

Successful Delivery of RRT in Ebola Virus Disease

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ABSTRACT

AKI has been observed in cases of Ebola virus disease. We describe the protocol for the first known successful delivery of RRT with subsequent renal recovery in a patient with Ebola virus disease treated at Emory University Hospital, in Atlanta, Georgia. Providing RRT in Ebola virus disease is complex and requires meticulous attention to safety for the patient, healthcare workers, and the community. We specifically describe measures to decrease the risk of transmission of Ebola virus disease and report pilot data demonstrating no detectable Ebola virus genetic material in the spent RRT effluent waste. This article also proposes clinical practice guidelines for acute RRT in Ebola virus disease.

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Zaire ebolavirus (EBOV) is a highly infectious filovirus that is transmitted by contact with blood and body fluids, including saliva, stool, urine, sweat, and vomit, and causes infection by entering mucous membranes and areas of skin breakdown.¹ Ebola virus disease (EVD) is well known to induce severe diarrhea and vomiting as well as increases in vascular permeability and decreased serum albumin that often lead to intravascular volume depletion.¹ Elevations in BUN and creatinine have been reported in EVD in Africa and are associated with increased mortality.² It has been unclear whether these elevations represent prerenal azotemia or true parenchymal AKI. Recently, multiple hospitals caring for patients with EVD in environments outside of resource-limited settings have described critically ill patients with EVD who develop AKI (T. Uyeki, B. Wall, J. Beige, and S. Büttner, personal communications), but there have been no previously published cases describing delivery of RRT in patients with EVD with AKI.

In addition to helping the patient, the goals of therapy in patients with EVD also include protecting healthcare workers and the community from secondary infections.³ Healthcare workers are at the highest risk for contracting EVD in Africa and transmission to Western health care workers was recently reported.⁴ Clinical care of the patient with EVD requires adhering to strict isolation (biocontainment) practices, utilizing impermeable personal protective equipment (PPE), minimizing the amount of blood and other contaminated fluids generated, and properly disposing of waste, contaminated items, and body fluids to decrease risk of EBOV transmission to healthcare workers and the surrounding communities. Thus, protocols for RRT in patients with EVD must endeavor to maximize patient, staff, and community safety.

Here we describe the successful, safe application of RRT at Emory University Hospital in Atlanta, Georgia, for a patient with EVD and discuss the unique challenges

that providing RRT in this setting presented to our team. Rather than focus on the specifics of RRT prescription, this article aims to describe the safety considerations that inform and affect the delivery of RRT in patients with EVD and it proposes clinical practice guidelines for acute RRT in EVD on the basis of this experience.

CASE DESCRIPTION

A governmental organization–based healthcare worker contracted EVD while working at an Ebola treatment unit in Sierra Leone, and was evacuated to Emory University Hospital for supportive care of EVD in the Severe Communicable Disease Isolation Unit. The patient received aggressive supportive care with intravenous fluids as well as experimental antiviral treatments, and did not have secondary infection or hypotension. Yet the patient acutely developed hypoxic acute respiratory failure and AKI secondary to

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acute tubular necrosis on day 8 of illness with progressive respiratory distress, oxygen requirements, oliguria, metabolic acidosis, azotemia, and hypervolemia. This patient demonstrated no irreversible organ failures and, importantly, there was an absence of hypotension or shock requiring vasopressor support.

In general, with aggressive life and organ support therapies, it is thought that patients with EVD can be maintained awaiting resolution of symptoms and patient recovery as virus is cleared by the immune system *via* advancing humoral and cellular immunity.^{1,5} On the basis of this viral biology, the patient was judged to be a good candidate for advanced organ support therapies. Intubation and mechanical ventilation were initiated on day 9 of illness. After intubation, secondary to high-dose sedative requirements (fentanyl and propofol infusions), the patient required intermittent low-dose norepinephrine (the peak dose for a short period was 0.2 $\mu\text{g}/\text{kg}$ per minute) for several days. High-dose diuretic challenge failed to induce a desired negative fluid balance, and thus continuous RRT (CRRT) *via* a nontunneled temporary right internal jugular dialysis catheter was initiated on day 11 of illness for hypervolemia and progressive azotemia. CRRT initiation did not significantly alter hemodynamic status, but ongoing low-dose vasopressor support was provided to facilitate extracorporeal volume removal. The patient required prolonged mechanical ventilation for 12 days and remained on CRRT for 11 days. As the overall clinical condition improved, the patient was transitioned to prolonged intermittent RRT (PIRRT) performed for 6–12 hours daily using the CRRT device. The patient recovered renal function, allowing for discontinuation of RRT after 24 days with a steadily improving eGFR to 33 ml/min per 1.73 m² (calculated by the Modification of Diet in Renal Disease equation) 7 days after the discontinuation of RRT.

