Case Report: A Health Care Worker with Ebola Virus Disease and Adverse Prognostic Factors Treated in Sierra Leone

Matthew K. O'Shea,* Katherine A. Clay, Darren G. Craig, Alastair J. Moore, Stephen Lewis, Melanie Espina, Jeff Praught, Simon Horne, Raymond Kao, and Andrew M. Johnston*

Department of Academic Medicine, Royal Centre for Defence Medicine, Birmingham, United Kingdom; U.K. Defence Medical Services Ebola Treatment Unit, Kerry Town, Sierra Leone; Royal Canadian Medical Services, Ottawa, Canada

Abstract. We describe the management of a Sierra Leonean health care worker with severe Ebola virus disease complicated by diarrhea, significant electrolyte disturbances, and falciparum malaria coinfection. With additional resources and staffing, high quality care can be provided to patients with Ebola infection and adverse prognostic factors in west Africa.

INTRODUCTION

The Ebola virus epidemic started in December 2013 in Guinea and rapidly spread to Sierra Leone and Liberia.¹ The outbreak led to infections in health care workers (HCWs) who had inadequate or no personal protective equipment (PPE) when treating patients with Ebola virus disease (EVD).² In contrast to international staff, local HCWs with EVD had little realistic chance of evacuation to countries with the treatment facilities, skills, and experience of managing EVD. Interventions such as intravenous fluids, blood product administration, blood chemistry monitoring, and electrolyte replacement were not reliably available at local EVD care centers, and there was no access to intensivist-delivered care for most patients.³ Our treatment center, staffed by U.K. and Canadian military personnel, provided care to international and local HCWs with suspected or confirmed EVD, and offered comprehensive nursing care and medical expertise, including infectious diseases and critical care.^{4,5} We placed peripheral venous cannulas, central venous cannulas under ultrasound guidance, and intraosseous needles.⁶ We also had access to point-of-care electrolyte testing and laboratory support with biochemistry, hematology, blood product transfusion, and microbiology including novel multiplex polymerase chain reaction (PCR)-based pathogen identification. We describe our treatment of a Sierra Leonean HCW who survived EVD despite adverse prognostic factors associated with poor outcome.⁷

CASE REPORT

A 21-year-old nursing student from Sierra Leone with a 3-day history of fever, malaise, headache, and general lethargy presented to our unit. He had worked with EVD-positive patients but reported no known PPE breaches; however, he had shared a room with two colleagues prior to their diagnoses of EVD.

On arrival, he was admitted to our 'suspected' ward in a stable condition. He did not report vomiting, diarrhea, or hemorrhage. His temperature was 37.1°C and his vital signs were normal with an unremarkable physical examination. Hematology, biochemistry, clotting, renal, and liver function tests performed in our laboratory were all within normal parameters. Aerobic and anaerobic blood cultures were negative at 24 hours. He was empirically treated for helminth infection with ivermectin and albendazole. A diagnostic Ebola virus real-time RT-PCR (EBOV RT-PCR) was performed and was positive with a cycle threshold (Ct) of 30 cycles (of 40). A rapid diagnostic test was positive for *Plasmodium falciparum* malaria. He was transferred to the 'confirmed' EVD ward early in the course of his EVD with an additional diagnosis of falciparum malaria.

He received oral artemether and lumefantrine and remained clinically well over the next few days, complaining only of malaise and headache. He continued to eat and drink, remained afebrile, and had normal vital signs. Daily blood tests remained unchanged. However, on day 5 of admission, he was febrile (38.8°C) and reported the onset of diarrhea.

Laboratory blood tests showed renal impairment, raised transaminases, elevated creatine kinase (CK), thrombocytopenia, a prolonged prothrombin time, and prolonged activated partial thromboplastin time, suggesting rapid development of advanced EVD with organ dysfunction (Figure 1). A central venous catheter (CVC) was inserted into the right subclavian vein and he received four units of fresh-frozen plasma and one unit of cryoprecipitate to reduce the risk of bleeding associated with line insertion (a complication noted in other patients). Intravenous vitamin K was administered daily for the next 8 days. A reduction in oral intake necessitated giving intravenous Ringer's lactate solution (Figure 1), although the patient was encouraged to take oral rehydration solution throughout. Blood samples were taken from the CVC by aseptic use of a needleless closed sampling system and tested once daily using the Piccolo Xpress Chemistry Analyzer (Abbott Point of Care, Princeton, NJ) within a biosafety cabinet in our laboratory. In addition, point-of-care electrolyte testing was carried out at the bedside using the iSTAT handheld system (Abbott Point of Care) as required. On day 7 after admission, a coagulase-negative *Staphylococcus* was isolated from a single set of blood cultures and was considered likely a contaminant. Profuse watery diarrhea (several episodes per day) persisted with evidence of melena and he subsequently developed gingival hemorrhage. This ongoing diarrhea was attributed to advanced EVD. Empirical treatment

*Address correspondence to Matthew K. O'Shea, The Jenner Institute, Old Road Campus Research Building, Roosevelt Drive, Oxford, OX3 7DQ, United Kingdom, E-mail: matthew.oshea@ndm.ox.ac.uk or Andrew M. Johnston, Academic Department, Royal Centre for Defence Medicine (Academia & Research), Medical Directorate, ICT Building, Birmingham Research Park, Vincent Drive, Edgbaston, Birmingham, B15 2SQ, United Kingdom, E-mail: amcdjohnston@gmail.com.

