ORIGINAL ARTICLE

Clinical Presentation of Patients with Ebola Virus Disease in Conakry, Guinea

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ABSTRACT

BACKGROUND

In March 2014, the World Health Organization was notified of an outbreak of *Zaire ebolavirus* in a remote area of Guinea. The outbreak then spread to the capital, Conakry, and to neighboring countries and has subsequently become the largest epidemic of Ebola virus disease (EVD) to date.

METHODS

From March 25 to April 26, 2014, we performed a study of all patients with laboratory-confirmed EVD in Conakry. Mortality was the primary outcome. Secondary outcomes included patient characteristics, complications, treatments, and comparisons between survivors and nonsurvivors.

RESULTS

Of 80 patients who presented with symptoms, 37 had laboratory-confirmed EVD. Among confirmed cases, the median age was 38 years (interquartile range, 28 to 46), 24 patients (65%) were men, and 14 (38%) were health care workers; among the health care workers, nosocomial transmission was implicated in 12 patients (32%). Patients with confirmed EVD presented to the hospital a median of 5 days (interquartile range, 3 to 7) after the onset of symptoms, most commonly with fever (in 84% of the patients; mean temperature, 38.6°C), fatigue (in 65%), diarrhea (in 62%), and tachycardia (mean heart rate, >93 beats per minute). Of these patients, 28 (76%) were treated with intravenous fluids and 37 (100%) with antibiotics. Sixteen patients (43%) died, with a median time from symptom onset to death of 8 days (interquartile range, 7 to 11). Patients who were 40 years of age or older, as compared with those under the age of 40 years, had a relative risk of death of 3.49 (95% confidence interval, 1.42 to 8.59; P=0.007).

CONCLUSIONS

Patients with EVD presented with evidence of dehydration associated with vomiting and severe diarrhea. Despite attempts at volume repletion, antimicrobial therapy, and limited laboratory services, the rate of death was 43%.

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Ebola virus is one of three members of the Filoviridae family and comprises five distinct species. Infection with *Zaire ebolavirus* (EBOV) has historically resulted in the highest case fatality rate — up to 90%.[1] Outbreaks typically originate with introduction of the virus into humans from a wild animal reservoir, with subsequent human-to-human transmission, often fueled by nosocomial amplification in resource-poor settings. Aside from a single infection with *Tai Forest ebolavirus*, West Africa has never had an outbreak of Ebola virus disease (EVD).[2,3]

The Republic of Guinea, on the west coast of Africa, has a population of approximately 11 million persons, a life expectancy at birth of 58 years, and an annual gross national income of 970 international dollars, with an expenditure on health care of 67 international dollars per capita per year.[4] Conakry, the capital and largest city, with an approximate population of 2 million persons, is served by a number of large hospitals, including Donka Hospital (the major public and university-affiliated medical center), Ignace Deen Hospital, and the Hôpital de l'Amitié Sino-Guinéenne, in addition to a number of privately funded health clinics.

On March 21, 2014, the World Health Organization (WHO) was formally notified of a rapidly evolving outbreak of EVD centered in the prefecture of Guéckédou, in the forested region of southeastern Guinea, with potential spread to border areas in Liberia and Sierra Leone.[5] Infected travelers from Guéckédou subsequently initiated chains of transmission of EVD in Conakry, more than 600 km away, marking the world's largest urban EVD outbreak and heralding the largest ever EVD epidemic, involving Guinea, Sierra Leone, Liberia, Nigeria, Senegal, and Mali.[6] A concurrent but epidemiologically unrelated outbreak has also been recognized in the Democratic Republic of Congo.[6]

The care of patients with EVD in Conakry initially occurred at two sites: the Hôpital de l'Amitié Sino-Guinéenne, which mainly focused on a large nosocomial outbreak affecting health care workers, and a stand-alone EVD treatment unit established on the grounds of Donka Hospital by the Ministry of Health, supported by Médecins sans Frontières and the WHO. As of October 31, 2014, the Guinea Ministry of Health had reported a cumulative total of 1667 clinical cases of EVD (with 1018 deaths), including 244 cases (and 98 deaths) in Conakry; a total of 13,562 cases (and 4950 deaths) were reported throughout West Africa.[7] Here we describe demographic and clinical characteristics of the patients at presentation, the clinical course of EVD, and outcomes of all patients admitted for care in Conakry during a 1-month period at the onset of the outbreak.