RRT PROTOCOL AND RATIONALE

In planning for delivery of RRT in a patient with EVD, the highly infectious

nature of EBOV and strict isolation requirements introduced several important safety concerns that we had to satisfy before initiating RRT:

1. Patient Safety—By its nature, RRT is complex. Providing RRT in a strict containment isolation environment (where contact between nurses/clinicians and patient was limited) introduces possible barriers to safe delivery of RRT to patients.
2. Healthcare Worker Safety—Protecting healthcare workers from exposure to highly infectious blood, other blood contaminated products (dialyzer, tubing, vascular access, *etc.*), and other contagious body fluids by minimizing exposure opportunities for staff and minimizing number of staff who could potentially be exposed.
3. Community Safety—RRT generates large amounts of potentially infective waste material (dialyzer membrane, and tubing, effluent waste, *etc.*) which would require special disposal mechanisms to prevent spread to healthcare workers and the wider population.

RRT and Patient Safety

Providing adequate dialysis is essential for patient outcomes in dialysis-dependent AKI.^{6,7} To date, there are no clear data that continuous modes of hemodialysis provide a mortality advantage over appropriately and adequately dosed intermittent hemodialysis (IHD) in AKI.^{8,9} At the time of RRT initiation, the patient remained critically ill with borderline hemodynamics. Although IHD could have been applied to this patient, intermittent modes of therapy negatively affected staff safety (described below), so CRRT was chosen. For patient safety reasons, we chose to use the Prismaflex device (Gambro/Baxter, Lakewood, CO) as the largest number of our intensive care unit nurses at bedside had experience with this device. Nursing staff underwent additional CRRT training sessions

as a refresher because the biocontainment isolation also isolates the bedside nurse, slowing the arrival of rapid help from other support resources (*e.g.*, other nurses/staff). Furthermore, any nursing error in performing CRRT would trigger additional training.

The Kidney Disease Improving Global Outcomes AKI clinical guidelines support the right internal jugular position as the preferred site for RRT vascular access given favorable performance characteristics.¹⁰ Based on the patient's height, a 24-cm right internal jugular dual lumen Schon XL dialysis catheter (AngioDynamics, Latham, NY) was inserted under direct ultrasound visualization and positioned in a deep position at the level of the caval atrial junction with the location confirmed by portable chest radiography. This deep position provides superior flows and catheter life. A bacteriostatic, Biopatch CHG (Ethicon Inc., Somerville, NJ) and standard occlusive dressing were used to reduce exit-site infections and were changed weekly or when soiled. With an ongoing functional coagulopathy, the biopatches did saturate with blood requiring exchanges and resulted in increased nursing interaction with blood-contaminated products.

RRT was performed using regional citrate anticoagulation (RCA) in continuous venovenous hemodialysis mode to minimize filtration fraction and maximize circuit survival. Systemic anticoagulation was avoided because the patient was experiencing a functional bleeding diathesis behaving as disseminated intravascular coagulopathy, but limitations in laboratory assessments in our biocontainment facility limited complete characterization. Specifically, initial CRRT settings included the following: Gambro HF1400 filter set, blood flow rate 150 ml/min, trisodium citrate 1.24% (trisodium citrate 46.7% 30-ml vial attached to 1-liter bag of sterile water for total volume 1030 ml) at 250 ml/h, dialysate flow rate 30 ml/kg per hour, and variable ultrafiltration rate to target net negative fluid balance of approximately 100 ml/h. Finally, a calcium chloride infusion was administered *via* the patient's central line and titrated as needed to maintain systemic ionized calcium between 0.9 and