FIGURE 1. Laboratory values, intravenous fluids, and blood product administration during admission. (A) Liver enzymes, amylase, and creatine kinase; (B) C-reactive protein concentration and leukocyte counts; (C) platelet counts and clotting parameters; (D) renal parameters, potassium, bicarbonate, and albumin; (E) intravenous fluid and blood products administered. The administration of convalescent whole blood transfusion is indicated by the vertical, grey dashed line (A–D).

with ceftriaxone and metronidazole was administered to cover possible secondary infections. He was given two pooled units of platelets and one unit of cryoprecipitate. There was evidence of progressive organ failure with worsening renal and hepatic function and an elevated amylase. In addition, his CK increased above the laboratory limit of detection ($> 5,000$ U/L) and he also had a granulocytosis and elevated C-reactive protein (CRP) (Figure 1). Intravenous fluid resuscitation continued, guided by clinical examination and electrolyte testing. Gingival hemorrhage resolved within 24 hours. On day 8 of admission, his condition deteriorated with the onset of vomiting and worsening diarrhea with several episodes of large volume watery stool. He had a persistent fever attributed to EVD and right upper quadrant abdominal tenderness developed, consistent with an EVD-associated hepatitis. No focus of secondary infection was identified clinically and blood cultures from the CVC were negative. Symptomatic relief was provided with antiemetics and acetaminophen. The patient developed hypokalemia, presumed secondary to gastrointestinal (GI) losses, and required intravenous potassium chloride. Renal function worsened and urethral catheterization was unsuccessful due to patient intolerance of the procedure. A Flexi-Seal® (ConvaTec, Greensboro, NC) bowel management system (BMS) was sited. With informed consent and established protocols at the referring hospital, two units of con-

valescent whole blood were administered. This blood was obtained from a convalescent patient treated at the referring hospital and had been typed, crossmatched, and screened for human immunodeficiency virus (HIV) and for hepatitis B and C viruses, but not for malaria. It was administered at the request of the referring doctor on compassionate grounds and not as part of a clinical trial.

Vomiting and large volume diarrhea with melena continued. At day 11, the patient remained febrile (40.1°C) and his total leukocyte count increased (predominant granulocytosis). A presumptive diagnosis of sepsis secondary to a bacterial infection was made. The CVC was considered to be a possible focus of infection, therefore it was removed and a new CVC inserted at a different site. Blood cultures were taken from both the old and new CVCs, which subsequently showed no growth. At this point he remained on ceftriaxone and metronidazole. A repeat EBOV RT-PCR on day 14 remained positive (Ct 28.1).

On day 13, the patient remained febrile and developed signs of encephalopathy, manifesting as delirium but with no gross focal neurological deficit. He was confused, forcibly removed his BMS, and was incontinent of urine. The BMS was reinserted. The following day, there was no appreciable change in the patient's condition, and his empirical antibiotic therapy was changed to piperacillin-tazobactam and a single dose of gentamicin.

On day 18, his EBOV RT-PCR was negative and he began to clinically improve; however, low volume diarrhea persisted and occasional low-grade fever continued. An HIV test was negative. A stool sample was negative for GI pathogens on multiplex PCR using the BioFire FilmArray GI panel (BioFire Diagnostics, Salt Lake City, UT), as described elsewhere.⁸ Over several days, his granulocytosis and CRP began to normalize and renal and liver function improved (Figure 1). Intravenous antibiotics were replaced with oral amoxicillin-clavulanate. Oral diet was reintroduced and electrolytes were closely monitored for refeeding syndrome. On day 19 of admission, his coagulopathy resolved and low-molecular weight heparin was administered for venous thromboembolism prophylaxis.

The patient's fever resolved and vital signs normalized. He reported pain over his right buttock and on examination, a stage 2 decubitus ulcer was noted with skin breakdown but without extension to the underlying tissue. The ulcer was dressed according to standard regimens. By day 22, his diarrhea was resolving, and the BMS and CVC were removed. He steadily improved and by day 26 had regained sufficient strength to walk short distances, enabling discharge from our facility to the care of the referring hospital. At follow-up 8 days after discharge, he had no gross neurocognitive defects and while deconditioned, his physical weakness was resolving. He had no recollection of his stay in our treatment center.