METHODS

STUDY DESIGN

We conducted a retrospective, observational study of all patients with suspected or confirmed EVD who were admitted for care in Conakry from March 25 to April 26, 2014 (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). We used a standard case definition that was established by the WHO and the Guinea Ministry of Health (Table S1 in the Supplementary Appendix). Laboratory confirmation of EVD was made on the basis of results on quantitative reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay in a laboratory established at Donka Hospital by the Institute Pasteur in Dakar, Senegal. Laboratory staff members used rapid Taqman RT-PCR assays for the detection of EBOV using 5-FAM and 3-TAMRA tagged probes and a portable SmartCycler TD. EBOV RNA in patient samples was measured according to the standard described by Weidmann et al.,[8] in which the sample is diluted to a range of 1 copy to 1 million copies and is then tested in quadruplicate to construct a standard curve for estimating the number of genome copies. Follow-up testing for antibodies against EBOV by means of enzyme-linked immunosorbent assay (ELISA) was performed as needed. Patients were treated in accordance with protocols established for viral hemorrhagic fever by Médecins sans Frontières and WHO urgent interim guidance for case management, endorsed by the Ministry of Health.[9,10]

DATA COLLECTION

Data-collection forms encompassed epidemiologic and demographic data, exposure history, occupation and recent travel, symptoms, onset date, vital signs at admission, and medical history. Also recorded were daily symptoms, vital signs, complications, treatments, laboratory test results when available, and outcomes. The clinical care team collected data from patients who

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were admitted to EVD treatment units. Admission data were reviewed daily by clinicians. Approval and a waiver from the need to provide written informed consent were obtained from the ethics review committees for the Guinean government and the WHO.

STATISTICAL ANALYSIS

We used Student's t-test, Fisher's exact test, or the Wilcoxon rank-sum test, as appropriate, to determine the association between mortality and the clinically informed variables of age, sex, occupation, the presence of gastrointestinal hemorrhage, the number of days between symptom onset and presentation, and viral load at presentation. We used Kaplan–Meier methods and log-rank tests to determine survival curves for various groups of patients, using the interval from the onset of symptoms to death for those who died within 28 days, with data censored at 28 days for survivors. We explored associations between the above-mentioned variables and death in univariate analyses.

We used a multivariate Poisson regression analysis with robust standard errors to investigate our three primary clinically informed hypotheses: that mortality was associated with older age, an increased interval from symptom onset until presentation to a treatment facility, and an increased viral load.[11,12] We examined survival according to age using a scatter plot and 5-year age bins to determine the most appropriate dichotomous age comparisons. We log-transformed viral loads for primary comparisons among survivors and nonsurvivors and performed sensitivity analyses dichotomizing viral loads using two sets of values (less than the sample median vs. greater than or equal to the sample median and <100,000 copies per milliliter vs. ≥100,000 copies per milliliter). All statistical tests were two-tailed, with a P value of less than 0.05 considered to indicate statistical significance. All analyses were performed with the use of SAS software, version 9.3 (SAS Institute), and R software, version 2.15.1.

