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Clinical Management of Ebola Virus Disease in the United States and Europe

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Abstract

Background—Available data on the characteristics of patients with Ebola virus disease (EVD) and clinical management of EVD in settings outside West Africa, as well as the complications observed in those patients, are limited.

Methods—We reviewed available clinical, laboratory, and virologic data from all patients with laboratory-confirmed Ebola virus infection who received care in U.S. and European hospitals from August 2014 through December 2015.

Results—A total of 27 patients (median age, 36 years [range, 25 to 75]) with EVD received care; 19 patients (70%) were male, 9 of 26 patients (35%) had coexisting conditions, and 22 (81%) were health care personnel. Of the 27 patients, 24 (89%) were medically evacuated from West Africa or were exposed to and infected with Ebola virus in West Africa and had onset of illness and laboratory confirmation of Ebola virus infection in Europe or the United States, and 3 (11%) acquired EVD in the United States or Europe. At the onset of illness, the most common signs and symptoms were fatigue (20 patients [80%]) and fever or feverishness (17 patients [68%]). During the clinical course, the predominant findings included diarrhea, hypoalbuminemia, hyponatremia, hypokalemia, hypocalcemia, and hypomagnesemia; 14 patients (52%) had hypoxemia, and 9 (33%) had oliguria, of whom 5 had anuria. Aminotransferase levels peaked at a median of 9 days after the onset of illness. Nearly all the patients received intravenous fluids and electrolyte supplementation; 9 (33%) received noninvasive or invasive mechanical ventilation; 5 (19%) received continuous renal-replacement therapy; 22 (81%) received empirical antibiotics; and 23 (85%) received investigational therapies (19 [70%] received at least two experimental interventions). Ebola viral RNA levels in blood peaked at a median of 7 days after the onset of

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illness, and the median time from the onset of symptoms to clearance of viremia was 17.5 days. A total of 5 patients died, including 3 who had respiratory and renal failure, for a mortality of 18.5%.

Conclusions—Among the patients with EVD who were cared for in the United States or Europe, close monitoring and aggressive supportive care that included intravenous f luid hydration, correction of electrolyte abnormalities, nutritional support, and critical care management for respiratory and renal failure were needed; 81.5% of these patients who received this care survived.

The Ebola Virus Disease (EVD) Epidemic in West Africa had resulted in more than 28,600 reported cases and more than 11,300 deaths through December 2015; mortality reported for patients with EVD cared for in Ebola treatment units in West Africa has ranged from 37 to 74%.[1-5] The provision of clinical care to patients with EVD in Ebola treatment units in West Africa has involved the need to balance many challenges, such as overwhelming numbers of severely ill patients, limited medical and nonmedical supplies, insufficient numbers of caregivers and resources, and hot and humid working conditions that limit the time that health care personnel in full personal protective equipment can attend to each patient.[3,6,7] Thus, although most patients with EVD have received supportive care with oral rehydration solutions, antiemetic agents, analgesics, and antibiotics, not all Ebola treatment units have had intravenous and electrolyte-replacement fluids available. It is believed that aggressive intravenous fluid hydration and correction of electrolyte abnormalities may improve the outcomes among severely ill patients with EVD.[3,5,7-9]

Since early August 2014, several patients who received a diagnosis of EVD in West Africa were medically evacuated for care in higher-resource settings in Europe and the United States.[10-16] In addition, a small number of patients received a diagnosis of EVD in Europe or the United States after they were infected by Ebola virus (EBOV) in West Africa or through nosocomial transmission in Europe or the United States.[17,18] Beginning in September 2014, conference calls among physicians in the United States and Europe who were caring for patients with EVD were held regularly — often weekly — to share detailed information and experiences in clinical care. Patients with EVD who were cared for in Europe and in the United States received close monitoring of hemodynamic status, underwent extensive laboratory investigations, were provided supportive critical care management and nursing care, and were given the opportunity for treatment with investigational therapies that were not routinely available in Ebola treatment units in settings with limited resources. In this report, we describe the clinical characteristics and clinical care of all the patients with EVD who were cared for in the United States and Europe.

