Studies of survivors of the outbreak showed that viral RNA sequences could be detected in the semen for up to 91 days after disease onset[26]; studies from a 2000 Gulu, Uganda, outbreak showed that virus could be isolated from semen 82 days after disease onset.[27,28] Patients typically seroconvert around days 8–12,[9] but in fatal cases, antibodies are often not be detected before death.[12] IgM antibodies detected by enzyme-linked immunosorbent assay may be detected in early convalescence,[12] but IgG serologic testing may yield false-positive or irreproducible results.[9] Gingival brushings may yield positive RT-PCR results during later stages of infection when gingival bleeding is common.[10] Virus can be identified in postmortem tissue, such as skin, with immunohistochemical identification of antigen.

[10] There is currently no specific treatment for EVD. Supportive care with special attention to fluid and electrolyte management and maintenance of circulatory function is indicated.[10,25] Analgesia and sedation may be useful to prevent agitation.[10] Procedures and medications that increase the risk of bleeding should be considered weighing the potential benefits and risks to the patient. Replacement of coagulation factors and platelets may be necessary.[9] Male patients who recover should be counseled regarding the risk of sexual transmission to partners for at least approximately 3 months after recovery, based on isolation of infectious virus from the semen of a survivor 82 days after disease onset and of viral sequences 91 days after symptom onset.[27,28] Even though there are no approved therapies for patients with EVD, experimental therapies are in development. A cocktail of 3 monoclonal antibodies directed against the Ebola viral glycoprotein (ZMapp) prevented the death of Ebola-infected macaques, even when initiated after the animals had developed full clinical symptoms.[29] This cocktail has been administered to 4 healthcare workers during the 2014 outbreak, 2 of whom survived and recovered.[30,31] Controlled studies are needed to evaluate this and other novel treatments.[32]

A WHO expert panel[33] has recommended considering the use of whole blood or serum from convalescent EVD survivors in the treatment of affected patients. Additionally, in the only human trial of convalescent serum, 7 of 8 patients who received the product survived, but these same 7 patients were in the second week of illness (and therefore more likely to recover regardless of intervention) and the 1 patient who died received the transfusion at day 4.[34] Once data were adjusted for age, sex and the days since onset of symptoms, no statistical evidence of a survival benefit because of the receipt of blood transfusion was evident in this small sample.[35] At this time, there are no approved forms of preexposure or post-exposure prophylaxis; however, several vaccine candidates are in development or about to be tested in clinical trials.[36]

Although guidelines on infection control procedures in the US are evolving, the most updated Centers for Disease Control and Prevention (CDC) guidance can be found on the CDC website.[33] Soiled items and infectious secretions should be handled in a way that protects both healthcare personnel and the community.[37,38] Environmental cleaning and disinfection with appropriate hospital disinfectants are needed.[9,10,37] Heightened awareness in recognition of initial cases and institution of appropriate barrier nursing[17,37] remain essential for the containment of outbreaks,[9] as is strict isolation of cases.[17,37,39] Primary prevention measures are limited by the lack of knowledge of the natural reservoir. Community education that attempts to modify high-risk practices in African settings, for example, through altering traditional funeral practices and avoiding contact with bush meat, has been used during outbreaks. However, acceptance is often limited

by prevailing cultural practices highlighting the need for inclusion of cultural anthropologists and sociologists or others with knowledge of local cultures in the outbreak response team.25

Ebola in Infants and Children

Although children become infected with EBOV (indeed, the suspected first case of the current 2014 outbreak is believed to be a 2-year-old child in Guinea40), they typically comprise only a minority (approximately 10%) of cases during recognized human outbreaks.10,41 The highest risk of contracting the infection is among the people who take care of ill individuals, either in a healthcare setting or at home, or those who handle the remains of individuals who have died.10 Young children are largely spared of these exposures, which may, to a large extent, explain their relatively low representation among EVD victims.42

Evidence on whether children have different disease severity or prognosis, compared with adults, is limited. In a report summarizing the pediatric burden of EVD during an outbreak in the Northern Uganda, Gulu district, in 2000–2001 caused by SUDV, 20 of 218 (9%) of laboratory-confirmed cases were in children less than 18 years of age; their mean age was 8.2 years, and 35% of them were under 5 years of age. Among these children, the case fatality was 40%, whereas the overall case fatality for that outbreak was 50%. There was a slight female preponderance among infected children (M:F, 3:4).41 All Ebola-positive children had fever. Other common symptoms included vomiting (70%), diarrhea (60%) and cough (65%). Prolonged close contact with an infected relative was associated with fatality.41 Further analysis of case fatality of all laboratory-confirmed cases in children from that outbreak revealed that children 59 years of age. In the same outbreak, 7.5% of case patients were children or adolescents <16 years of age.17

In the current 2014 EBOV outbreak, and as of mid-September 2014, children less than 15 years of age comprise approximately 14% of all reported confirmed and probable EVD cases6 ; case fatality for children <15 years of age was 73.4%, 66.1% among those 15–44 years of age and 80.4% among those older than 45 years.6 It has not been reported how many cases are in neonates or infants. The findings from the current outbreak, taken together with those of the 1995 Kikwit and 2001 Gulu outbreaks (the latter was caused by SUDV, whereas the 1995 and 2014 outbreaks were caused by EBOV), may indicate that children, adolescents and young adults have lower fatality from EVD, compared with older adults.