Table 1. Characteristics, Symptoms, Vital Signs, and Time Course of Clinical Progression of 37 Patients with Confirmed Ebola Virus Disease (EVD).*

Variable	Value
Median age (IQR) — yr	38 (28–46)
Male sex — no. (%)	24 (65)
Health care worker — no. (%)	
Yes	14 (38)
No	23 (62)
Known mechanism of contact — no./total no. (%)†	
Health care	12/34 (35)
Household	23/37 (62)
Funeral	6/37 (16)
Known coexisting medical condition — no. (%)	
Hypertension	2 (5)
Human immunodeficiency virus	2 (5)
Diabetes	1 (3)
Renal insufficiency	1 (3)
Tuberculosis	1 (3)
Malaria at presentation — no. (%)	4 (11)
Symptoms — no./total no. (%)	
Fever	31/37 (84)
Fatigue	24/37 (65)
Diarrhea	23/37 (62)
Headache	12/21 (57)
Vomiting	21/37 (57)
Anorexia	16/37 (43)
Vital signs at admission	
Temperature — °C	38.6±1
Heart rate — beats/min	93±14
Systolic blood pressure — mm Hg	125±25
Median interval from onset of symptoms (IQR) — days	
To hospital admission	5 (3–7)
To death	8 (7–11)

* Plus–minus values are means ±SD. IQR denotes interquartile range.
† Some patients had more than one exposure.

RESULTS

STUDY PATIENTS

Eighty patients who had symptoms meeting the definition of suspected EVD were admitted to the two treatment facilities in Conakry. Among these patients, 37 (46%) were confirmed to have EVD, 36 (97%) by means of RT-PCR and 1 who had negative results on RT-PCR assay but had positive results for IgG antibodies on ELISA (Table 1). The latter patient had a clinical syndrome compatible with EVD and was a close contact of another patient with confirmed disease.

The median age of the confirmed cases was 38 years (range, 19 to 61), and 24 (65%) were men. The most common mechanism of contact was through household clusters, which accounted for 23 cases (62%). Fourteen patients (38%)

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were health care workers, in whom nosocomial transmission was implicated in 12 of 34 patients (35%). Participation in funeral ceremonies of confirmed cases was an additional risk factor for 6 of these patients (16%).

Clinical features at presentation were nonspecific and included fever in 31 patients (84%; mean temperature, 38.6°C), fatigue in 24 patients (65%), gastrointestinal symptoms (in 23 patients with diarrhea [62%] and 21 with vomiting [57%]), headache in 12 of 21 patients who were evaluated (57%), and anorexia in 16 patients (43%) (Table 1). At admission, patients had mild tachycardia (mean [±SD], 93±14 beats per minute) with a mean systolic blood pressure of 125±25 mm Hg. Hiccups occurred in 28% of patients during the period of hospitalization. The median time from symptom onset to presentation was 5 days (interquartile range, 3 to 7), and the median time from symptom onset to death was 8 days (interquartile range, 7 to 11).

Oral rehydration solution was given to 36 patients (97%), and 28 patients (76%) received additional intravenous fluid resuscitation (Table 2). A median of 1 liter of intravenous crystalloids was administered during the first 24 hours after admission. Antibiotics were administered empirically in 37 patients (100%) with gastrointestinal symptoms, and artemisinin-based combination therapy was administered in 7 patients (19%), of whom 4 had confirmed *Plasmodium falciparum* infection on rapid diagnostic testing. One patient (3%) received supplemental oxygen therapy for hypoxemia.

For the first 3 weeks of the outbreak, no routine clinical laboratory testing was available. For approximately 1 week, we used an i-STAT System point-of-care device with CHEM8+ and CG4+ cartridges (Abbott Point of Care) to perform limited diagnostic testing in 3 patients with clinical symptoms in the treatment center. In 1 patient, we found severe prerenal kidney dysfunction (creatinine, 13.9 mg per deciliter [1229 μmol per liter]; and blood urea nitrogen, >140 mg per deciliter [>50.0 mmol per liter]) and accompanying metabolic acidosis (pH, 7.21; and lactate, 7.4 mmol per liter), results that improved after the administration of approximately 5 liters of intravenous crystalloid fluids per day for 3 days (creatinine, 2.4 mg per deciliter [212 μmol per liter]; blood urea nitrogen, 40 mg per deciliter [14.3 mmol per liter]; pH, 7.46; and lactate, 1.1 mmol per liter). Similar findings were noted in a second patient (creatinine, 4.9 mg per deciliter [433 μmol per liter]; and blood urea nitrogen, 73 mg per deciliter [26.1 mmol per liter]), findings that were probably caused by profound diarrhea (potassium, 2.4 mmol per liter; and bicarbonate, 15 mmol per liter), which also resolved after the administration of approximately 4 liters of intravenous crystalloid fluids per day for 3 days along with potassium. Among 3 patients in whom anemia was suspected, including 1 patient with clinical evidence of lower gastrointestinal bleeding, hematocrit levels were not profoundly low (mean, 31.2±3.4).