Methods

Study Design

Anonymized demographic, clinical, laboratory, and virologic data were collected retrospectively for all patients with confirmed EBOV infection who received treatment in the United States and Europe from August 2014 through December 2015. All care and testing were clinically driven. Laboratory assays used in the care of patients with EVD are listed in the Methods section in the Supplementary Appendix, available with the full text of this

article at NEJM.org. An Excel form was used as a standard data-collection tool by clinicians at each participating hospital. Data were uploaded through a secure server at the Centers for Disease Control and Prevention (CDC) and pooled for descriptive analyses.

Study Population

A patient with confirmed EVD was defined as an ill person with a blood, serum, or plasma specimen that tested positive on a reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay that used primers and probes specific for EBOV. A medically evacuated patient with EVD was defined as a patient who had the onset of illness and laboratory confirmation of EBOV infection in West Africa and was then transported by air ambulance for care in Europe or the United States. A patient with an imported case of EVD was defined as a patient who had been exposed to and infected with EBOV in West Africa and had onset of illness and laboratory confirmation of EBOV infection in Europe or the United States. A locally acquired case was defined as a patient in whom exposure to EBOV, onset of illness, and laboratory confirmation of EBOV infection by RT-PCR occurred in Europe or the United States.

Study Oversight

This data-collection activity was determined to constitute a public health response not requiring institutional board review at the CDC. However, for some participating institutions, written informed consent by the patient or the patient's family was required and obtained for data collection. No specific funding was provided for this work. Clinical data for some of these patients with EVD have been published previously.[10-16,18-20]

Statistical Analysis

Statistical significance was assessed with the use of Fisher's exact test for binary values and a nonparametric two-sample test for median values equivalent to the Brown–Mood test; P values of less than 0.05 were considered to indicate statistical significance, without correction for multiple testing. Analyses were performed with the use of SAS statistical software, version 9.3 (SAS Institute), and Excel (Microsoft).

Results

Patients

A total of 27 patients with EVD received care in Europe or the United States at 15 hospitals in nine countries. Overall, the median age of the patients was 36 years (range, 25 to 75); 19 patients (70%) were male and 9 of 26 patients (35%) had coexisting conditions (Table S1 in the Supplementary Appendix). Twenty patients (74%; median age, 36.5 years) were medically evacuated from West Africa, and 3 patients (11%; median age, 29 years) were health care personnel who acquired EVD locally in the United States or Europe while caring for patients with EVD; in addition, there were 4 patients (15%; median age, 38.5 years) with imported cases of EVD. A total of 22 patients (81%) were health care personnel, of whom 17 (77%) had worked in an Ebola treatment unit in West Africa. Among the 27 patients with EVD, the median time from the onset of illness to the diagnosis of EVD was 3 days (range, 1 to 9), and the median time from the onset of illness to hospitalization was 4 days (range, 0

to 15) (Table S1 in the Supplementary Appendix). The median time from the onset of illness to hospitalization was 2 days among patients with imported cases and 4 days among both medically evacuated patients and patients with locally acquired cases.

Clinical Findings

At the time of the onset of illness, the most common sign or symptom reported was fatigue, which affected 20 patients (80%); fever or feverishness was reported in 17 patients (68%). Other symptoms are shown in Figure 1A. By the time of admission to a hospital in Europe or the United States, most patients had fever, weakness, and gastrointestinal symptoms (Fig. 1B). Clinical findings during hospitalization are summarized in Table 1 and Table 2. Nearly half the patients had hypoxemia, with a median oxygen saturation of 84.5% while they were breathing ambient air, as measured by means of pulse oximetry. All the patients had diarrhea, with a median duration of 6 days and an estimated median maximum stool output of 3000 ml per 24 hours (range, 100 to 10,000). A total of 33% had renal abnormalities, as manifested by oliguria or anuria during the hospitalization. Sixteen patients (59%) received a clinical diagnosis of the systemic inflammatory response syndrome. Neurologic complications such as encephalopathy or encephalitis were reported in one third of patients. A total of 9 patients (33%) had some evidence of bleeding (epistaxis, petechiae, melena, bloody diarrhea, or oozing around an intravenous catheter site) at the time of hospital admission in the United States or Europe, and 14 (52%) had oozing around an intravenous catheter site during hospitalization; however, gross hemorrhage was observed in only 2 patients (7%) at any time during hospitalization.

