

Clinical Management of Patients with Ebola Virus Disease in High-Resource Settings

G. Marshall Lyon, Aneesh K. Mehta and Bruce S. Ribner

Abstract Like most viral illnesses in humans, supportive care of the patient is the mainstay of clinical care for patients with Ebola virus disease (EVD). The goal is to maintain and sustain the patient until a specific immune response develops and clears the viral infection. Clearly, antiviral therapy may eventually help speed recovery, but supportive care will likely always be the centerpiece of care of the patient with EVD. While terrible in terms of human suffering and loss, the EVD outbreak of 2014–2016 provided an unheralded opportunity to advance our understanding in the care of patients (WHO 2016). Regardless of the care setting, resource-rich or resource-constrained, it is beneficial to have an established team of care providers. This team should consist of nurses and physicians who are familiar with clinical care of patients with EVD and have demonstrated competency using necessary personal protective equipment (PPE). Consideration should be given to having several physician specialties on the team, including critical care, infectious diseases, and anesthesiology. Additional individuals in other medical specialties should be identified in case needed during the course of caring for a patient. The National Ebola Training and Education Center (NETEC) has detailed guidance on preparations for developing a high-containment unit and care team (NETEC 2016).

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1 Symptoms and Clinical Manifestations

After an incubation period of two to 21 days (mode 8–10), patients will have the onset of symptoms (Fig. 1). Initial symptoms are not specific and can have the appearance of a myriad of tropical infections, including those which are most common, i.e., malaria, typhoid, influenza. These initial symptoms include fever, headache, myalgias, malaise, and sore throat (Del Rio et al. 2014). Toward the end of the first week, fever, headache, and malaise continue and the onset of the gastrointestinal (GI) phase begins (Chertow et al. 2014; Lyon et al. 2014). After the first few days of illness, a rash may also appear. The rash can be either a classic viral exanthem or petechial. The rash may begin as an exanthem but progress to petechial as the platelets drop and vascular leakage becomes more pronounced.

The GI phase is critical for patient care as this is when many patients become critically ill with volume and electrolyte derangements. The first days of the GI phase are characterized by both vomiting and diarrhea. The vomiting makes oral rehydration difficult as the patient is losing 2–3 L per 24-h period orally (Chertow

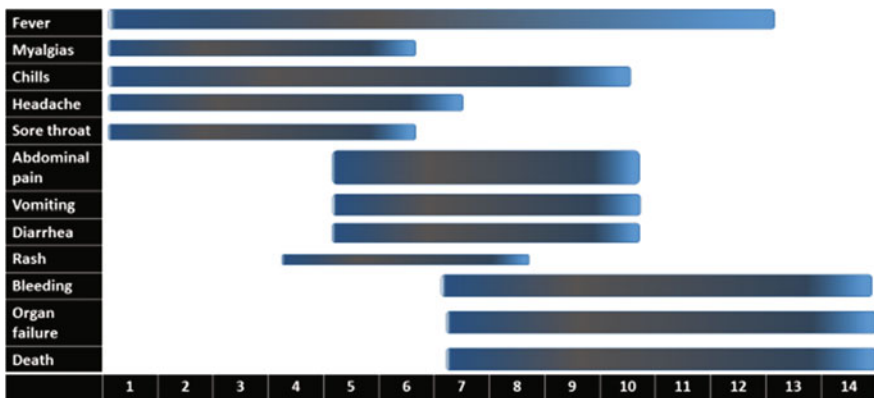


Fig. 1 Relative timing of symptoms with Ebola virus disease (EVD) as well as the relative intensity of symptoms

et al. 2014). After 2–3 days, the vomiting begins to improve, but the diarrhea continues to worsen. It is common for many patients to continue losing between 3 and 5 L of fluid per day and in the severest cases can be up to 10 L of output per day per rectum (Kraft et al. 2015). Massive fluid loss along with vascular leakage which occurs in Ebola virus disease (EVD) can lead to intravascular hypovolemic dehydration. Uncorrected, these derangements may lead to cardiac arrhythmias which can be fatal (Liddell et al. 2015; Lyon et al. 2014).

It is during the GI phase when laboratory abnormalities start to become evident. One of the hallmarks of EVD is a rise in aspartate aminotransferase (AST) concentrations, which is markedly higher than the rise of alanine aminotransferase (ALT) concentrations. Thrombocytopenia is also an early abnormal laboratory finding which appears to precede clinical bleeding (Kraft et al. 2015; Lyon et al. 2014). With fluid loss also comes abnormal low electrolyte concentrations, most notably potassium and calcium (Lyon et al. 2014). Albumin concentrations are also low early in the illness. Hypoalbuminemia may be a result of loss through the GI tract, decreased nutritional intake, or due to vascular leakage. Low albumin concentrations complicate the physiology and management of patients with EVD as it leads to low oncotic pressure and contributes to hypovolemia and hypotension.

The GI phase lasts into the first part of the second week. As a consequence of the GI phase and viral sepsis, intravascular hypovolemia and vascular leakage, organ failure can develop. Coagulopathy, renal failure, and respiratory failure are the most commonly encountered organ systems which fail. Coagulopathy typically manifests as clinical bleeding. GI bleeding is the most common manifestation. Patients may also experience oozing from venipuncture sites and intravenous catheter sites (Uyeki et al. 2016b; Respiratory vaccine shows promise 2014; Qin et al. 2015; Bah et al. 2015). In previous EVD outbreaks, bleeding from gums and the urinary tract have also been noted. Bleeding complications has also been linked to poor outcomes (Ndambi et al. 1999). Renal failure is an uncommon complication of EVD occurring in about 5% of cases (Bah et al. 2015). Although uncommon, renal failure has historically been associated with increased mortality (Schieffelin et al. 2014). Renal failure is felt to be either pre-renal from shock (Bah et al. 2015) or from acute tubular necrosis (ATN) from direct infection of the renal tubules by Ebola virus (Martines et al. 2015).