DISCUSSION

This patient with EVD progressed within 5 days of presentation from early nonspecific constitutional symptoms to a GI syndrome and subsequently to organ dysfunction, which is associated with high mortality.⁹ It has been suggested that electrolyte and fluid derangement, sepsis, and multiorgan failure are the most likely causes of death among such patients.^{10,11}

Severe EVD often manifests as a GI syndrome with additional organ failure and coagulopathy in the majority of symptomatic patients. Guidelines support the use of aggressive intravenous fluid resuscitation.¹² Although most Ebola treatment centers in Sierra Leone at this time could provide intravenous fluids, our facility had the advantage of being able to place CVCs, urinary catheters, BMS, and if necessary, to administer vasopressors. We did not use an explicit algorithm to guide the volume of fluid administered. Instead, fluid administration and electrolyte replacement were based on clinical assessment and regular point-of-care and laboratory testing. Previous reports describe severe capillary leak, but we did not find any clinical evidence of fluid overload in our patients.⁹

Furthermore, in response to coagulopathy and hemorrhage, we were able to administer a range of blood components. Our patient also received EVD-survivor whole blood that has been used as an empirical treatment in some facilities, with World Health Organization support.^{13,14} However, it should be noted that in a resource-limited setting, blood products cannot typically be screened for all blood-borne pathogens. In our case, the source of the blood transfusion was a local hospital, which excluded hepatitis B and C viruses and HIV-1 and -2. It was not screened for cytomegalovirus or human T-cell lymphotropic virus.

Additional laboratory support included the BioFire multiplex PCR that could be applied to samples of blood, urine,

stool, and nasopharyngeal swabs, and was of great utility in excluding secondary infections. Although we were mindful that the negative predictive value of the BioFire assays was not known in this clinical setting, we felt that it was a useful adjunct to clinical assessment.

Although the age of the patient we describe has been associated with favorable prognostic outcomes, he had several adverse clinical features including GI hemorrhage, encephalopathy, and significant renal impairment.¹⁵ We were able to provide comprehensive medical and nursing care to this critically ill patient in a well-resourced center, together with interventions such as central venous access that facilitated treatment. In addition, we were able to provide advanced diagnostic testing including on-site laboratory and bedside point-of-care electrolyte testing, microbiological laboratory support, and blood product administration. We demonstrate that it is possible to provide limited critical care interventions for patients with EVD in an austere environment.

Received June 24, 2015. Accepted for publication December 8, 2015.

Published online February 22, 2016.

Acknowledgments: We would like to thank the U.K. Ministry of Defence and Public Health England laboratories for support and Thomas E. Fletcher and Sewa Mansaray for their comments and suggestions.

Authors' addresses: Matthew K. O'Shea, Katherine A. Clay, Darren G. Craig, Alastair J. Moore, Stephen Lewis, Simon Horne, and Andrew M. Johnston, Department of Academic Medicine, Royal Centre for Defence Medicine, Birmingham, United Kingdom, and U.K. Defence Medical Services Ebola Treatment Unit, Kerry Town, Sierra Leone, E-mails: matthew.oshea@ndm.ox.ac.uk, kate.clay@nhs.net, darrencraig@doctors.org.uk, alastair.moore@ouh.nhs.uk, stephenedward.lewis@nhs.net, psihorne@doctors.org.uk, and andy.johnston@uhb.nhs.uk. Melanie Espina, Jeff Praught, and Raymond Kao, Royal Canadian Medical Services, Ottawa, Canada, and U.K. Defence Medical Services Ebola Treatment Unit, Kerry Town, Sierra Leone, E-mails: melanie.espina@gmail.com, jcpaught@gmail.com, and rkao@foxflight.com.