Laboratory Findings

Leukopenia was prominent in the first week of illness, with the nadir white-cell count at a median of 6 days after the onset of illness and the highest white-cell count at a median of 13 days after the onset of illness. Thrombocytopenia was reported in nearly all the patients. (Daily hematologic values are shown in Figs. S1–S5 of the Supplementary Appendix.) Most patients had an elevated international normalized ratio during their hospitalization (median, 1.49) (Table S2 in the Supplementary Appendix). Aminotransferase levels peaked in the second week of illness; the median maximum aspartate aminotransferase level was more than three times the median maximum alanine aminotransferase level. Bilirubin levels, however, were only slightly elevated in most patients. Creatine kinase levels were markedly elevated in most patients tested, with a median maximum level of 1007.5 U per liter. Serum lactate levels were elevated in most patients who were tested, with a median maximum value of 2.8 mmol per liter. Five patients (19%) had elevated creatinine levels at admission, and 11 patients (41%) had elevated creatinine levels at any time during hospitalization. Of those tested, the majority of patients with EVD had metabolic abnormalities that included hyponatremia, hypokalemia, hypocalcemia, and hypomagnesemia, and all the patients had hypoalbuminemia during their hospitalization (Table 2).

Supportive Clinical Care

All patients received oral or intravenous electrolyte-replacement fluids to correct metabolic abnormalities. All but 1 patient received intravenous fluids, and 15 patients (56%) received total parenteral nutrition. A total of 11 patients (41%) had a peripherally inserted central

catheter, and 18 (67%) had a central venous catheter placed (Table 1). Fluids were administered intravenously in 18 of 20 medically evacuated patients before their arrival in the United States or Europe, either initiated in West Africa or initiated during the evacuation flight. Antiemetics were given to most patients, but few received antidiarrheal medications (Table S3 in the Supplementary Appendix). A total of 22 patients (81%) received empirical antibiotic treatment with a median of 2 antibiotics (range, 0 to 7), the most common of which was a third-generation cephalosporin. Of the 24 patients with EVD who had been in West Africa, 17 received antimalarial prophylaxis or treatment (or both) during their illness; of 14 patients who received antimalarial prophylaxis or treatment in West Africa, 1 had confirmed malaria. Of 8 patients who were treated for malaria in the United States or Europe, 2 had malaria that was confirmed by parasitologic testing. A total of 11 patients with EVD (41%) received nonconvalescent blood products, including nonconvalescent whole blood in 4 patients, fresh-frozen plasma in 6 patients, and platelets in 5 patients.

Respiratory supportive care was provided frequently; 19 patients (70%) received supplemental oxygen, of whom 9 (47%) had respiratory failure (Table 1). The median time from illness onset to respiratory failure was 9 days (range, 4 to 18). Four patients (15%) received noninvasive ventilation, of whom 2 also received invasive mechanical ventilation after noninvasive ventilation failed.

In total, 7 patients (26%) received invasive mechanical ventilation. Five of the 7 patients who received invasive mechanical ventilation also received continuous renal-replacement therapy; 4 had been medically evacuated.

Investigational Therapies

Investigational therapies, which included immunotherapies (convalescent plasma or whole blood or triple monoclonal antibody cocktails [ZMapp, ZMab, or MIL77]) and products that had presumed antiviral activity (TKM-Ebola, favipiravir, brincidofovir, or amiodarone), or therapies that were administered to counteract vascular leak (FX06 or melanocortin) were administered to 23 patients (85%) off-label or on a compassionate-use basis (Table 3). Only patients in Europe received ZMab, MIL77, favipiravir, FX06, or melanocortin. A total of 19 patients (70%) received at least two investigational therapies. A wide range of possible adverse effects was reported from these investigational therapies, such as the systemic inflammatory response syndrome, hypotension, elevated aminotransferase levels, and transfusion-associated acute lung injury (Table 3).