Death from EVD has been associated with several clinical features or demographic characteristics. Older age is associated with a higher risk of dying from EVD. For patients who have or might get EVD, forty years is old. This has been noted across multiple outbreaks of EVD with different variants of Ebola viruses, from Kikwit in the 1990s to West Africa in 2014–2016. In addition to age, severity of illness is another predictor of mortality. For EVD, this is borne out as higher viral load, higher temperature, higher blood urea nitrogen (BUN) and creatinine (Cr) concentrations, and higher AST concentrations. Higher BUN and Cr concentrations represent renal failure, and higher AST concentration represents increased liver injury. Clinically evident hemorrhagic manifestations such as melena, petechiae, ecchymoses, and oozing puncture sites are all associated with

increased mortality (Roddy et al. 2012; Geisbert 2015). The 2014–2016 outbreak in West Africa may have indicated that the level of care is also associated with mortality. The overall mortality from EVD in West Africa was 40% (WHO 2016). However, in persons who were evacuated from West Africa to either Europe or the USA, the mortality rate was 18.5% (Uyeki et al. 2016b). This suggests that the higher level of care provided outside of West Africa decreased the mortality rate by half. Of the 27 patients who were evacuated out of Africa, five died and three of those had respiratory and renal failure (Uyeki et al. 2016b). However, there were nine total patients who had respiratory failure and nine patients who had oliguria indicating possible renal failure. Seven of the nine with respiratory failure received mechanical ventilation, and five of the nine with renal failure received dialysis (Uyeki et al. 2016b). These patients had severe illness yet the mortality rate was half of what was seen in West Africa. What is not clear is whether these patients would have lived or died had they remained in West Africa. But, it seems plausible that improving the level of supportive care in West Africa may reduce the mortality associated with any future outbreaks of EVD.

2 Management of Complications

Given the severity of illness many patients with EVD have, it is important to have an almost “expectant management” philosophy. Expectant management means anticipating potential problems and pitfalls and taking corrective action before they actually arise. In this way, problems can be avoided or mitigated. Knowing that patients with EVD can develop hypokalemia, providers may choose to supplement potassium as the gastrointestinal phase develops. Similarly, expecting hemorrhage to potentially be an issue, transfusing platelets when the platelet counts reach 30–50 K/ μ L (as opposed to <20 K/ μ L), or providing fresh frozen plasma when the international normalized ratio (INR) is 1.5 should be strongly considered. Anticipating problems and intervening at an earlier time point than in usual clinical practice may help prevent a very sick patient from becoming a critically ill patient, hopefully saving the patient’s life.

Volume and electrolytes

Volume loss can be significant in EVD during the gastrointestinal phase with up to 10 L of fluid loss in a 24-h period. Matching this volume loss with oral rehydration or intravenous fluids is challenging. However, it should be the goal of fluid replacement to maintain intravascular volume to avoid shock. If the patient has a lot of vomiting, it may be very difficult to do this with oral rehydration, and intravenous access should be obtained before significant dehydration develops. Intravenous replacement fluids should ideally be done with balanced crystalloid solutions such as lactated ringers, though the use of normal saline is certainly appropriate if balanced crystalloid solutions are not readily available. There is

concern that relying solely on normal saline or similar fluids can result in hyperchloremia and potentially induce or exacerbate renal failure (Guidet et al. 2010). However, in EVD patients where colloidal products may also be needed, using normal saline as a carrier or to supplement colloids is likely very appropriate. Normal saline should not be avoided at the expense of maintaining intravascular volume.

Electrolyte loss can be significant during the GI phase especially if diarrhea is voluminous on several consecutive days. Of patients medically evacuated to Europe or the USA, hyponatremia, hypokalemia, hypocalcemia, hypomagnesemia, and hypoalbuminemia were seen in the majority of patients (Uyeki et al. 2016b; Lyon et al. 2014; Kraft et al. 2015; Wolf et al. 2015). Whether a consequence of the electrolyte imbalance or as a part of the EVD, cardiac arrhythmias were seen in almost half of the patients medically evacuated out of West Africa (Uyeki et al. 2016b).

One word of caution on aggressive rehydration—in resource-constrained areas overly aggressive rehydration with intravenous fluids can lead to additional problems. As the septic phase begins, patients develop vascular leakage. While this is not an issue in subcutaneous tissues, it can be problematic in the lungs. Pulmonary edema can lead to hypoxia and the need for supplemental oxygen or mechanical ventilation. Clinicians need to be aware of the potential to overhydrate and cause additional problems. In areas where renal replacement therapy is not readily available, correcting overhydration may not be easily accomplished.

Gastrointestinal

The GI phase of the disease is where significant morbidity and mortality happens with EVD (Dallatomasina et al. 2015). In one center with a mortality rate of about 50%, nearly 90% of the deaths occurred during the GI phase (Dallatomasina et al. 2015). It should again be noted that the later part of the GI phase overlaps with the beginning of sepsis and multi-organ failure. Therefore, aggressive care during the GI phase may help ameliorate mortality in patients with EVD.

Antiemetic medications can help reduce the amount of vomiting experienced by patients. Clinicians should be proactive when using antiemetic medications especially if they have to rely heavily on oral rehydration. Similarly, antidiarrheal medications may help diminish volume loss and electrolyte loss (Chertow et al. 2015). Although antidiarrheal medications like loperamide may not abate diarrhea altogether, one or two fewer liters of diarrheal loss may be the difference between life and death. However, the use of loperamide and similar agents has not been definitively shown beneficial in EVD.