1.2 mmol/L. Laboratory evaluation in EVD is challenging and is usually performed, as at our center, with commercially available point-of-care testing devices.¹¹ However, this limits the diversity of tests available. In this case, we used serial systemic arterial blood gas measurements for ionized calcium measurements every 6 hours for the first 2–3 days and then every 12 hours afterward on a steady dose of calcium supplementation. BUN, creatinine, and other electrolytes were measured every 12 hours initially and then every 24 hours. Our testing devices were unable to measure phosphorus. In the United States where CRRT solutions do not contain phosphorus, serum phosphorus levels progressively decline with CRRT and usually require supplementation. We felt that the potential negative effects of hypophosphatemia outweighed the risks associated with hyperphosphatemia¹²; thus, we elected to provide empirical phosphorus supplementation *via* total parenteral nutrition and enteral routes throughout the entire duration of CRRT.

After correction of the acidosis, the dialysate flow rate was reduced to 20 ml/kg per hour. However, as the patient developed increasing metabolic alkalosis, the CRRT mode was switched to continuous venovenous hemodiafiltration without RCA with settings including blood flow rate of 300 ml/min, prefilter replacement fluid at 1500 ml/h (filtration fraction approximately 8.3%), and the remainder as dialysate for a total effluent flow rate of approximately 20 ml/kg per hour. After the patient was extubated, the RRT modality was changed to PIRRT 6–12 hours a day with the same blood flow and prefilter replacement fluid, but the dialysate flow was adjusted to deliver the equivalent of what the patient would receive if total flows of 20–25 ml/kg per hour were delivered over 24 hours.

RRT and Healthcare Worker Safety

Protecting healthcare workers (clinical staff) is of paramount importance in the care of EVD. At our institution, the principal modes of maintaining staff safety are to (1) minimize the number of people who enter the isolation room, (2) reduce staff exposures to blood and body fluids, (3) provide extensive

training on the institution's PPE protocol, and (4) leave all nondisposable equipment in the isolation room until completing the final terminal cleaning after patient discharge from isolation. For example, at our institution, IHD is performed by specialized dialysis nurses who were not fully trained on strict isolation requirements and PPE. All patients with EVD in our biocontainment unit continuously have an intensive care unit (ICU) nurse at the bedside in full PPE and all nurses have a broad background in providing CRRT in the ICUs of our institution. These nurses rotate in and out of the isolation room on a regular schedule during their 12-hour shifts. Leveraging these CRRT-trained ICU nurses already at the bedside to deliver CRRT in the biocontainment isolation room avoided the necessity of exposing specialized dialysis nurses to the EVD isolation environment. Furthermore, the larger size and lower flexibility of the IHD machine would have required us to remove it from the room should CRRT be required later in the course of management. Using a CRRT device provided the additional flexibility of transitioning to PIRRT with the same device. Thus, only one CRRT machine was utilized throughout the entire duration of the patient's hospital stay and allowed the trained ICU nurses to provide ongoing RRT needs for the patient throughout the stay in the biocontainment isolation room.

In summary, using CRRT minimized exposure of additional staff and equipment to the isolation environment. For a similar reason, the ultrasound machine used for line placement had capability for diagnostic studies and remained in the room until final cleaning. Finally, consulting physicians did not enter the room unless they were performing a procedure or it was absolutely necessary, so that the ICU nurse and the Severe Communicable Disease Isolation Unit infectious disease physician in the biocontainment isolation provided the primary clinical care. A glass wall allowed visualization of the machine settings and for the nephrologist or dialysis nurses to assist with troubleshooting with the ICU nurse if needed. For terminal cleaning after patient discharge, the CRRT machine surface was first disinfected with bleach solution

according to the manufacturer's specifications, followed by disinfection of the entire room and equipment by vaporized hydrogen peroxide performed by a specialty contractor.