Results from Virologic and Immunologic Examination

At admission to a facility (mainly in the United States or Europe), the median RT-PCR cycle-threshold value for detecting EBOV RNA was 24 at a median of 5 days after the onset of illness (Table 4); for patients with available data on EBOV load, the median EBOV RNA level on admission was 2.7×10^7 copies per milliliter at a median of 6.5 days after the onset of illness. The median lowest cycle-threshold value was 21 at a median of 7 days after the onset of illness, and the median of the highest EBOV RNA level was 7.3×10^7 copies per milliliter at a median of 7 days after the onset of illness. The median time from the onset of illness to the first negative RT-PCR assay result for EBOV RNA in a blood specimen was

17.5 days. (Daily EBOV levels in blood specimens are shown in Figs. S6 and S7 of the Supplementary Appendix.) EBOV RNA was detected in saliva, sweat, stool, rectal swab, semen, vaginal, and skin swab specimens (Table S4 in the Supplementary Appendix). After the exclusion of recipients of antibody-based immunotherapies (convalescent plasma, ZMapp, ZMab, and MIL77), IgM antibodies to EBOV were first detected in five patients at a median of 10 days (range, 6 to 11) after the onset of illness, and IgG antibodies to EBOV were first detected in six patients at a median of 11 days (range, 9 to 11) after the onset of illness.

Outcomes

Overall, 5 patients with EVD died (mortality was 11.1% after 14 days of illness and 18.5% after 28 days of illness), 20 were discharged home, and 2 were discharged to a rehabilitation facility (Table S5 in the Supplementary Appendix). The patients who died were older than the patients who survived (median age, 56 years [range, 42 to 75] vs. 34.5 years [range, 25 to 59]; P = 0.01). Among the 5 critically ill patients who had multiorgan failure and received both invasive mechanical ventilation and continuous renal-replacement therapy, 3 died. The 2 patients who received only noninvasive ventilation survived. A total of 8 patients (30%), including the 5 patients who died, received vasopressors or inotropes. No patient received cardiopulmonary resuscitation; 2 of the patients with fatal cases of EVD received resuscitation medications, and 1 of these patients also received transcutaneous pacing.

Patients who survived were hospitalized sooner after the onset of illness than were the patients who died (median, 3.5 days vs. 5 days; P = 0.03) (Table S1 in the Supplementary Appendix). Among the medically evacuated patients, the median time from the onset of illness to initial hospitalization was shorter for the 16 patients who survived than for the 4 patients who died (4 days vs. 5 days, P = 0.02), as was the time from the onset of illness to hospital admission outside West Africa (6 days vs. 7.5 days, P = 0.03).

Among the patients with available data on creatinine and bilirubin levels at hospital admission in the United States or Europe, the proportion of patients with elevated levels of creatinine (>1.3 mg per deciliter [115 μmol per liter]) was significantly higher among the patients who died than among the patients who survived (3 of 5 patients vs. 2 of 22 patients, P = 0.03); similarly, the proportion of patients with elevated levels of bilirubin (>1.5 mg per deciliter [25.7 μmol per liter]) was significantly higher among the patients who died than among those who survived (2 of 5 patients vs. 0 of 17 patients, P = 0.04). The initial median RT-PCR cycle-threshold value was lower, reflecting higher EBOV RNA levels, among the patients who died than among the patients who survived (21.2 vs. 24.9, P = 0.08), as was the median of the lowest RT-PCR cycle-threshold value anytime during the hospitalization (17.9 vs. 22.8, P = 0.08), but these differences were not significant.

The median duration of hospitalization in Europe or the United States was 20 days among the patients who survived and 7 days among the patients who died. Among the patients who survived, the median time from illness onset to discharge was 28 days (range, 14 to 48), and among the patients who died, the median time from illness onset to death was 14 days (range, 11 to 15). A high proportion of patients who survived had weakness, weight loss,

anemia, and other laboratory abnormalities at the time of discharge (Table S5 in the Supplementary Appendix).

Discussion

The severity of disease among the patients with EVD who received care in Europe and the United States ranged from moderate to critical and fatal illness. Overall, mortality among those who were cared for in Europe or the United States was substantially lower (18.5%) than that among those who were cared for in Ebola treatment units in West Africa (37 to 74%).[2-5] All 5 patients who died were 42 years of age or older; in various studies, age older than 40 years or older than 45 years has been identified as a risk factor in West Africa.[2,21,22] The percentage of patients who died could have been as high as 41% (11 of 27 patients), with up to six additional deaths, if advanced organ support had been unavailable for 2 survivors who received noninvasive ventilation, 2 survivors who received invasive mechanical ventilation, and 2 survivors who received both invasive mechanical ventilation and continuous renal-replacement therapy. A key feature of the clinical care of patients with EVD who were treated in Europe and the United States was the availability of laboratory testing to closely monitor electrolyte levels and hematologic status. Our experience suggests that early presentation and receipt of supportive care, intravenous fluid resuscitation, careful fluid management and electrolyte replacement to correct metabolic abnormalities, nutritional support, and critical care support may reduce mortality among patients with EVD.