Hemorrhage

Hemorrhage is historically a hallmark of EVD. In studies which have examined the correlation, there is an association between hemorrhage and mortality (Ndambi et al. 1999). Therefore, correcting coagulopathy is a goal of supportive care in EVD. Again, early transfusion of platelets or infusion of clotting factors via fresh

frozen plasma should be a goal when feasible. This may be more easily achieved in resource-rich environments where platelet counts and INR can be more closely monitored. As a surrogate, oozing from intravenous catheter sites or phlebotomy sites should prompt transfusion of platelets and fresh frozen plasma. If frank hemorrhage occurs as manifested by visible bleeding, hematemesis or melena, transfusion of platelets, clotting factors, and red blood cells is likely warranted. Here, the goal is to maintain acceptable hemoglobin levels and correct coagulopathy. Transfusion will likely also help maintain intravascular hydration and blood pressure.

Organ failure

Organ failure is a rare but serious, life-threatening complication in EVD.

Renal failure develops in about 5% of patients with EVD historically (Bah et al. 2015), but was seen in 20% of medical evacuees in the 2014–2016 West Africa outbreak (Uyeki et al. 2016b). In patients evacuated to Europe or the USA, 20% had renal failure and two were described as having renal failure with anuria (Wolf et al. 2015; Connor et al. 2015). Both of these patients received renal replacement therapy with dialysis. Both patients also had recovery of renal function such that dialysis was no longer needed by 2 months past onset of symptoms. In both of these cases, dialysate fluid was tested for the presence of Ebola virus (EBOV) RNA and was found in one instance at one of the institutions (Connor et al. 2015; Wolf et al. 2015). It should be noted that dialysis membranes are designed to allow the passage of electrolytes but not larger molecules such as proteins or viruses. Therefore, it would be expected that dialysate fluid should be without EBOV. But both institutions autoclaved dialysate fluid so as to eliminate the potential for environmental contamination (Wolf et al. 2015; Connor et al. 2015). While renal failure is associated with a higher risk of dying from EVD, aggressively supporting the patient with dialysis or continuous renal replacement therapy can have positive, life-saving effects. Bah et al. (2015) reported severe pre-renal kidney failure in one of their patients. This patient responded well to intravascular rehydration with crystalloid intravenous solutions.

Respiratory failure is also an uncommon but ominous development in patients with EVD. In patients who were medically evacuated to either Europe or the USA, respiratory failure was described as hypoxic or mixed hypercapneic/hypoxic respiratory failure (Sueblinvong et al. 2015; Kraft et al. 2015; Uyeki et al. 2016b; Wolf et al. 2015). Patients who had mild isolated hypoxia often responded to supplemental oxygen (Uyeki et al. 2016b). Some of these evacuated patients progressed to respiratory failure, requiring either noninvasive positive pressure ventilation or endotracheal intubation with mechanical ventilation (Uyeki et al. 2016b; Sueblinvong et al. 2015; Wolf et al. 2015). Despite going on to need mechanical ventilation, the majority of patients eventually recovered from their respiratory failure.

Cardiac abnormalities were frequently noted (41%) in patients medically evacuated from West Africa to Europe or the USA (Uyeki et al. 2016b). Most of these abnormalities were arrhythmias seen on cardiovascular monitoring or

electrocardiogram (Uyeki et al. 2016b). However, life-threatening arrhythmias, such as atrial fibrillation, are also possible and require intervention in order to correct the abnormal rhythm (Kraft et al. 2015; Sueblinvong et al. 2015). Fatal arrhythmias developed in patients who die from EVD.

Vascular leakage is a common phenomenon in EVD. In some patients, this can lead to third spacing of fluid and resultant intravascular hypovolemia. This vascular leakage typically develops about the same time as the GI phase and quickly reverses once recovery begins (Lyon et al. 2014). Two patients evacuated to Atlanta in the USA were noted to quickly mobilize and auto-diurese about 10 L of fluid in less than 48 h (Lyon et al. 2014). In patients who develop sepsis cardiovascular collapse may occur (Wolf et al. 2015; Sueblinvong et al. 2015; Kraft et al. 2015). Aggressively supporting the patient with the use of inotropes and volume resuscitation can result in survival and recovery (Kraft et al. 2015; Sueblinvong et al. 2015; Wolf et al. 2015).

Coincidental infections in patients with EVD are frequently noted. The WHO Handbook for EVD care recommends giving antimalarial therapy and antibacterials empirically because of the high rates of malaria, typhoid, and other infections in Africa. At least one patient who was medically evacuated from West Africa to Germany developed sepsis and was treated with several sequential and concomitant antibiotics (Wolf et al. 2015). While only one blood culture was positive for a *Staphylococcus* species (Wolf et al. 2015), processing of blood cultures is difficult in high-containment units due to a lack of availability of automated blood culture incubation systems. The sensitivity of detecting bacterial sepsis is likely lower than in normal care settings, and routine blood culturing of patients with EVD in resource-constrained areas is unlikely to be feasible.

Neurologic complications are commonly noted in patients with EVD. Most patients display some degree of cognitive impairment, likely from dehydration and severe illness. Seizures have been seen as well (Bah et al. 2015). At least one patient medically evacuated to the USA was felt to have hemorrhagic encephalitis based on magnetic resonance imaging obtained after recovery from EVD (personal knowledge of authors). One survivor of EVD had a late-onset meningoencephalitis due to EBOV (Jacobs et al. 2016). This resulted in prolonged illness with neurologic complications and deficits which slowly resolved over time (Jacobs et al. 2016).