Neonatal case fatality of EVD appears to be very high. Neonates born to mothers with EVD have not survived; in the 1976 outbreak in Zaire, which was linked to receipt of injections using contaminated needles and where a disproportionately high proportion of EBOV infected EBOV infected women were pregnant, there were 11 neonates born to mothers with EVD; all died within 19 days of life.43 The causes of these deaths are uncertain; 7 of the 11 neonates had fever.43 Subsequent outbreaks have confirmed high neonatal fatality.44 SUDV has been detected in breast milk 15 days after disease onset27; however, it is unknown whether these viruses can be transmitted from mothers to infants through that route.44 Breastfeeding infants of infected mothers may be at high risk.10 Anecdotal evidence from local practitioners suggests that Ebola survivors may not be able to maintain lactation after recovery (G. Risi, World Health Organization's Global Outbreak Alert and Response Network, personal communication, September 30, 2014); more information is needed. Pediatric, but not adult, survivors of SUDV infection had higher levels of the chemokine regulated on activation of normal T cell expressed and secreted (RANTES) and lower levels of plasminogen activator inhibitor 1, soluble intracellular adhesion molecule and soluble vascular adhesion molecule, compared with their counterparts who died, which may indicate differences in pathophysiology as well as potentially approaches to treatment for children versus adults.24

Implications for Pediatric Clinical Care and Infection Control

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Because of the length of the incubation period, the potential exists for persons with incubating infection to travel from an outbreak-affected area to a distant location, as illustrated by the patients diagnosed with EVD in Dallas and in New York City.45 The following guidance applies to health care workers in the US or a similar setting; guidance is posted on the CDC website, which should be checked for updates.38 Evaluation of an acutely ill child, as always, should begin with a thorough medical history, including a travel history. If a child with an acute febrile illness has resided in or traveled to a country where there is active transmission of EVD in the preceding 3 weeks, EVD should be considered in the differential diagnosis. Of course, other febrile illnesses related to similar travel exposures, such as malaria and typhoid fever, should also be considered,46 as should febrile illnesses common in the US, with diagnostic testing as clinically indicated. A patient with an epidemiologic risk factor within the 21 days before symptom onset who has a febrile illness (with or without other symptoms of EVD) is considered a person under investigation.47–49 Infection control precautions should be employed in the initial medical evaluation (detailed on the CDC website),38,50 and public health authorities should be notified as soon as possible. Guidelines for the evaluation of exposure risk can be accessed on the CDC website.48 The case definitions for EVD on the CDC website47 apply to all age groups.

If EVD is suspected, infection control precautions should be instituted immediately, if not already in place. Appropriate protocols for the isolation of suspected EVD cases and health care worker precautions are updated by the CDC in collaboration with state and local health care authorities. A full list of up-to-date infection control precautions33 and environmental infection control guidance37 can be accessed on the CDC website. Visitors should be limited to those essential to the patient's wellbeing, and all visitors, including parents, should be educated on hand hygiene and proper use of the necessary personal protective equipment.33 The duration of precautions should be determined on a case-by-case basis in conjunction with laboratory confirmation and local, state and federal health authorities.48,50

Diagnostic testing capability for EVD has been established within selected state public health laboratories in the US, with confirmation of presumptive results being performed at CDC. If diagnostic testing for EVD is indicated, the state or local health department should be immediately notified. Staff collecting specimens should use all personal protective equipment indicated in the infection control precautions, including a full face shield.51 To test for EBOV, a minimum of 4 mL whole blood should be collected in a plastic collection tube and immediately stored or transported at 2–8°C or frozen on cold packs. Whole blood preserved with ethylenediaminetetraacetic acid is preferred, but whole blood preserved with sodium polyanethol sulfonate, citrate or with clot activator is acceptable.51 Specimens should not be submitted to the CDC in glass containers or heparinized tubes nor should samples be sent without prior consultation. If short-term specimen storage is necessary before shipment, the specimen should be frozen or stored at 4°C. Confirmation of acute infections is performed by real time RT-PCR assay in a Clinical Laboratory Improvement Amendments-certified laboratory. Detailed instructions on packaging and shipping specimens can be accessed on the CDC website51; the state and/or local health departments need to be involved when EVD diagnostic testing are considered, and CDC needs to be notified before specimens are sent.

CONCLUSIONS

The current outbreak of EVD in West Africa is the largest in history greater than one in duration, and more than 8 months into the outbreak numbers of new reported cases and deaths continue to rise.6 Large increases in population size, increased urbanization with human penetration into previously remote areas of forest and better connectivity of the population internally and across country borders likely contributed to

this change.8 If drastic measures to curb it are not taken, the current outbreak could increase by many orders of magnitude, and EVD could even become endemic.6 The main control measures to prevent EBOV spread include isolation of cases, improved contact tracing, increased capacity for clinical care, safe funeral practices, greater community engagement and trust, support from international partners and the availability of an efficacious vaccine.6 Currently, a major international effort is being undertaken in aiding the local response, educating healthcare personnel and the public on infection control practices and establishing treatment facilities in the hopes of increasing survival rates and slowing disease transmission. Evidence-based responses that are adapted to the affected communities52 are necessary to combat this epidemic, as are efforts to support the affected countries' healthcare systems so that they can respond both to the EVD epidemic and to the many other pressing health needs of the local populations.

The current outbreak can provide the opportunity to improve our understanding of EVD in children by systematically collecting information on disease course and predictors of survival in children of different ages. This could be accomplished through the development and implementation of uniform data collection forms on patient and disease characteristics for those treated at Ebola treatment centers, through the collaboration of local ministries of health and international relief organizations. Information on length of viral shedding in different secretions (including saliva, breast milk and genital secretions) and their potential to transmit disease is also needed to help inform guidance on preventing secondary transmission of EVD.

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