A total of 5 patients had anuric renal failure and received continuous renal-replacement therapy; the details regarding 3 of these patients have been published previously.[11,12,16,23] Acute renal failure could be caused by hypovolemic shock and acute tubular necrosis; EBOV infection of renal endothelial, interstitial, and tubular cells; or other factors.[24] The high creatine kinase levels observed in most of the 27 patients with EVD we evaluated suggest that the elevated aspartate aminotransferase levels in most patients with EVD could originate from both hepatic and muscle sources, with rhabdomyolysis and myo-globinuria also potentially contributing to renal injury.

Although EVD is not typically thought to have a clinically significant respiratory component, 8 of the 27 patients (30%) we evaluated had cough at admission, a finding that is consistent with previous observations.[21] Difficulty breathing at admission was associated with a fatal outcome among patients with EVD in Guinea.[22] Overall, 9 of the patients with EVD (33%) who were cared for in the United States or Europe received noninvasive ventilation or invasive mechanical ventilation for respiratory failure. The 2 patients with EVD who received noninvasive ventilation alone survived; however, of the 7 patients who received invasive mechanical ventilation, the 3 patients who also had renal failure that required continuous renal-replacement therapy died. The pathophysiological mechanism of pulmonary disease in patients with EVD is unknown, but there could be multiple contributing factors, including vascular leak from endothelial infection or cytokine dysregulation or direct damage to EBOV-infected cells. Evidence of replicating EBOV in alveolar macrophages and free EBOV in alveolar spaces has been reported in autopsy studies.[24] Among the patients with EVD who were cared for in Europe and the United States, other possible factors may contribute to pulmonary disease, such as aggressive

intravenous fluid repletion or acute lung injury caused by or exacerbated by investigational therapies.[15]

Most patients with EVD who were cared for in the United States or Europe received investigational therapies. Several patients had adverse events that were suspected to be related to the administration of these therapies. However, the clinical benefit as well as any harms associated with these experimental treatments cannot be independently assessed or distinguished from the supportive care administered because of their uncontrolled administration and because most patients received multiple, overlapping investigational therapies. In addition, it has been noted recently that the case-fatality proportion has been reduced over time in West Africa[25]; whether this may be a result of improvements in supportive care, observed reductions in EBOV RNA levels, or other factors is unknown. These issues argue against the use of historical controls and highlight the need for well-designed controlled clinical trials, including trials in settings that can provide critical care.

Our findings have several limitations. First, the number of patients with EVD who were treated in the United States and Europe was very small relative to the number of patients in West Africa, and the study was underpowered to detect significant differences between fatal and nonfatal cases. Second, all the patients were adults, most were not African, and data on the medical care that was provided to medically evacuated patients while they were in West Africa were limited. It is unknown whether recall bias regarding symptoms at the onset of illness was greater for medically evacuated patients who presented to medical care slightly later than patients with imported or locally acquired cases of EVD. Third, laboratories at participating sites used different RT-PCR assays to detect EBOV RNA, and therefore the cycle-threshold values and EBOV RNA levels were not comparable. Clinical laboratory testing was not performed systematically for all the patients, and the clinical diagnoses of conditions, clinical management, and decisions to use investigational therapies were not standardized. Discharge criteria were not uniform at all clinical sites, and the most reliable testing indications for discharge among survivors remain uncertain.[26] Fourth, although most of the patients with EVD who were treated in Europe or the United States received investigational therapies, the clinical benefit of these uncontrolled interventions in addition to supportive management is unknown. Finally, given the retrospective nature of the collection of observational data without a comparison group and given the aforementioned limitations, our findings might not be generalizable to adult or pediatric patients with EVD in West Africa.