Post-Ebola syndrome

The most common symptoms experienced by survivors of EVD are fatigue, musculoskeletal pain (70%), headache (48%), and eye abnormalities (14%) (Scott et al. 2016). The musculoskeletal pain is often joint pain primarily affecting large joints (Scott et al. 2016). Pain in tendon insertions, or enthesitis, is also commonly noted. Eye disease has been described as either an anterior, posterior, or pan uveitis and can be associated with virus detected by PCR in conjunctival swabs, or detection of virus by PCR in the aqueous fluid of the eye (Varkey et al. 2015; Kibadi et al. 1999). Post-Ebola syndrome is poorly understood, and at the time of

this writing, there are ongoing efforts to better characterize the symptoms of post-Ebola syndrome as well as attempts to gain an understanding of the pathophysiology.

3 Therapeutics for Ebola Virus Disease

EVD can be caused by any of four ebolaviruses: Ebola virus (EBOV, previously known as Zaire ebolavirus), Sudan virus (SUDV, previous known as Sudan ebolavirus), Bundibugyo virus (BDBV), and Tai Forest virus (TAFV). In addition, there exists an additional ebolavirus, Reston virus (RESTV) that is only known to cause disease in non-human primates. While aggressive supportive care remains the only therapeutic modality proven to be efficacious in treating patients with EVD, there have been ongoing efforts to develop agents specifically for EVD. The magnitude and longevity of the 2014–2016 West Africa EVD outbreak highlighted the need for efficacious therapeutics against Ebola viruses to augment the supportive care measures in the treatment of individual patients and also to assist in diminishing the spread of the virus in communities. Thus, the 2014–2016 EVD outbreak allowed for greater attention and support for research into the development of these therapeutics, many of which are now in clinical studies (WHO Web site http://www.who.int/medicines/emp_ebola_q_as/en/). These therapeutics fall into three main categories: immunologic therapies, antiviral molecules, and vaccines.

3.1 *Passive Immune Therapy*

Convalescent blood and plasma

The idea of transferring protective immunity from survivors of an infectious disease to patients with an active infection has been studied and used since the beginning of the twentieth century, including such pathogens as polioviruses, influenza viruses, hepatitis B virus, cytomegalovirus, and Ebola viruses (Winkler and Koepsell 2015). The first known use of this modality in EVD occurred during the 1976 outbreak when a laboratory worker had an occupational exposure and was infected with an Ebola virus. This patient received transfusions of two units of convalescent plasma and had a full recovery (Emond et al. 1977; Winkler and Koepsell 2015). Following this experience, eight patients received whole blood transfusions obtained from five different EVD survivors during the 1995 EVD outbreak in Kikwit, Democratic Republic of Congo (Mupapa et al. 1999). While only 1 patient who received these transfusions succumbed to EVD, this cohort received significantly higher levels of care than the majority of patients in the Kikwit outbreak (Mupapa et al. 1999). Since this time, multiple animal studies have

shown the potential efficacy of transferring a high-quality, species-specific convalescent serum/plasma for EBOV infections (Winkler and Koepsell 2015; Zeitlin et al. 2016).

Once the 2014–2016 EVD outbreak caught international attention, there were calls from WHO and other agencies to explore the utilization of convalescent blood products for the multitude of patients in the EVD treatment units (ETUs) in affected nations (World Health Organization (WHO) 2014). The ability to safely separate and store vast amounts of whole blood or plasma from EVD survivors proved to be difficult in these resources-constrained environments undergoing a devastating epidemic. As a few nationals of European nations and the USA responding to the outbreak became infected with Ebola and were repatriated for treatment of EVD, the receiving centers began to explore collecting convalescent plasma from their recovered patients. The first use of a convalescent blood product for EVD outside of Africa occurred at the University of Nebraska Medical Center (UNMC), when plasma collected from a previous EVD survivor was transfused after informed consent to another patient in that ETU (Kraft et al. 2015). Since that time, a national repository of Ebola Convalescent Plasma (ECP) has been created at Emory University in Atlanta, GA, USA, from survivors living in the USA, and multiple units have been distributed for the care of EVD patients in the USA (Kraft et al. 2015; Florescu et al. 2015; Liddell et al. 2015; Winkler and Koepsell 2015). There were also several patients in Europe who received convalescent blood products (Uyeki et al. 2016b). However, these few cases, in the absence of controlled clinical trials, do not provide adequate data to assess efficacy or safety of these products. Three clinical trials of ECP were initiated in West Africa, though enrollment was slow as the outbreak began to wane and data are not yet available. Until clinical trials of standardize convalescent plasma products are performed, it will remain unclear what is the role of these products in the treatment of EVD.

Ebola virus-specific antibodies

Another approach to passive immunity is the use of monoclonal antibodies (mAb) with known activity against EBOV. The challenges to isolating and producing EBOV-specific antibodies with activity in humans have been recently reviewed by Zeitlin et al. (2016). A significant advance in this area came as the developers of two different mAb cocktails, ZMab and MB-003, which had shown good antiviral activity in NHP models, developed a collaboration to identify the best mAbs to include into a cocktail (Zeitlin et al. 2016). This novel combination, later termed ZMapp™ (Mapp Biopharma), was tested in a pivotal study by Qiu et al. (2014), showing 100% protection in EBOV-infected rhesus macaques (*Macaca mulatta*) when treatment with this cocktail was initiated within 5 days of infection. Furthermore, the study demonstrated rescue of animals even with advanced EVD (transaminitis and hemorrhages) with ZMapp™ (Qiu et al. 2014).

This study of ZMapp™ in non-human primates (NHP) had just completed, when in August of 2014 two humanitarian aid workers from the USA developed EVD. The medical team caring for these two patients was offered the use of ZMapp™,

and after consenting the patients for the compassionate use of this experimental agent, they became the first human recipients of ZMapp™ (Lyon et al. 2014). Since this experience, EBOV-specific monoclonal cocktails, including ZMapp™, ZMab, and MIL77, have been used in 11 other patients evacuated from West Africa (Uyeki et al. 2016b). However, given that all of this experience was outside of controlled clinical trials, it is impossible to ascertain the impact of any of these agents on the outcomes of these patients.

