ASN LEADING THE FIGHT AGAINST KIDNEY DISEASE

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Frequently Asked Questions (FAQs) Regarding Ebola Virus Disease and Dialysis

Ebola virus disease (EVD) can result in shock and multiorgan failure, and has been associated with mortality rates exceeding 70%. In many cases, acute kidney injury (AKI) and kidney failure will develop during the disease course. Here, the American Society of Nephrology (ASN) provides an overview of considerations for nephrology health professionals who may care for patients infected with Ebola virus. More general information regarding EVD can be found at: http://www.cdc.gov/vhf/ebola/index.html and the CDC's "Recommendations for Safely Performing Acute Hemodialysis in Patients with Ebola Virus Disease in U.S. Hospitals" can be found at: http://www.cdc.gov/vhf/ebola/hcp/guidance-dialysis.html

1. How does EVD affect kidney function?

- Some degree of AKI is likely to be common in patients with EVD. As in many cases of AKI, the cause is likely to be multifactorial. Specific factors that may lead to AKI include hypovolemia due to the massive fluid losses from vomiting and diarrhea that patients with EVD experience, which may cause pre-renal azotemia and ischemia. Second, EVD is known to cause a systemic inflammatory response syndrome and capillary leak akin to what occurs in patients with sepsis. Third, AKI may result from factors related to hemorrhagic fever and the clotting abnormalities that include increased susceptibility to bleeding and disseminated intravascular coagulation (DIC). Finally, some data exist to suggest that the Ebola virus enters tubular epithelial cells and may thus directly contribute to AKI.
- Given the fluid losses that patients with EVD experience, which can be dramatic, it should be emphasized that a cornerstone of care for EVD patients rests on adequate fluid resuscitation with close attention to electrolyte and acid-base balance. In particular, hyponatremia, hypokalemia (potassium < 2 mEq/L) and acidosis are common.
- Independent of the Ebola virus infection, up to half of critically ill patients develop AKI due to secondary sepsis, nephrotoxic medications and other commonly known factors. Thus, AKI in EVD patients may occur in two phases – an early phase due to factors described above, and a later phase due to secondary insults such as sepsis.

2. What is the most important thing nephrologists need to know about treating a patient with EVD?

- Successful treatment of a patient with EVD centers on excellent care for the patient and prevention of exposure to health care professionals and the general public. Thus, it is critical for nephrologists to understand what is known about the infectivity of the Ebola virus in order to plan for the care of EVD in a manner that maximizes infection control and minimizes threat to health care professionals.
- Several EVD patients who have been cared for in North America and Europe have developed multiorgan failure, including dialysis-requiring AKI. Thus, given the potential need for dialysis and the complexity of performing dialysis in a patient with EVD, nephrologist

involvement is essential in the planning phases of hospitals intending to care for patients with EVD.

3. What are the indications for dialysis in patients with EVD?

- In general, medical indications to initiate dialysis in patients with EVD will be similar to other patients with AKI and will involve considerations such as volume control, electrolyte, acid-base balance, and severity of kidney dysfunction.
- Unlike many other diseases, EVD is associated with substantial risk of nosocomial transmission (including to health care professionals) and a very high mortality rate. As such, health care worker safety and the risk of transmission to other hospitalized patients is a mandatory consideration in medical decision making for critically ill patients with EVD. This is not limited to the provision of dialysis, but is also a relevant factor for other potential interventions, both invasive and non-invasive. For example, the decision to reduce the risk of nosocomial transmission by creating bio-containment facilities limits the laboratory and radiological studies that patients with presumed or documented EVD infection will receive. Only if health care professionals can be appropriately protected from Ebola virus exposure should dialysis be initiated.
- In critically ill patients, nephrologists have extensive experience considering the risks and benefits of dialysis. The medical decision to initiate dialysis in patients with EVD should follow the usual course, which involves consultation with the other care providers, consideration of risks and benefits to the patient, consideration of overall prognosis, and – most importantly – consultation with the patient (if possible) or family members or other patient decision makers and consent from the patient or patient decision makers.
- Practitioners should be cognizant of what has been described as the "twin traps of overtreatment and therapeutic nihilism" – in this context, discussions with other practitioners, including ethics consultants who are not directly involved in the care of the individual patient, can be very helpful. Furthermore, individual centers must carefully consider if they have the resources – both physical and human – to provide dialysis in a manner that is safe both for the patient and for practitioners. Knowing – and respecting – the limits of an individual hospital system is a fundamental tenet of above all, doing no harm.