REFERENCES

1. Baize S, Pannetier D, Oestereich L, Rieger T, Koivogui L, Magassouba N, Soropogui B, Sow MS, Keita S, De Clerck H, Tiffany A, Dominguez G, Loua M, Traoré A, Kolié M, Malano ER, Heleze E, Bocquin A, Mély S, Raoul H, Caro V, Cadar D, Gabriel M, Pahlmann M, Tappe D, Schmidt-Chanasit J, Impouma B, Diallo AK, Formenty P, Van Herp M, Günther S, 2014. Emergence of Zaire Ebola virus disease in Guinea. *N Engl J Med* 371: 1418–1425.
2. Bausch DG, 2015. The year that Ebola virus took over west Africa: missed opportunities for prevention. *Am J Trop Med Hyg* 92: 229–232.
3. Fowler RA, Fletcher T, Fischer WA 2nd, Lamontagne F, Jacob S, Brett-Major D, Lawler JV, Jacquerioz FA, Houlihan C, O'Dempsey T, Ferri M, Adachi T, Laham MC, Bah EI, Mayet T, Schieffelin J, McLellan SL, Senga M, Kato Y, Clement C, Mardel S, Vallenat Bejar De Villar RC, Shindo N, Bausch D, 2014. Caring for critically ill patients with Ebola virus disease. Perspectives from west Africa. *Am J Respir Crit Care Med* 190: 733–737.
4. Jacobs M, Beadsworth M, Schmid M, Tunbridge A, 2014. Provision of care for Ebola. *Lancet* 384: 2105–2106.
5. Johnston A, Bailey M, 2014. Operation Gritrock: first UK army medics fly to Sierra Leone. *BMJ* 349: g6237.
6. Roberts I, Perner A, 2014. Ebola virus disease: clinical care and patient-centred research. *Lancet* 384: 2001–2002.
7. Bah EI, Laham MC, Fletcher T, Jacob ST, Brett-Major DM, Sall AA, Shindo N, Fischer WA 2nd, Lamontagne F, Saliou SM, Bausch DG, Moumié B, Jagatic T, Sprecher A, Lawler JV,

- Mayet T, Jacquerioz FA, Méndez Baggi MF, Vallenat C, Clement C, Mardel S, Faye O, Faye O, Soropogui B, Magassouba N, Koivogui L, Pinto R, Fowler RA, 2015. Clinical presentation of patients with Ebola virus disease in Conakry, Guinea. *N Engl J Med* 372: 40–47.
8. O'Shea MK, Clay KA, Craig DG, Matthews SW, Kao RL, Fletcher TE, Bailey MS, Hutley E, 2015. Diagnosis of febrile illnesses other than Ebola virus disease at an Ebola treatment unit in Sierra Leone. *Clin Infect Dis* 61: 795–798.
 9. Sanchez A, Geisbert TW, Feldmann H, 2007. Filoviridae: Marburg and Ebola viruses. Knipe DM, Howley PM, Griffin DE, Lamb RA, Martin MA, Roizman B, Straus SE, eds. *Fields Virology*. Philadelphia, PA: Wolters Kluwer/Lippincott Williams and Wilkins.
 10. Lyon GM, Mehta AK, Varkey JB, Brantly K, Plyler L, McElroy AK, Kraft CS, Towner JS, Spiropoulou C, Ströher U, Uyeki TM, Ribner BS, Emory Serious Communicable Diseases Unit, 2014. Clinical care of two patients with Ebola virus disease in the United States. *N Engl J Med* 371: 2402–2409.
 11. Rollin PE, Bausch DG, Sanchez A, 2007. Blood chemistry measurements and D-Dimer levels associated with fatal and nonfatal outcomes in humans infected with Sudan Ebola virus. *J Infect Dis* 196: S364–S371.
 12. World Health Organization, 2014. Clinical Management of Patients with Viral Haemorrhagic Fever: A Pocket Guide for the Front-line Health Worker. Available at: http://apps.who.int/iris/bitstream/10665/130883/2/WHO_HSE_PED_AIP_14.05.pdf?ua=1. Accessed June 22, 2015.
 13. Mupapa K, Massamba M, Kibadi K, Kuvula K, Bwaka A, Kipasa M, Colebunders R, Muyembe-Tamfum JJ, 1999. Treatment of Ebola hemorrhagic fever with blood transfusions from convalescent patients. International Scientific and Technical Committee. *J Infect Dis* 179: S18–S23.
 14. World Health Organization, 2014. Use of Convalescent Whole Blood or Plasma Collected from Patients Recovered from Ebola Virus Disease for Transfusion, as an Empirical Treatment during Outbreaks. Available at: http://apps.who.int/iris/bitstream/10665/135591/1/WHO_HIS_SDS_2014.8_eng.pdf?ua=1. Accessed June 22, 2015.
 15. Schieffelin JS, Shaffer JG, Goba A, Gbakie M, Gire SK, Colubri A, Sealfon RS, Kanneh L, Moigboi A, Momoh M, Fullah M, Moses LM, Brown BL, Andersen KG, Winnicki S, Schaffner SF, Park DJ, Yozwiak NL, Jiang PP, Kargbo D, Jalloh S, Fonnine M, Sinnah V, French I, Kovoma A, Kamara FK, Tucker V, Konuwa E, Sells J, Mustapha I, Foday M, Yillah M, Kanneh F, Saffa S, Massally JL, Boisen ML, Branco LM, Vandi MA, Grant DS, Happi C, Gevao SM, Fletcher TE, Fowler RA, Bausch DG, Sabeti PC, Khan SH, Garry RF, KGH Lassa Fever Program, Viral Hemorrhagic Fever Consortium, WHO Clinical Response Team, 2014. Clinical illness and outcomes in patients with Ebola in Sierra Leone. *N Engl J Med* 371: 2092–2100.