While sources (i.e., recovered patients) of convalescent blood products may or may not be readily available during a progressive outbreak, these products will always remain difficult to use given the measures needed to collect, store, and administer them safely. In addition, there is heterogeneity between batches. The advent of recombinant mAb, with known specificities and activities and more ease of storage and delivery, will likely prove to be a promising therapeutic strategy for EVD and other similar outbreaks in the near future. Hopefully, manufacturing techniques to scale up production when needed and the studies needed to assess the efficacy and safety of these products will be ready for next outbreak.

3.2 *Antiviral Agents*

Pharmaceutical antiviral agents for EBOV generally fall into two categories: compounds that inhibit viral replication and small-molecule inhibitors of virus entry and endosomal escape.

Inhibitors of Ebola virus replication

Favipiravir (T-705; Toyama Chemical Co Ltd) is a broad-spectrum antiviral purine analog, which becomes phosphorylated into its active form intracellularly and inhibits RNA-dependent RNA polymerase (Furuta et al. 2013). Favipiravir has many appealing characteristics to support its use in EVD: a good safety profile in humans, large amounts of the drug are readily available (having been produced for pandemic influenza), and good preliminary data in animal models of EVD (Madelain et al. 2016). The drug was used in 10 of the 27 EVD patients evacuated to the USA and Europe, and was overall well tolerated (Uyeki et al. 2016b). In addition, a non-comparative proof-of-concept trial (JIKI trial) was conducted in Guinea, in which all patients received favipiravir along with standardized care. While the study design did not allow for assessing the efficacy of the drug, overall it was well tolerated by the study participants (Sissoko et al. 2016).

BCX4430 (BioCryst Pharmaceuticals), an adenosine nucleoside analogue, inhibits viral RNA-dependent RNA polymerase activity indirectly through non-obligate RNA chain termination and has shown a broad spectrum of activity against RNA viruses, including filoviruses, flaviviruses, bunyaviruses, arenaviruses, paramyxoviruses, picornaviruses, and coronaviruses (Taylor et al. 2016). The efficacy of BCX4430 has been studied in two different NHP models of EVD (Madelain et al.

2016). In a cynomolgus macaque (*Macaca fascicularis*) model, animals which were given BCX4430 48 h after an otherwise lethal EBOV exposure had prolonged survival time but a similar survival rate (Madelain et al. 2016). In a rhesus macaque model, animals were given high doses of BCX4430 intramuscularly after an otherwise lethal EBOV exposure and 67% of treated animals survived versus none of the untreated animals. A phase I study to evaluate the safety, tolerability, and pharmacokinetics of BCX4430 is ongoing (Madelain et al. 2016).

Small-molecule inhibitors of Ebola virus

TKM-Ebola (Tekmira Pharmaceuticals, British Columbia, Canada) is a lipid nanoparticle containing a combination of small interfering RNA (siRNA) molecules that block the translation of three Ebola viral proteins: RNA-dependent RNA polymerase, VP24, and VP35 (Geisbert et al. 2010; Mendoza et al. 2016). The original formulation, TKM-100802, was designed to target these three genes of the 1995 Kikwit EBOV variant. It was shown to prevent disease in 66 and 100% of rhesus macaques given four or seven, respectively, treatments of the agent after an otherwise lethal EBOV infection (Geisbert et al. 2010). The first human use of TKM-100802 occurred in two patients evacuated to the USA from West Africa in late 2014 (Kraft et al. 2015) and subsequently in three additional evacuated patients (Uyeki et al. 2016b). However, these patients received advanced supportive and other experimental agents, making it difficult to ascertain any treatment effect of TKM-100802. Investigations in the matching of TKM-100802 to the new West African EBOV variant (Makona) revealed mismatches for the polymerase gene and the VP35 gene (Thi et al. 2015). A new formulation, TKM-130803, was designed to better match the circulating EBOV strain and demonstrated good protection in a small study of rhesus macaques given an otherwise lethal inoculum of EBOV (Thi et al. 2015). Based on these results, the Rapid Assessment of Potential Interventions and Drugs for Ebola (RAPIDE-TKM) trial was designed and launched in early 2015. In this single-arm phase 2 trial, patients with EVD were administered a 0.3 mg/kg intravenous infusion of TKM-130803 daily for up to seven days (Dunning et al. 2016). The study enrolled 14 patients, of whom 11 died and 3 survived, and subsequently, the trial was halted due to meeting its pre-specified futility threshold (Dunning et al. 2016).

AVI-7537 (Sarepta Therapeutics Inc, Cambridge, Massachusetts) is an antisense small nucleic acid oligomer, known as a phosphorodiamidate morpholino oligomer (PMO), which targets the VP24 gene of EBOV and interferes with its translation (Madelain et al. 2016). AVI-7537 has been evaluated in NHP models of EBOV infection, though usually in combination with AVI-7539, a PMO targeting the VP35 gene of EBOV (Madelain et al. 2016). However, in one study, rhesus monkeys received either AVI-7537+AVI-7539, AVI-7537, AVI-7539, or placebo and found to have survival rates of 62.5, 75, 0, and 0%, respectively (Warren et al. 2015). In addition, viral loads were similar in the AVI-7537 and AVI-7537 +AVI-7539 groups, but lower than the AVI-7539 and control groups (Warren et al. 2015). These data indicated that AVI-7537 was potentially sufficient to prevent

disease and thus moved forward for clinical development (Madelain et al. 2016). AVI-7537 (in combination with AVI-7539) was evaluated in a phase I human study, showing it was well tolerated and without severe adverse reactions (Heald et al. 2014). However, plans for further clinical trials are unknown at this time.