4. What should nephrologists know about the infectivity of the Ebola virus?

- During acute infection, Ebola virus levels increase in the blood logarithmically and can reach levels greater than 10^{10} copies/mL of blood (compared to 10^{6}-10^{7} copies/mL during acute HIV infection). Patients with EVD warranting consideration of dialysis are, by default, the highest risk patients for nosocomial transmission to hospital professionals based on blood levels of virus.
- Like other blood borne pathogens such as HIV and Hepatitis B and C, Ebola virus is spread through direct contact with blood from infected patients. Ebola virus is also spread via contact with other infectious bodily fluids such as vomitus and diarrhea.
- From an infection risk standpoint, EVD is currently considered a greater concern to health care professionals in the acute setting than some other blood borne viruses because Ebola virus particles can be found on the skin of infected patients. It is unknown if this is due to direct infection of skin cells by the virus or micro-contamination of the skin with other bodily fluids.
- Finally, it is possible that the Ebola virus may be transmitted via aerosolization of infected bodily fluids, including blood. The risk of aerosolization in the acute care setting has prompted the use of droplet precautions for health care professionals with direct patient contact in the acute setting. Suctioning of respiratory secretions and intubation are examples of aerosol generating procedures. Transmission via aerosolized particles is

distinct from the concept of respiratory transmission naturally through the air – specifically, the Ebola virus is not transmitted through the respiratory route like other viruses such as influenza.

5. What procedures should be considered to maximize infection control and minimize any potential threats to health care professionals?

- Healthcare worker safety starts with the fundamental aspects of infectious disease isolation. It is recommended that each medical center create and adhere to isolation policies as per the Centers for Disease Control and Prevention (CDC) recommendations for Personal Protective Equipment (PPE). Please note that these recommendations were accurate as of Wednesday, October 22, 2014; those in involved in the care or the planning of care for EVD patients are advised to check frequently for new updates regarding PPE.
- Health care delivery for patients with EVD in general, and the dialysis procedure in particular, must occur in an isolation unit where direct contact with all bodily fluids and skin is avoided. In this setting, providers cannot readily enter the patient's room, and instead must first don PPE using standard procedures under direct supervision, as outlined in the CDC PPE guidelines.
- The number of health care professionals with direct patient contact should be minimized. To this end, the nephrology care team should only be involved in direct patient contact when directly contributing to the physical care of the patient (line placement, dialysis machine setup). Additionally, consideration should be given to excluding nephrology trainees from direct care of EVD patients; guidance regarding the involvement of trainees in the care of EVD may be found on the Accreditation Council for Graduate Medical Education (ACGME) web site which has been updated regularly. Decisions regarding trainees and designated health care professionals for EVD patients should be made on an individual center basis.
- Health care delivery to patients with EVD requires strong administrative support; a team concept where professionals are responsible for each other's safety; regular and rigorous training in the use of isolation rooms and proper PPE; procedures for handling breaches in protocol; and a process for constant refinement of safety practices.
- All procedures must be carefully planned and ideally not performed under urgent or emergent circumstances.
- The CDC recommendations for PPE include droplet precautions, which should be meticulously followed throughout the dialysis procedure given the potential risk of aerosolization of infectious fluids during the acute care of patients with EVD. Additionally, contact precautions must be adhered to in order to avoid exposure to blood or other infectious bodily fluid; thus head-to-toe impermeable or fluid-resistant PPE must be worn, with no skin exposed.
- The following CDC links will be useful to nephrologists considering and planning the care of patients with EVD:
    - Human to human transmission overview (includes summary of exposure to health care professionals): http://www.cdc.gov/vhf/ebola/transmission/human-transmission.html
    - Bloodborne pathogens and aerosols as relates to Hepatitis B and HIV: http://www.cdc.gov/oralhealth/infectioncontrol/faq/aerosols.htm
    - PPE: http://www.cdc.gov/media/releases/2014/fs1020-ebola-personal-protective-equipment.html

6. How has dialysis been employed to address EVD's deleterious effects on kidney function?

- Information on if, and to what extent, dialysis has been employed in Africa is not yet available. To ASN's knowledge as of October 22, 2014, only two EVD patients have received dialysis in the United States. Dialysis was used in the care of at least one patient with EVD in Germany. Thus, information regarding the treatment of EVD and other hemorrhagic fevers in countries with healthcare infrastructure similar to the United States is limited. Dialysis was part of the successful treatment strategy that led to the survival of one patient in the U.S. Thus, dialysis may reasonably be considered in the context of the treatment plan for patients with EVD.
- It is important to realize that many experts believe that enhanced supportive care, in general, is likely to greatly improve outcomes in EVD patients currently in Africa who have an approximately 70% mortality. By analogy, during the 1960s, mortality rates of Marburg hemorrhagic fever reached 70 to 85% in Africa, whereas an outbreak of Marburg fever in Germany and the former Yugoslavia had mortality rates of 20 to 25%.