Reducing exposure to blood and body fluids in performing RRT was a major safety goal, and the integrated CRRT cartridge system with preconnected filter and tubing minimized blood exposure. We used RCA to maximally extend the filter life and thus reduce the number of times the nurses were required to exchange the CRRT circuit; as a result, all filters during the CRRT period experienced patency for 60–72 hours. We utilized no-reflux Tego needle-free connector caps (ICU Medical Inc., San Clemente, CA) to decrease risk of accidental blood exposure during connection and disconnection of CRRT. Although the caps are rated by the manufacturer for three connections, we found that the caps occasionally required more frequent exchange, which increased potential blood exposure for the bedside nurse. In disconnecting the system, we found that the best practice was to both clamp and cap the blood lines before removing the cartridge from the machine to decrease risk of blood contamination.

The potential largest single exposure to blood was anticipated to occur during dialysis access placement. As with insertion of any central venous line, the needle and aspiration of blood could create aerosols and the guide wire must be handled carefully to prevent blood exposure. Although no obvious surface contamination occurred during access insertion, in retrospect, additional draping of nearby surfaces (beyond the standard full-barrier precautions used for central line insertion) may have been helpful to decrease potential blood transfer to these surfaces. Using standard central line insertion and maintenance protocols allowed the use of a single catheter throughout the entire duration of RRT (24 days) without evidence of catheter-related infectious complications.

RRT and Community/Population Safety

RRT generates a copious amount of highly infectious and potentially infectious material. The disposable hardware, including

dialyzers, tubing, and catheters, will have direct contact with any patient's highly contagious blood, and therefore, must be handled with extreme caution and disposed in accordance with national guidelines.¹³ As discussed above, steps were taken to decrease the amount of disposable waste generated by maximizing filter life. Furthermore, despite the copious volumes of spent effluent waste generated in CRRT (2–4 L/h), the volumes are still much lower than those generated in IHD (approximately 48 liters for each hour of the IHD session).

EBOV is an elongated structure measuring 80 nm in diameter and ranging from 800 to 1000 nm long. It most often exists in a long convoluted, branching structure in blood. The virion consists of an approximately 50-nm helical nucleocapsid surrounded by a spike-studded membrane formed as the virus buds from the host cell.¹⁴ EBOV is a single-stranded negative-sense RNA virus approximately 19,000 nucleotides long with a molecular mass of 4.2×10^6 D (4200 kD). The genome encodes for seven structural proteins, which include an approximately 120-kD glycoprotein, the 180-kD polymerase, and several nucleocapsid and other proteins with the smallest approximately 40–50 kD.^{14–16}

High-flux, high-efficiency dialyzers used in modern RRT treatments are generally impermeable (by both diffusion and convection) of substances above a molecular mass of 60–70 kD.^{17,18} The HF1400 filter set used with the Prismaflex machine at our institution is one such high-flux, high-efficiency dialyzer composed of a polyarylethersulfone membrane. Based on the molecular mass of the genetic material and the size of the EBOV virion (relative to the pore diameter and membrane thickness), we hypothesized that conventional high-flux, high-efficiency membranes would be impermeable to, and hence exclude, EBOV genetic material and intact viable EBOV virions from the effluent waste.

With the absence of data to confirm the safety of RRT effluent, our local authorities and institution elected to treat all RRT effluent as infectious waste for population safety reasons. In this regard,

CRRT provides an additional advantage of minimizing daily effluent production (total daily effluent 48–96 L/d versus up to 192 L/4-h IHD session). This concern further solidified the selection of CRRT as the initial primary method or RRT support in EVD.