Among the 16 patients (43%) who died, the median duration of hospital stay was 5 days, as compared with 9 days (interquartile range, 6 to 11) among survivors. The most common clinical complication was hemorrhage, which was reported in 19 patients (51%), most frequently gastrointestinal bleeding (in 9 patients), of whom 8 patients had melena and 1 patient each had hematemesis and hematochezia (Table 3).

In univariate analyses, the viral load appeared to be higher among patients who died than in survivors (Table 4), but this finding was influenced by the deaths of all 4 patients who had a viral load of more than 100,000 copies per milliliter on admission, and viral load was not significantly associated with death on nonparametric testing. Mortality was not significantly higher among the few patients who had coexisting conditions than in those without such conditions (57.1% vs. 40.0%, P=0.44). However, an older

Table 2. Therapies Received by 37 Patients Hospitalized for EVD.

Therapy	Value
Oral rehydration solution — no. (%)	36 (97)
Intravenous fluids — no. (%)	28 (76)
Median volume of crystalloid solution administered in first 24 hr (IQR) — liters	1 (1–1)
Antibiotic treatment — no. (%)	
Any	37 (100)
Ciprofloxacin	20 (54)
Ceftriaxone	13 (35)
Cefixime	5 (14)
Amoxicillin–clavulanic acid	1 (3)
Antimalarial treatment — no. (%)	7 (19)
Supplemental oxygen therapy — no. (%)	1 (3)

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Table 3. Clinical Complications and Outcomes for 37 Patients with EVD.

Variable	Value
Hospital mortality — no. (%)	16 (43)
Median length of stay in hospital (IQR) — days	8 (6–11)
Known complications in hospital — no. (%)	
Hemorrhage	
Any	19 (51)
Gastrointestinal	9 (24)
Subconjunctival	4 (11)
Intravenous catheter site	4 (11)
Nasorespiratory tract	2 (5)
Renal failure*	2 (5)
Seizure	2 (5)
Oral candidiasis	1 (3)
Hypoxemia	1 (3)

* Renal failure was defined as a serum creatinine level of more than 4 mg per deciliter (350 μmol per liter).

age was associated with an increased risk of death, with a median age of 29 years in survivors as compared with 45 years in those who died (P=0.005) (Fig. 1). In a multivariable Poisson regression analysis that was adjusted for age, viral load, and time from symptom onset to presentation, patients who were 40 years of age or older had a relative risk of death of 3.49 (95% confidence interval [CI], 1.42 to 8.59), as compared with those under the age of 40 years (P=0.007). There were no significant differences between survivors and nonsurvivors in the number of days between symptom onset and admission (relative risk in survivors, 0.94; 95% CI, 0.86 to 1.04; P=0.22) and viral load on admission (relative risk, 0.98; 95% CI, 0.91 to 1.07; P=0.72).

DISCUSSION

Patients, on average, presented 5 days after symptom onset, and the most common manifestations of EVD during hospitalization were fever, vomiting, diarrhea, and related volume depletion requiring the administration of intravenous fluids and electrolyte therapy. Overall mortality among patients presenting for treatment was 43%, and only the age of the patient was a significant predictor of outcome. In contrast to previous Ebola virus outbreaks in which an older age was also associated with a worse outcome, the mean age of nonsurvivors in our study was low.[13,14] The association between an older age and a worse outcome among patients with viral infections is often attributed to an increased number of coexisting conditions. However, in our study, the relative absence of known coexisting conditions suggests that an older age may have an independent association with mortality. We also found that patients who presented for care with the highest viral loads were the least likely to survive, as has been shown for other strains of Ebola virus.[15] After adjustment for dif-

Table 4. Characteristics of Survivors and Nonsurvivors.