Although mortality due to EVD remains high, our findings indicate that close monitoring and aggressive supportive care, including intravenous fluid hydration, correction of electrolyte abnormalities, nutritional support, and critical care management for respiratory and renal failure, can improve survival among patients with EVD. Our findings also suggest that efforts should be made to improve the clinical care of patients with EVD in settings with limited resources, such as making certain that serum electrolyte levels and hematologic status can be closely monitored and intravenous fluid resuscitation and hydration, electrolyte replacement, and close supportive care can be provided, while ensuring adherence to recommended personal protective equipment and infection control precautions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Appendix

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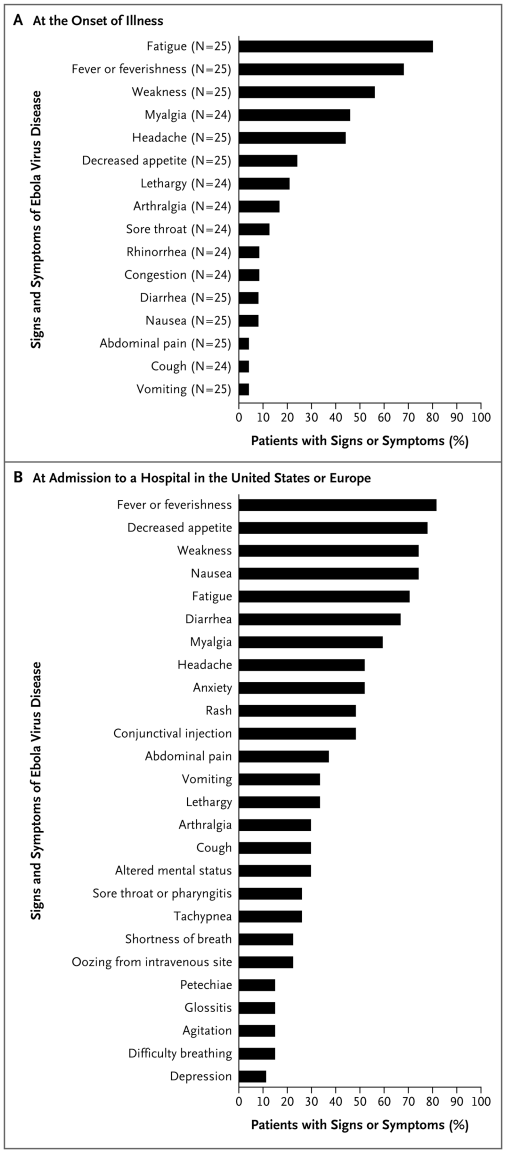

Figure 1. Signs and Symptoms of Ebola Virus Disease Reported at the Onset of Illness and at Admission to a Hospital in Europe or the Unites States

In Panel A, data were not available for all patients; the numbers in parentheses signify the numbers of patients with available data. In Panel B, data were available for all 27 patients for all signs and symptoms.

Table 1

Clinical Findings and Interventions for 27 Patients with Ebola Virus Disease during Hospitalization in the United States or Europe

Clinical Finding or Intervention*	Patients (N = 27)
	no. (%)
Fever†	25 (93)
Pulmonary findings	
Hypoxemia‡	14 (52)
Pulmonary edema	12 (44)
Pneumonia	7 (26)
Respiratory failure	9 (33)
ARDS§	6 (22)
Supplemental oxygen¶	19 (70)
Noninvasive ventilation	4 (15)
Invasive mechanical ventilation	7 (26)
Renal findings	
Oliguria (urine <500 ml/day)	9 (33)
Anuria (urine <100 ml/day)	5 (19)
Dialysis catheter	5 (19)
CRRT	5 (19)
Cardiac findings	
Arrhythmia or electrocardiographic changes	11 (41)
Vasopressors or inotropes	8 (30)
Gastrointestinal findings	
Diarrhea‖	27 (100)
Vomiting	20 (74)
Ileus**	4 (15)
Intestinal paresis	4 (15)
Abdominal distention	10 (37)
Infectious findings	
Sepsis††	7 (26)
Septic shock††	2 (7)
SIRS††	16 (59)
Malaria‡‡	2 (7)
Neurologic findings	
Delirium§§	9 (33)
Encephalopathy or encephalitis§§	9 (33)

Clinical Finding or Intervention*	Patients (N = 27)
	no. (%)
Seizures	1 (4)
Coma	3 (11)
Hematologic findings	
Oozing from intravenous sites	14 (52)
Frank hemorrhage	2 (7)
Intravenous access¶¶	27 (100)
Peripherally inserted central catheter	11 (41)
Central venous catheter	18 (67)
Other intervention	
Rectal tube	12 (44)
Indwelling urinary catheter	17 (63)
Critical illness////	11 (41)
Resuscitation attempt	2 (7)

*Information on the median duration (range) of the clinical finding or intervention was collected for only a small number of variables: fever, 7.5 days (1–16); noninvasive ventilation, 4 days (1–7); invasive mechanical ventilation, 5 days (0.5–13); continuous renal-replacement therapy (CRRT), 4 days (2–28); diarrhea, 6 days (1–20); and vomiting, 2 days (1–27).