4 Vaccines

Developing an effective vaccine against EBOV is a paramount aim for preventing outbreaks of EVD and may play an important role tempering an ongoing outbreak and caring for those who have been exposed to EBOV. While research into EBOV vaccines was ongoing, the West African EVD outbreak brought much needed attention and resources to these endeavors. Currently, almost 20 different vaccines are in preclinical or clinical development, almost 10 times the number in 2013 (Ohimain 2016). Of these, EBOV vaccines utilizing recombinant vesicular stomatitis virus (rVSV), chimpanzee adenovirus (ChAd), or adenovirus type 26 vectors have made the most progress to date.

Recombinant vesicular stomatitis virus-vectored vaccine

VSV belongs to the *Rhabdoviridae* virus family and causes vesicles and ulcerations of the mouth, feet, and teats of livestock (Roberts et al. 1999). A replication-competent recombinant VSV (rVSV)-vectored EBOV vaccine (rVSV-ZEBOV) was developed by the Public Health Agency of Canada (PHAC). In August of 2014, PHAC donated 800 vaccine doses to the WHO to conduct rapid human studies. The VSV Ebola Consortium (VEBCON) designed a group of studies of these vaccines to assess the safety and immunogenicity of various doses of rVSV-ZEBOV in Gabon, Kenya, Germany, and Switzerland (Agnandji et al. 2016). A total of 158 healthy adults received either rVSV-ZEBOV in doses of ranging from 300,000 to 50 million plaque-forming units (PFU) or placebo. EBOV-specific antibody responses were detected in all the study participants with higher neutralizing antibody titers seen at higher doses of the vaccine (Agnandji et al. 2016). The vaccine was also found to have significant rates of reactogenicity, with fever in 30% of vaccine recipients and vaccine-related arthritis in 22% of recipients at one center (Agnandji et al. 2016). rVSV was detected in the blood of 95% of vaccinees, skin vesicles of two recipients and in the synovial fluid aspirate of an additional subject (Agnandji et al. 2016). Contemporaneous to these studies, the rVSV Δ G-ZEBOV-GP group conducted two phase 1, placebo-controlled, trials of the same vaccine in the USA, at Walter Reed Medical Center and at the National Institutes of Health (Regules et al. 2017). A total of 40 adults received the rVSV-ZEBOV vaccine at a dose of 3 million or 20 million PFU. All vaccine recipients developed EBOV-specific antibodies, with recipients of the higher doses having statistically higher antibody titers and higher levels of neutralization (Regules et al. 2017). Again, reactogenicity was very common with 55% of

recipients reporting fevers and >75% reporting significant injection site pain (Regules et al. 2017). rVSV viremia was found in all vaccinees, though no significant arthritis nor skin disease was reported in this study (Regules et al. 2017). Given the concerns of arthritis from the previous studies, the VEBCON group developed a dose comparative study, evaluating 300,000 versus 10 million versus 50 million PFU dosages of the vaccine (Huttner et al. 2015). As expected, EBOV-specific antibody titers and neutralizing titers were lower with the low-dose vaccine (Huttner et al. 2015). Reactogenicity remained common even at the lower dose (88 vs. 98% in the higher doses), though fevers, chills, and myalgias were all significantly lower in the low-dose group. Importantly, the investigators found no significant reduction in the rates of vaccine-related arthritis or dermatitis (Huttner et al. 2015). Taking these data together, the developers of this vaccine (NewLink Genetics [Ames, IA, USA] and Merck Sharp and Dohme [Kenilworth, NJ, USA]) moved forward trials of 20 million PFU dosage of the rVSV-ZEBOV, renamed V920.

The pivotal study of this vaccine was conducted in Guinea with an innovative cluster-ring strategy trial. In this open-label study, 90 clusters of contacts of known cases of EVD, 7651 subjects in total, were randomized to immediate vaccination or 21-day delay of vaccination with V920 at 20 million PFU (Henao-Restrepo et al. 2015). In the immediate vaccination group, there were no cases of EVD, but in the delayed vaccination group, 16 cases of EVD from seven clusters were diagnosed. These data indicated 100% efficacy of the vaccine (Henao-Restrepo et al.). From these results, V920 was granted “Breakthrough Therapy Designation” from the FDA and PRIME (Priority Medicines) Status from European Medicines Agency (EMA) (New Link Genetics Corporation 2016).

Adenovirus-vectored vaccines

Vaccines utilizing adenoviruses as vectors have been in development for many different pathogens; however, these efforts have been hampered by preexisting immunity to several adenoviruses in the majority of the humans (Martins et al. 2016). For protection against EBOV, two different strategies have been developed to utilize these vectors, a chimpanzee adenovirus and human adenoviruses with little preexisting immunity.

A vaccine candidate employing chimpanzee adenovirus 5 (ChAd5) has been developed with the NIH’s National Institute of Allergy and Infectious Diseases Vaccine Research Center (Martins et al. 2016). In a phase 1 study of this non-replicating VRC-EBOADC076-00-VP (ChAd3-EBOZ; GlaxoSmithKline) vaccine, three different doses (10 billion, 25 billion, and 50 billion viral particles) were given to 20 participants each at one center in the UK (Ewer et al. 2016). Then, a booster of modified vaccinia Ankara (MVA) vector (MVA-BN Filo; Bavarian Nordic), which encodes the same EBOV isolate glycoprotein antigen as that encoded by the ChAd3-EBOZ vaccine, in addition to glycoproteins of Sudan virus and Marburg virus and the nucleoprotein of TAFV, was given to 10 participants in each dose group. EBOV-specific antibody titers and neutralization activity were

similar to those reported in rVSV-ZEBOV studies. The boosting with the MVA-BN-Filo significantly increased EBOV-specific antibody and CD8+ T cell responses, although the antibody responses were more long lived (Ewer et al. 2016). Overall, the vaccine was well tolerated (Ewer et al. 2016). In the combined data from two phase 1 dose-finding studies, one in the USA ($n = 20$) and the other in Mali ($n = 91$), with 52 of the Malians receiving MVA-BN-Filo boosters, the 1 billion viral particle dose was found to be the optimal dose in phase 3 efficacy trials (Tapia et al. 2016). Currently, the ChAd3-EBOZ vaccine is being tested in several clinical trials and has been included as a comparator arm in the PREVAIL study (Partnership for Research on Ebola Virus in Liberia) evaluating rVSV-ZEBOV.