Characteristic	Survivors (N=21)	Nonsurvivors (N=16)	P Value
Median age (IQR) — yr	29 (26–37)	45 (40–47)	0.005
Male:female ratio	14:7	10:6	1.00
Viral load at admission			
Mean ±SD — copies/ml	8207±17,189	68,361±111,340	0.02
Median (IQR) — copies/ml	1079 (148–5059)	1915 (141–12,998)	0.47
>100,000 copies/ml — no. (%)	0	4 (25)	0.02
Health care worker — no. (%)	6 (29)	8 (50)	0.31
Clinical features			
Hemorrhage — no. (%)			
Any visible	8 (38)	11 (69)	0.1
Gastrointestinal	4 (19)	6 (38)	1.0
Interval from symptom onset to presentation (IQR) — days	5 (4–8)	5 (2–7)	0.49

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ferences in age and time to presentation, this relationship was not significant. However, our study had limited power to detect all predictors of outcome because of the small number of patients.

The case fatality rate that we observed in this cohort in the capital city of Conakry was lower than the rate reported in most studies of previous EVD outbreaks[1] (although not in all studies[7]) and was lower than the rate in most other regions in Guinea at that point in the epidemic.[7,13] Clinical care at the main isolation facility near Donka Hospital was jointly provided by the Ministry of Heath, Médecins sans Frontières, and the WHO during the study period. Adherence to new guidelines promoting increased medical interventions, particularly related to the use of oral and intravenous fluids and electrolyte replacement, appropriate antibiotics, and targeted clinical laboratory testing,[9] may have contributed to the reduced case fatality rate, as compared with past outbreaks. However, assessing associations between treatments and outcomes in small observational studies is challenging. In our study, there were approximately three clinical rounds per day, with two or three doctors and two or three nurses for each round, and depending on the type of personal protective equipment that was used, rounds were limited to either 1 hour or 3 hours because of the intense heat and humidity inside some types of personal protective equipment. Although we attempted to deliver oral and intravenous fluids to correct dehydration and metabolic abnormalities, care was still suboptimal. With more clinical personnel in each treatment center, better supportive care could be delivered more consistently, and we think that mortality could be driven lower.

The predominant clinical syndrome of EVD involves substantial volume loss due to vomiting and diarrhea. This requires aggressive oral and intravenous volume repletion and close follow-up to avoid further complications and hypoperfusion-associated organ dysfunction. Point-of-care diagnostic testing provided additional insights in a small number of patients, suggesting inadequate tissue perfusion — lactic acidosis, base deficits, prerenal kidney dysfunction, and low venous oxygen saturations. However, we could not perform such testing early or frequently enough to properly define the patterns. The substantial volume loss and profound electrolyte derangement from copious diarrhea represent opportunities to intervene clinically to improve outcomes. Notably, hypoxemia was rarely seen in these patients, despite attempts at aggressive volume repletion. However, this finding may still represent inadequate volume administration, and hypoxemia caused by pulmonary vascular leak may be more common in other care settings. Consideration may also be given to the empirical use of antimalarial therapy, especially if rapid diagnostic testing is not immediately available. Patients with severe gastrointestinal symptoms were also routinely treated with a finite empirical course of antibiotics with activity against gram-negative, gram-positive, and anaerobic organisms. However, the effect of this intervention remains unknown.

