Clinical Features and Outcome of Ebola Virus Disease in Pediatric Patients: A Retrospective Case Series

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Clinical and outcome data on pediatric Ebola virus disease are limited. We report a case-series of 33 pediatric patients with Ebola virus disease in a single Ebola Treatment Center in 2014-2015. The case-fatality rate was 42%, with the majority of deaths occurring within 10 days of admission. *(J Pediatr 2017;182:378-81).*

In 2014-2016, West Africa experienced the largest outbreak of Ebola virus disease (EVD) since the virus was discovered in 1976.[1] In Sierra Leone, more than 8700 persons were confirmed with EVD, and almost 4000 died of EVD by April 13, 2016.[2] Before the West Africa outbreak, our understanding of the clinical features and outcomes of pediatric EVD was limited to data from fewer than 100 children.[3-5] Consequently, we did not have a pediatric case definition of EVD when the outbreak began, nor a clinical management plan focused on pediatric EVD care.[6] Ebola Treatment Centers (ETCs) in West Africa were not consistently staffed with pediatricians, pediatric nurses, or healthcare providers with experience in caring for children who are sick.

Most of our knowledge on clinical EVD comes from aggregate data across all ages,[7-10] in which adults account for up to 79% of the study population.[11] These limited data suggest important differences in EVD epidemiology between children and adults. EVD case fatality rate (CFR) was higher for children than adults, yet children probably were less likely to become infected following EVD exposure.[12] Across Guinea, Sierra Leone, and Liberia, the age-specific diagnosis of EVD was lowest in children and highest in adults,[13] either reflecting lower incidence or lower rates of EVD testing. In a retrospective cross-sectional study of household contacts of EVD survivors, 50% of children exposed to an infectious household member with "wet" symptoms (vomiting, diarrhea) remained uninfected, as corroborated with serologic testing after the incubation period.[14] The finding may not translate to pediatric contacts of individuals who died of EVD and who may have been more viremic (potentially more infectious) during early infection. Together, existing pediatric data suggest that children may be less susceptible to EVD than adults because of differences in biological susceptibility and/or the intensity, frequency, or duration of exposures; but if infected, children experience a higher CFR, potentially mediated by differences in immunologic response to EVD.[4]

We sought to describe the clinical features, management, and outcomes of pediatric EVD from a single ETC and contribute to the small but growing knowledge of key clinical features and outcomes of pediatric EVD.

CFR	Case fatality rate
ETC	Ebola Treatment Center
EVD	Ebola virus disease
NCITs	Noncontact infrared thermometers
PCR	Polymerase chain reaction

Methods

We conducted a retrospective case series study using routine clinical and laboratory data collected from patients aged <18 years of age admitted to the Mathaska ETC in Port Loko, Sierra Leone between December 12, 2014, and March 14, 2015. We obtained ethical approval for the retrospective study from the Sierra Leone Ethics and Scientific Review Committee.

The 100-bed ETC was staffed with national and international personnel, including pediatricians and pediatric nurses. The ETC received patients from Port Loko and Kambia districts through 2 referral paths: (1) patients transferred from community care or holding centers with EVD confirmed before transfer and ETC admission; or (2) patients directly admitted from the community to the ETC. This latter group comprised patients who met the Sierra Leone Ministry of Health and Sanitation case definition of a presumed EVD infection, and who were identified via active monitoring of EVD contacts in quarantine, or via passive surveillance in communities and non-EVD facilities. In Port Loko and Kambia, EVD was confirmed by real-time polymerase chain reaction (PCR) performed on venous blood at the Public Health England laboratory in Port Loko. All patients were tested for malaria with a rapid diagnostic test for *Plasmodium falciparum* antigen detection. Patients with confirmed EVD were included in this study.

We developed and used a pediatric management protocol by adapting the generic World Health Organization guidance[15] for the care of children. The rationale was to provide a simple, systematic approach to managing children in the ETC with fluid and nutrition within the restrictions posed by the personal

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protective equipment. At admission, we recorded the patient's temperature (using noncontact infrared thermometers [NCITs] aimed at the temple), midupper-arm circumference, and weight. Symptoms on admission were obtained by questioning in the local language and were recorded using a structured case report form. We asked children who were able to answer about symptoms. For younger children and those unable to answer, we obtained information from their parent or guardian. We clinically assessed and recorded temperature and hydration status during ward rounds 3 times a day. The patient's daily weight was measured every morning and monitored as an indicator of hydration. Weight loss was managed by increasing the intravenous fluid volume accordingly.