CRRT EFFLUENT STUDIES

To address the concerns for potential infectiousness of the CRRT effluent, we performed a pilot study to detect the presence of EBOV genetic material in the CRRT effluent by real-time quantitative RT-PCR (qRT-PCR). In CRRT, in which blood flow rates greatly exceed effluent flow rates, small molecule concentrations in effluent theoretically reach equilibrium with plasma. Thus, systemic (prefilter) blood and spent effluent should demonstrate similar concentrations of any measured small solute including many drugs.¹⁹ However, transport of large molecular mass molecules (>15 kD) across the membrane progressively decreases as molecular mass increases with current high-flux, high-efficiency hemodialysis filters such that albumin (66.5 kD) is virtually excluded from effluent. Specifically, the HF1400 filter membrane is virtually impermeable to albumin²⁰ and the mode of transport (convection or diffusion) does not affect permeability with high-flux, high-efficiency hemodialysis membranes.¹⁸

Methods

On three separate occasions during the initial 9 days of CRRT, we collected paired CRRT spent effluent samples and blood samples to quantify the presence of EBOV

genetic material by qRT-PCR, which was performed by the US Centers for Disease Control and Prevention (CDC) utilizing previously published methods in EBOV.²¹

Results

Table 1 demonstrates the results of CRRT spent effluent PCR analysis and paired blood and urine qRT-PCR cycle threshold values (when urine was available). In all three samples of CRRT effluent, no EBOV genetic material was detected by qRT-PCR, whereas the paired blood and urine samples demonstrated medium to low viral loads as indicated by cycle threshold values of 26–36. These results confirm, as expected, that there is no evidence of transfer of EBOV genetic material across the CRRT membrane to the spent effluent.

DISCUSSION

EVD is a complex disease characterized by massive fluid shifts and enteral volume losses, severe viremia, direct viral infection of many organs including renal tubular cells, and cytokine surges.²² Although the overall incidence of AKI in EVD is unknown, autopsy series suggest that it may be common in severe disease and portends a dismal prognosis in resource-limited settings.² Given that EVD severity generally correlates with viral load and symptoms persist until the virus is cleared by the immune system, advanced organ support including RRT could substantially lower the mortality rate of EVD by maintaining life and allowing time for development of EBOV-specific immunity.¹ However, RRT in EVD involves access to highly infectious

Table 1. RT-PCR results for EVD

CRRT Day	Specimen Type	qRT-PCR Cycle Threshold Value
0	Blood	23.6
1	Blood	26.5
	CRRT effluent	Undetectable (>40)
3	Blood	34.0
	CRRT effluent	Undetectable (>40)
9	Blood	35.9
	Urine	32.7
	CRRT effluent	Undetectable (>40)

blood, which endangers caregivers and presents unique challenges due to isolation procedures. RRT also generates significant waste with disposable hardware (dialysis filters, tubing, *etc.*) and spent effluent, which may have the potential to spread the virus to healthcare workers and the community if not disposed of properly. Our report of a method of successful RRT in the setting of a modern biocontainment unit provides an important step into developing sophisticated protocols to provide advanced life support for serious contagious diseases. Although performing RRT carries some risk of transmission of blood-borne pathogens, none of our staff developed EVD after a 21-day observation period. In a setting where success in EVD treatment is measured as much by avoiding the spread of the disease to healthcare workers and contacts as it is by the patient's outcome, we cannot be satisfied and must constantly refine our techniques.

We elected to perform CRRT in this critically ill patient with EVD after careful consideration of several safety implications of RRT. In our opinion, CRRT provided the best opportunity to maximize patient, healthcare worker, and

community/population safety. The minimizing of personnel in the patient room was only possible with volunteer ICU nurses with specialized training in isolation protocols and in CRRT. The role of this additional training and experience in our success cannot be overstated. In the traditional ICU setting, the bedside ICU nurse has the ready support of an entire ICU of colleagues to troubleshoot and assist in ensuring accurate and safe delivery of CRRT. However, in our specialized isolation unit, the bedside ICU nurse was working alone in the patient's room with a "buddy" nurse immediately available in the anteroom. Therefore, troubleshooting and assistance could only be readily provided *via* voice/telephone communication with careful coordination. In the future, a remote monitoring video link (*e.g.*, an electronic ICU platform) may be a beneficial additional resource to support nursing staff and allow additional monitoring of patients.