Crucell Holland B.V. has developed another potential vaccine candidate, Ad26.ZEBOV, utilizing their human adenovirus 26 vector (Martins et al. 2016). In the first phase 1 study, 87 subjects at a single center received a priming vaccination of either Ad26.ZEBOV or MVA-BN-Filo, followed by a booster of the other vaccine or placebo (Milligan et al. 2016). One month after primary immunization, 97% of the Ad26.ZEBOV and 23% of MVA-BN-Filo recipients had detectable EBOV-specific antibodies, and all recipients had detectable antibodies 21 days after the booster vaccination. The majority of subjects demonstrated EBOV-specific T-cell responses as well (Milligan et al. 2016). Fevers were reported in 9% of Ad26.ZEBOV and none of MVA-BN-Filo recipients (Milligan et al. 2016). This heterologous prime-boost model is being further assessed in phases 2 and 3 studies.

5 Infection Control

Although patients with EVD have been cared for in resource-constrained environments for nearly 40 years, it was not until 2014 that two patients were transported to the USA to be cared for in a resource-rich environment at Emory University Hospital in Atlanta, GA (Lyon et al. 2014). Over the course of the 2014–2016 EVD outbreak that devastated West Africa, leading to 28,616 cases and 11,310 deaths, 27 individuals received their medical care in resource-rich environments (Uyeki et al. 2016b). While the care of these 27 individuals taught us much about the aggressive care required to improve patient survival, it also helped to clarify the key elements of infection control in caring for these patients.

Healthcare workers have historically been one of the highest risk groups for acquiring EVD from infected patients. In one outbreak in 1995, 25% of the infected were healthcare workers (Khan et al. 1999). The role of appropriate infection control precautions was demonstrated during this outbreak, as there were 80 infected healthcare workers prior to the implementation of appropriate barrier precautions, but only one additional case after barrier precautions were instituted. In the most recent 2014–2016 outbreak, there were 876 confirmed and probable cases of EBOV infection in healthcare workers of whom 509 died (WHO 2016). Healthcare workers were between 21 and 32 times more likely to be infected with EBOV than people in the general adult population, and nearly 60% of those

infected healthcare workers died. The importance of infection control in this setting was, as in the 1995 outbreak, demonstrated by the fact that healthcare workers represented 12% of all EVD patients in July 2014, but decreased to 1% by February 2015 as more rigorous infection control and occupational health and safety strategies were implemented. While the source of healthcare worker infection may be difficult to trace in locations where there is an ongoing community outbreak, such transmission is easier to identify when there is no ongoing community disease. The number of infected healthcare workers in resource-rich settings with no ongoing community disease was markedly less than the number in resource-constrained settings. However, one nurse in Spain and two nurses in the USA acquired EBOV infection from their patients who had acquired EBOV infection in West Africa. For these reasons, infection control has received a great deal of attention in the care of patients infected with Ebola viruses in both resource-rich and resource-constrained settings.

Ebolaviruses, with rare exceptions, are transmitted by contact with blood, body fluids, and contact with skin. In addition to blood, infectious virus has been documented in patients' saliva, stool, rectal swabs, vaginal secretions, breast milk, tears (conjunctival swab), urine, and seminal fluid, but not vomit or sweat (Bausch et al. 2007; Dowell et al. 1999). Although aerosol transmission has been suspected in outbreaks involving RESTV in non-human primates, such transmission of other Ebola viruses must be rare if it occurs at all in humans. There is no support for the transmission of the EBOV via the airborne route (Peters et al. 1996).

The role of fomites in Ebola virus transmission is unclear. A recent study found that the Ebola virus strain associated with the 2014–2016 West Africa outbreak was able to persist on stainless steel, plastic, and Tyvek[®] under environmental conditions reflective of the high temperatures and relative levels of humidity found in the outbreak regions (Fischer et al. 2015). However, in a study evaluating 31 environmental specimens from an EBOV isolation ward that were not visibly bloody, all specimens were negative by RT-PCR, suggesting that fomites in a clinical setting where cleaning and decontamination would be frequent are unlikely to be capable of EBOV transmission (Bausch et al. 2007). Similarly, multiple environmental samples obtained in a patient care room of a patient treated for severe EVD were negative by RT-PCR (Varkey 2016).

Persistence of infectious virus in immune-privileged sites has also been documented. EBOV has been detected in seminal fluid for months following patient recovery (Uyeki et al. 2016a). A secondary case has occurred following sexual exposure to semen 155 days after the source patient had cleared virus from his blood (Mate et al. 2015). One case of uveitis was diagnosed with infectious virus in the aqueous humor 9 weeks after the patient had cleared his viremia (Varkey et al. 2015). A nurse was diagnosed with meningitis, with recovery of EBOV from her cerebrospinal fluid, 9 months after clearing her viremia (Jacobs et al. 2016). While such events are concerning, the role of such persistence in person-to-person transmission is still being evaluated. However, patients who have recovered from

EBOV infection who require an invasive procedure of an immune-privileged site need to have special attention paid to the infection control measures followed during such a procedure.