The nutrition protocol included administration of F-75 therapeutic milk for the first 48 hours followed by F-100 therapeutic milk supplemented with ready-to-use therapeutic foods (BP-100 biscuits, Compact AS, Søfteland, Norway; Plumpy'Nut, Nutriset, Normandy, France). In alert children who were not classified as severely dehydrated, but in whom hydration could not be achieved sufficiently by therapeutic milk, we used ReSoMal (Nutriset; 5 mL/kg/hour) corresponding to a fluid volume of 120 mL/kg/day. For severely dehydrated children, we used intravenous administration of Hartman solution (**Table**; available at www.jpeds.com). Nursing staff specifically dedicated to nutritional management administered the therapeutic nutrition and rehydration solution 8 times per day. All children received zinc supplementation and multivitamins. Antimalarial treatment was administered to all who tested rapid diagnostic test-positive for malaria. We used oral artesunate-amodiaqine in alert children and intravenous artesunate for the severely ill. All children received intravenous ceftriaxone at a dose of 100 mg/kg. If bloody diarrhea was present or developed, we added intravenous metronizadole to the antibiotic regimen. Symptomatic management of nausea and epigastric discomfort included use of ondansetron and omeprazole. For terminally ill patients, we supplemented the above with a tailored palliative care protocol.[16]

Data Analyses

We extracted demographic (age, sex), clinical (symptoms at admission, time from symptom onset to EVD test, outcome) and laboratory (real-time PCR cycle threshold [C_t]) data from the clinical charts using EpiData (Version 3.1; EpiData Association, Odense, Denmark). The C_t is inversely proportional to the level of virus in the blood sample and was used as a proxy for measuring viral load in patients with confirmed EVD.[17] Time from symptom onset to EVD test was calculated by subtracting the date of self-reported symptom onset from the first EVD-positive test; the latter occurred on the date of admission to an EVD heath-facility (a holding center or an ETC). We assigned patients to 1 of 3 stages of severity at admission: (1) early or mild: nonspecific features, pyrexia, weakness, lethargy, myalgia, and arthritis; (2) moderate: nonbloody gastrointestinal involvement such as diarrhea, vomiting, or abdominal pain; and (3) complicated: hemorrhage, shock, neurologic involvement, or signs of organ failure.[8] Case-fatality was recorded as a death in the ETC. Survival was defined as 2 negative Ebola virus PCR tests at least 48 hours apart and followed by discharge from the ETC.

We use descriptive statistics to characterize the clinical and laboratory features of pediatric EVD. Hemorrhagic symptoms included any of the following: gingival bleeding, epistaxis, red eyes, bloody stools, or emesis. We compared differences in proportions using the χ^2 or Fisher exact test. We compared continuous variables using Student *t* test if the data were normally distributed and Wilcoxon-Mann-Whitney rank test otherwise. Kaplan-Meier survival curves were used to graphically represent the time to death. Analyses were performed using Stata v 12 (Stata Corp, College Station, Texas).

Results

Of 127 patients with confirmed EVD admitted to the ETC, 33 were less than 18 years of age and included in this study. The median age was 9 years (IQR 4-10), with 1 patient <1 year of age; 41% were female.

The median duration of reported symptoms before admission was 4 days (IQR 2-6 days). The majority reported fever (88%), anorexia (79%), and fatigue (79%). Headache (58%), muscle/joint pain (48%), diarrhea (42%), and abdominal pain (45%) were reported commonly. The least common symptoms included vomiting (36%), difficulty breathing (24%), difficulty swallowing (18%), unexplained bleeding (15%), and hiccups (12%).

Temperature on admission was recorded in 21 cases and missing for the remainder. The mean temperature was 38.8°C (IQR 38-39.5). Of the 21 pediatric patients, 21% were afebrile on admission (temperature <38°C). At admission, 36%, 49%, and 15% of patients were in clinical severity stage 1, 2, and 3 respectively. The mean C_t was 21.1 (IQR 19-23.9).

Fourteen children (42%) with EVD died in the ETC, and the remainder (n = 19) were discharged with a negative real-time PCR result. The majority of deaths occurred within the first 10 days of admission and none after day 13 of admission (**Figure**).

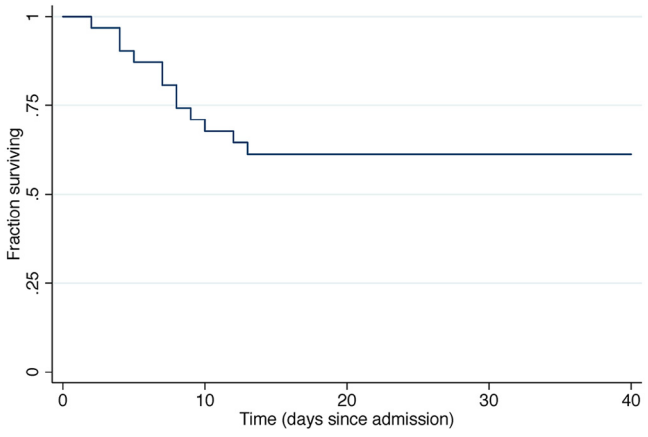

Figure. Kaplan-Meier curve showing survival in the ETC among pediatric patients with EVD.