CRRT provides several other advantages especially with regard to more accurate control of fluid balance and more successful volume removal by ultrafiltration.²³ However, it should be noted that

CRRT also enhances removal of amino acids, water-soluble vitamins, micronutrients, and other trace elements. Thus, these patients should receive augmented nutrition support as is recommended as standard of care in all patients requiring CRRT.^{24,25}

Delivery of care in an isolation unit requires the development of protocols that are specific to the particular hospital, based on the organization and training of the staff and the type of equipment available. For this reason, this report suggests general guidelines rather than specific protocols. We are refining our specific operating procedures in several areas after our experience. Most importantly, we are examining the vascular access procedures for ways to keep blood contained in the sterile field and off of PPE and equipment and to improve care for vascular access skin sites. Finally, on most CRRT devices, there are some less accessible/inaccessible sites such as pressure transducers with direct access to blood compartments, which may require special procedures for disinfection. The biocontainment room and all equipment (including the CRRT machine) underwent terminal disinfection with

Table 2. Proposed clinical practice guidelines for RRT in the acute phase of EVD

Parameter	Clinical Guideline
Modality	CRRT recommended for initial treatment Consider transition to PIRRT (using same CRRT equipment) for continued RRT until patient either (1) recovers renal function or (2) is capable of leaving biocontainment isolation (<i>i.e.</i> , negative viral PCR studies in blood)
Staff	If possible at the institution, all patients should receive RRT using CRRT equipment by extensively trained ICU nurses as primary clinical nurses at bedside Minimize additional staff entry in the biocontainment environment (<i>i.e.</i> , specialty dialysis nurses)
Access	Temporary nontunneled dialysis catheter placed at bedside under direct ultrasound visualization. Extra precautions should be taken to contain bloody waste from this procedure The right internal jugular vein is the preferred access site (with the left internal jugular vein as the backup site), given that this presents the lowest bleeding risk because patients with EVD may experience bleeding diatheses. Recommend that subclavian insertion sites be avoided Unless portable chest imaging after access insertion is unavailable, femoral access sites should be avoided secondary to bleeding risks (retroperitoneal bleeding) Consider use of nonreflux dialysis grade caps for dialysis vascular access
CRRT dosing	No EVD-specific dosing needs. Consistent with Kidney Disease Improving Global Outcomes statements, support target CRRT dose to deliver a total effluent dose of 20–25 ml/kg per hour ¹⁰ unless higher dosing is needed to augment small solute and electrolyte clearance or correction of acidemia
Anticoagulation	RCA is preferred and recommended in all patients to extend filter life and reduce potential staff exposures with filter exchanges
Effluent disposal	CRRT effluent has a low infectious risk, but because it is handled in an EVD-positive area and a small dialyzer leak may be undetected, recommend that effluent be treated as hazardous and disposed of in a similar manner as individual institution/local guidelines require for disposal of other bodily fluids in EVD ¹¹
Nutrition support during CRRT	Ensure that patients receive appropriate augmented nutrition support while receiving CRRT as recommended by clinical guidelines (total daily protein intake of approximately 2 g/kg per day) ^{24,25}

vaporized hydrogen peroxide after patient discharge. After a rest period of 7–10 days, this CRRT device will return to general service without plans to monitor subsequent patients using that machine for EVD.

As hypothesized, these pilot data demonstrate that there was no EBOV genetic material in spent effluent, suggesting that effluent is noninfectious and that it may be possible to discard spent effluent safely by conventional means. However, these data and recommendations are limited in so far as we have only three effluent samples on a single patient and further confirmatory PCR testing of spent effluent in other patients is likely warranted. It should also be noted that even though the effluent is likely noninfectious, it still must be handled in an EVD-positive environment, making secondary contamination possible.

It is notable that with aggressive life support therapy, this patient survived, recovered renal function, and was discharged from the hospital. This case confirms that with adequate training, preparation, and adherence to safety protocols, RRT can be provided safely and should be considered as a viable supportive care treatment option in patients with EVD. In light of the highlighted safety issues and the isolation environment in which RRT is provided in EVD, we strongly feel that CRRT should be considered the primary mode of RRT in patients with EVD regardless of hemodynamic status. Finally, on the basis of this experience, we propose clinical practice guidelines for providing RRT in the acute phase of EVD (Table 2), which have informed the recently published CDC guidelines regarding acute RRT in EVD.²⁶

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DISCLOSURES

None.

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