†Fever was defined as a temperature higher than 38.0°C. The median temperature of the 27 patients at admission was 38.2°C (range, 34.6 to 40.4).

‡The median minimum oxygen saturation while the patients were breathing ambient air was 84.5% (range, 65 to 93) as measured by pulse oximetry.

§Of the 9 patients with respiratory failure, 6 received a clinical diagnosis of the acute respiratory distress syndrome (ARDS), of whom 4 had concomitant pneumonia. One patient who received a clinical diagnosis of ARDS received supplemental oxygen without ventilatory support. Of the 4 patients with respiratory failure who did not receive a diagnosis of ARDS, 1 had pneumonia.

¶Supplemental oxygen was delivered through a nasal cannula or face mask. Of the 4 patients who received non-invasive ventilation, 2 subsequently received invasive mechanical ventilation after noninvasive ventilation failed.

//The median maximum volume of diarrhea per 24 hours was 3000 ml (range, 100 to 10,000).

**Ileus was diagnosed by means of ultrasonography; none of the 4 patients with ileus had received antimotility agents.

††Sepsis, septic shock, and the systemic inflammatory response syndrome (SIRS) were diagnosed clinically; 7 patients had both sepsis and SIRS reported, including the only patient with documented bacteremia.

‡‡Cases of malaria were confirmed through parasitologic examination in the United States or Europe; at least 1 additional patient had confirmed malaria that was treated in West Africa.

§§Delirium and encephalopathy or encephalitis were diagnosed clinically; lumbar puncture and neuroimaging were not performed.

¶¶The median maximum volume of intravenous fluid per 24 hours was 4000 ml (range, 0 to 13,734). One patient had a peripheral intravenous catheter placed and received intravenous fluids in West Africa but not after medical evacuation.

////Critical illness was defined as illness that necessitated a patient's receipt of noninvasive ventilation, invasive mechanical ventilation, CRRT, or vasopressors or inotropes.

Table 2

Proportion of Patients with Abnormal Laboratory Values at Admission or at Any Time during Hospitalization in the United States or Europe*

Abnormal Laboratory Result	At Admission	During Hospitalization	Treatment Received during Hospitalization†
	no./total no. tested (%)		*no./total no. (%)*
Hyponatremia (sodium <135 mmol/liter)‡	12/27 (44)	21/27 (78)	21/21 (100)
Hypokalemia (potassium <3.5 mmol/liter)	10/27 (37)	18/27 (67)	18/18 (100)
Hypocalcemia (total calcium <8 mmol/liter)	10/16 (62)	15/20 (75)	10/15 (67)
Hypomagnesemia (magnesium <0.85 mmol/liter)	9/10 (90)	14/17 (82)	10/14 (71)
Hypoalbuminemia (albumin <3.5 g/dl)	20/25 (80)	25/25 (100)	7/25 (28)
Elevated creatinine (>1.3 mg/dl)	5/27 (19)	11/27 (41)	
Elevated bilirubin (>1.5 mg/dl)	2/22 (9)	14/26 (54)	
Elevated aspartate aminotransferase (>98 U/liter)§	20/26 (77)	25/25 (100)	
Elevated alanine aminotransferase (>110 U/liter)¶	14/26 (54)	26/27 (96)	
Leukocytosis (white-cell count ≥15,000/μl)‖	3/25 (12)	17/27 (63)	
Leukopenia (white-cell count <3500/μl)‖	8/26 (31)	13/27 (48)	
Neutropenia (absolute neutrophil count <1500/μl)	3/23 (13)	4/23 (17)	
Lymphopenia (absolute lymphocyte count <1500/μl)	14/23 (61)	20/23 (87)	
Anemia (hemoglobin <11 mg/dl)**	1/27 (4)	16/27 (59)	3/16 (19)
Thrombocytopenia (platelet count <150,000/μl)	22/26 (85)	26/27 (96)	5/26 (19)
Thrombocytosis (platelet count >450,000/μl)††	0/26	9/27 (33)	2/9 (22)

* To convert the values for calcium to milligrams per deciliter, divide by 0.25. To convert the values for magnesium to milligrams per deciliter, divide by 0.4114. To convert the values for creatinine to micromoles per liter, multiply by 88.4. To convert the values for bilirubin to micromoles per liter, multiply by 17.1.