EBOV blood levels in infected patients increase rapidly during the first week after the onset of symptoms, going from undetectable to many log orders of virus (Towner et al. 2004). During the most symptomatic period, viral levels in the blood may reach 10^8 virions per milliliter of blood (Iwen et al. 2015; CDC 2016a), which is many logs higher than is seen with other blood borne pathogens. This helps to explain why individuals exposed to blood and body fluids of patients with Ebola infection during the early days of illness frequently do not become infected, while healthcare workers caring for the patient during the later stages of illness are at greatest risk. When this high viral load is added to the observation that symptomatic patients may excrete 8–10 L of infected fluid daily, one can readily understand why healthcare workers who do not use optimal PPE are at increased risk of occupationally acquired infection.

The importance of appropriate PPE and adequate training in using this equipment has been recognized for many years. In resource-constrained units, such equipment frequently consists of double gloving, impermeable suits, aprons, and surgical masks. In the absence of air conditioning, healthcare workers wearing such equipment are frequently limited to short periods of time in the patient care unit due to heat exhaustion, representing a challenge in the delivery of the aggressive supportive care required for optimal patient outcomes. Recommendations for PPE in resource-rich environments evolved rapidly in 2014. As the USA prepared for its first EBOV-infected patients in 2014, the official recommendation from the US Public Health Service was that healthcare workers should use standard contact precautions, with goggles or face shields, fluid resistant gowns, face masks, and gloves generally in use in healthcare facilities in the USA. Unfortunately, there was little emphasis on covering all skin surfaces and proper training in the use of PPE. The occurrence of EBOV infection in 2 nurses caring for a critically ill patient in October 2014 led to a reconsideration of these recommendations. What evolved was a new appreciation for effective training and complete covering of all skin and mucous membranes when caring for a patient with Ebola virus infection. New guidelines stress: Healthcare workers caring for patients with EVD must have received comprehensive training and demonstrated competency in performing EVD-related infection control practices and procedures; PPE that covers the clothing and skin and completely protects mucous membranes is required when caring for patients with EVD; personnel providing care to patients with EVD must be supervised by an onsite manager at all times, and a trained observer must supervise each step of every PPE donning/doffing procedure to ensure established PPE protocols are completed correctly; individuals unable or unwilling to adhere to infection control and PPE use procedures should not provide care for patients with EVD (CDC 2016a). In addition, there is a renewed emphasis on frequent cleaning of the floors and surfaces in the patient room and doffing area. Policies should be in place to limit room entry to only those healthcare workers essential to the patient's care and restrict non-essential personnel and visitors from the patient care area.

Such policies will need to balance any conflicts between healthcare worker safety and local work and union regulations.

Cleaning of floors and surfaces on a frequent basis requires special considerations. No environmental disinfectant has been labeled as effective in inactivating the Ebola virus. Although Ebola viruses produce enveloped virions, EPA has elected to take a cautious approach and require that all environmental disinfectants used in ETUs should meet the following criteria: (1) the use of an EPA-registered hospital disinfectant with a label claim for use against a non-enveloped virus (e.g., norovirus, rotavirus, adenovirus, poliovirus) and (2) the product label use directions for the non-enveloped viruses should be followed when disinfecting against EBOV (EPA 2016).

Delivery of aggressive supportive care requires access to laboratory testing. Institutions need to evaluate whether such testing will occur in a core hospital laboratory or in a point of care laboratory. Such decisions will need to be based on a risk assessment to determine the potential for exposure from sprays, splashes, or aerosols generated during all laboratory processes, procedures, and activities (Iwen et al. 2015). Many instruments require that the samples be in open vials or centrifuged, which must occur in an enclosed environment. Consideration will also need to be given to whether the use of the equipment for the testing of blood in patients who may have serious communicable pathogens requires that equipment to be removed from service if the patient tests positive. Laboratory personnel need to be trained in the donning and doffing of appropriate PPE, such training to be similar to that required of patient care personnel. There must also be an appropriate location for those activities to occur.

The disposal of regulated medical waste has been a major issue for units caring for patients with EVD and other serious communicable diseases. When the first patients with EBOV infection were brought to the USA in 2014, contractors initially refused to take the medical waste generated by their care. Eventually, contractors agreed to take the waste if it was first autoclaved prior to transport. However, even then such waste was transported separately from other regulated medical waste and only accepted for incineration in special facilities. For institutions that do not have the capability of autoclaving medical waste on site, contractors require that the waste be immersed in disinfectant inside 55-gallon metal drums, the drums sealed, and then transported by dedicated trucks to specially designated facilities (Stericycle). The expense of such special handling has been a major issue for patient care units. More recently, contractors have demonstrated a willingness to accept unit waste as standard regulated medical waste after it has been autoclaved. However, units without autoclave capability on site continue to be faced with logistic issues. All personnel who handle unit waste prior to autoclaving must be included in the unit PPE training. They must also be monitored using the same procedures as those used for other personnel in the unit.

Employee monitoring

Due to the concern about healthcare worker acquisition of Ebola virus infection, all personnel who have had potential exposure to the virus, either through patient care activity, laboratory processing of specimens, or exposure to potentially contaminated materials or surfaces, must be monitored for potential illness, starting with their first potential exposure and ending 21 days after their last potential exposure. While this monitoring can be performed by facility Employee Health Services, many facilities have utilized the services of local or state health departments to perform such monitoring.

Disposal of liquid and solid waste

Public health service policies have traditionally stated that patient liquid and solid waste may be discharged through municipal sanitary sewers, as such systems are designed to inactivate viruses (CDC 2016b). However, facilities must ensure that local and state regulations do not impose additional restrictions. In addition, concern has been raised due to the potential for plumbing leaks and stoppages within the patient care facility. For these reasons, most facilities have chosen to inactivate waste with an appropriate disinfectant before disposing of the waste into the sanitary sewers.

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