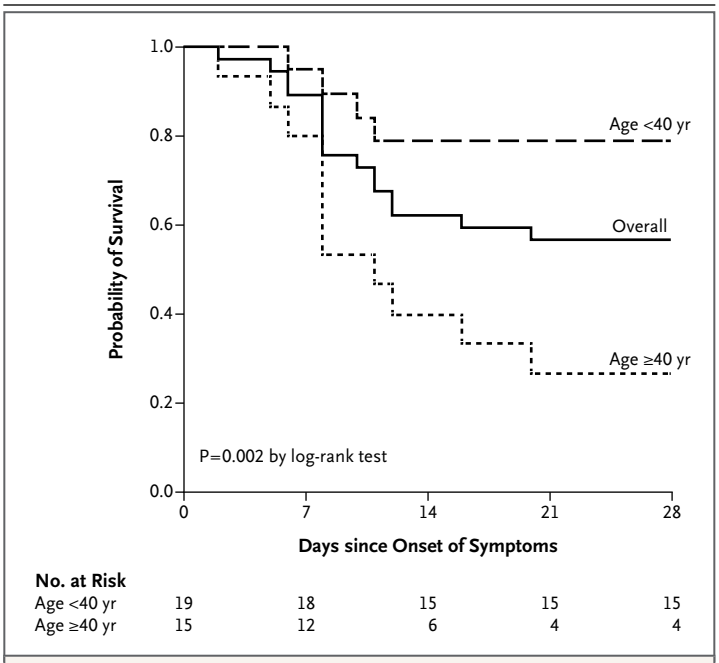

Figure 1. Kaplan–Meier Estimate of the Probability of Survival among Patients with Ebola Virus Disease, According to Age.

As has been seen in other disease outbreaks, but never before with EVD, large urban settings present special challenges to emergency health care facilities, and nosocomial transmission among health care staff members and patients represents an important potential outbreak amplification and new lines of transmission.[16,17] This finding highlights the importance of rapid support for infection control, not only in dedicated isolation facilities but also within existing treatment centers that will typically receive un-

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differentiated patients with fever and nonspecific symptoms. Infection-control practices to protect patients and health care workers can have unanticipated negative consequences, including fewer clinical assessments, which may be compounded by limited clinician time at the bedside because of heat exposure in personal protective equipment.[18,19]

Limitations of our study include reliance on estimates from a discrete but relatively small cohort of patients. However, the observed mortality in Conakry (43%) has remained relatively stable (40%) between April and October 2014.[20] Despite an active public health system for tracing contacts, case finding, and referral to an acute care facility, we inevitably are unable to identify all patients with suspected and confirmed EVD, since some will choose not to present to health care facilities and some will die before seeking medical attention. This potential selection bias will underestimate the number of cases and have uncertain effects on the case fatality rate for this epidemic. The inclusion of only patients who could be transported to our health care facilities may lead to a survivorship and immortal time bias, since patients with EVD needed to have survived long enough to get to a facility in order to be described and to receive certain treatments. Furthermore, selection of patients for certain treatments is subject to bias according to indication, which can lead to an overestimation of harm for certain therapies.[21] Therefore, in this observational study, we are unable to validly explore relationships between treatments received and clinical outcomes, which underscores the importance of enhanced strategies for supportive care and specific therapies in future clinical trials.

Our recording of simple clinical data was also limited by an inability to take any material, including paper, outside the treatment center, by limited electricity to power onsite electronic data capture, and by unreliable Internet access. Inside the treatment facility, with too few clinical staff members, there is often a trade-off between delivering and recording care. A further limitation is the paucity of basic data regarding blood chemistry and hematology that would better characterize metabolic abnormalities and help to direct care for future patients. Point-of-care testing inside treatment centers is challenging because of a lack of time to perform testing due to high temperatures and dehydration of health care providers. Routine deployment of basic chemistry and hematology analyzers in addition to RT-PCR assays for EBOV in international mobile laboratories would alleviate this limitation and may guide further improvements in patient care.

In conclusion, we found that among patients admitted to the hospital with confirmed EVD in Conakry, Guinea, the most common clinical syndrome was one of gastrointestinal illness, intravascular volume depletion, and related complications, which highlight the importance of enhanced levels of clinical assessment and diagnostic testing, along with fluid management.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

APPENDIX

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