† Data are listed only for laboratory measures for which treatments were administered.

‡ Isotonic intravenous fluid administration was considered as treatment for hyponatremia.

§ Aspartate aminotransferase levels peaked at a median of 9 days after the onset of illness.

¶ Alanine aminotransferase levels peaked at a median of 9 days after the onset of illness.

‖ White-cell count was lowest at a median of 6 days after the onset of illness and peaked at a median of 13 days after the onset of illness.

** Patients with anemia were treated with nonconvalescent whole blood or packed red-cell transfusion.

†† Patients with thrombocytosis were treated with low-molecular-weight heparin alone or with aspirin.

Table 3

Use of Investigational Therapies*

Investigational Therapy	Received at Least 1 Dose (N = 27)	Completed Course†	Adverse Reactions	Suspected Adverse Reactions
	number of patients (percent)			
ZMapp or MIL77	8 (30)	2 (25)	4 (50)	Fever, hypotension, agitation, tachycardia, tachypnea, flushing, palmar pruritus, rash
ZMab	5 (19)	1 (20)	2 (40)	Fever, urticaria, serum sickness
TKM-Ebola	5 (19)	1 (20)	5 (100)	Fever, chills, hypotension, the systemic inflammatory response syndrome, nausea, lipemia
Favipiravir	10 (37)	5 (50)	3 (30)	Nausea, vomiting, elevated aspartate amino-transferase, neutropenia, QTc prolongation
Brincidofovir	7 (26)	1 (14)	4 (57)	Diarrhea, nausea, vomiting, elevated amino-transferase levels, severe fatigue
FX06	2 (7)	NA	0	
Convalescent plasma‡	10 (37)	NA	3 (33)	Transfusion-related acute lung injury
Convalescent whole blood	1 (4)	NA	0	
Amiodarone§	2 (7)	NA	1 (50)	Bradycardia
Melanocortin	1 (4)	NA	0	

*Among the 27 patients, 4 (15%) received no investigational therapies, 4 (15%) received one investigational therapy, 12 (44%) received two investigational therapies, 5 (19%) received three investigational therapies, and 2 (7%) received four investigational therapies. NA denotes not applicable.

†A complete course was defined as three doses for ZMapp, ZMab, and MIL77; as seven doses for TKM-Ebola; as five doses for brincidofovir; and as 7 days (twice daily) for favipiravir. However, the most effective dose and duration of favipiravir treatment is unknown. There is no defined specific duration of treatment for amiodarone, FX06, melanocortin, convalescent plasma, or whole blood.

‡The median dose of convalescent plasma was 525 ml (range, 200 to 1200); the median number of doses administered was 2 (range, 1 to 6).

§Two patients received amiodarone for its presumed antiviral effect; one additional patient received amiodarone for treatment of an arrhythmia.

Table 4

Results of Virologic Testing*

Variable	No. of Patients	Value	No. of Days after Onset of Illness
			median (range)
EBOV RNA level at admission			
RT-PCR cycle-threshold value	19	24.0 (16.6–34.9)	5 (2–15)
EBOV RNA level — copies/ml	13	27×10^6 ($0.114–1200\times10^6$)	6.5 (5–11)
Peak viral detection			
Lowest RT-PCR cycle-threshold value	21	22.3 (13.2–39.5)	7 (2–15)
Highest EBOV RNA level — copies/ml	14	73×10^6 ($0.5–2100\times10^6$)	7 (2–11)
Duration of viremia — days†	22		17.5 (5–27)

*Virologic data from hospitalization in West Africa were unavailable for most medically evacuated patients; most results were from testing of blood specimens during hospitalization in the United States or Europe. EBOV denotes Ebola virus, and RT-PCR reverse-transcriptase–polymerase chain reaction.

†The duration of viremia was calculated as the number of days from the onset of illness to the first negative RT-PCR result on a blood specimen.