7. What special considerations regarding the dialysis procedure may be appropriate for patients infected with EVD?

- It is important to consider center-specific expertise with modes of therapy and equipment when faced with a decision to provide dialysis to a potential patient with EVD. Centers should carefully consider their level of capability with dialysis and whether they have the experience and expertise necessary to carry out the treatment safely when confronted with a potential EVD patient.
- Instituting multiple new procedures or methods of continuous renal replacement therapy (CRRT) outside of a center's expertise will likely increase errors that may affect patient outcome and healthcare worker safety.
- Limiting blood and bodily fluid exposure to health care professionals and other hospital employees is the top priority. As such, first consideration must be prior training of the staff members who will be providing the care.
- In the hemodynamically unstable patient who is undergoing massive volume resuscitation, CRRT may offer advantages over intermittent hemodialysis (IHD), with superior volume and electrolyte control.
- When providing CRRT, consideration should be given to appropriate disposal of the effluent. Machines with effluent drainage lines require less handling by the nurses, compared to those machines that require manual disposal of effluent and/or effluent bags. If the center uses CRRT machines that require effluent bags, re-use of the bags should be discouraged to minimize exposure to nursing personnel. Please refer to the section on "How should the nephrology care team handle the dialysate effluent/spent dialysate?" for additional information on this topic.
- Some CRRT systems are packaged as an integral cartridge and tubing set, thereby limiting the number of connections to be made and broken when a set is exchanged. Some CRRT systems require that the blood and dialysate pumps spin during cartridge unloading, which can result in sprays of contaminated fluid if a connection is inadequately clamped. Staff should be adequately trained before setting up and disconnecting the CRRT system.
- Hospitals and intensive care units where the bedside nurse is already familiar with setup and exchange of the CRRT system can limit the number of healthcare professionals coming into contact with the patient.
- Centers can also consider decreasing the frequency of filter change of the CRRT system. Centers should consider postponing "routine" system changes provided CRRT is still providing adequate clearance, with no evidence of malfunction.

- Once CRRT has been initiated, consideration should be given to restricting the patient to use a single machine during the entire hospitalization. CRRT machines have the capability to deliver higher blood and dialysate flow rates and thereby provide sustained low-efficiency dialysis (SLED). Once a patient is hemodynamically stable, the care team can consider transitioning the patient to SLED instead of using another machine to provide IHD. This approach may help minimize exposure to healthcare professionals and other patients.
- Electrolyte monitoring for patients on CRRT represents a significant ongoing health care worker exposure to infectious fluids. Centers should consider whether or not "routine" CRRT laboratory monitoring can be performed less frequently than is standard practice.
- At many centers, point-of-care laboratory testing will be used so that the clinical laboratory does not handle infectious specimens. Some centers may not be able to perform point-of-care testing of electrolytes that are routinely monitored for CRRT (specifically, phosphorus and magnesium). In these cases, empiric supplementation to avoid life-threatening hypophosphatemia and hypomagnesemia should be considered based on ongoing losses via the CRRT circuit, GI tract and other sources.

8. Are there particular vascular access requirements for dialyzing patients with EVD, such as line placement and site?

- Since there is no evidence to support one type of vascular access over another in the setting of EVD care, vascular access placement should be predicated on the experience, equipment available, and local standards of care of the treating physicians.
- Insertion of vascular access is the single largest exposure of personnel to large quantities of blood, so the initial placement of a good access is critical in maintaining the safety of healthcare professionals.
- Only healthcare professionals with abundant experience placing catheters should be designated to place vascular access in anticipation of dialysis.
- Dialysis catheter placement should be performed in the isolation room with ultrasound guidance to reduce the possibility of complications. Equipment used in the placement of the access (e.g., ultrasound) should remain in the room.
- While a temporary dialysis catheter may not provide the same blood flow rates as a larger bore permanent catheter, temporary access is preferred to minimize the rates of complications relating to access placement and blood exposure.
- Although the Kidney Disease Improving Global Outcomes AKI clinical guidelines support the right internal jugular (R IJ) position as the preferred site for dialysis vascular access, individual centers may consider femoral cannulation depending on resources immediately available in the isolation room. Femoral cannulation avoids the need for chest x-ray to assess for correct placement (and thus potential exposure of X-Ray technicians). In the presence of appropriate central venous catheter care and a patient with a body mass index (BMI) less than 35, there is no evidence to support an increased risk of infection in the presence of a femoral catheter.
- Left internal jugular (LIJ) venous dialysis catheter is usually associated with poor blood flow rates and may increase the risk of clotting of the CRRT circuit. Femoral cannulation may be considered to avoid the LIJ position.
- The team caring for the patient with AKI and EVD should consider having protocols in place to address potential complications of vascular access, including trauma to an artery or pneumothorax. Chest tube placement or operative repair of an arterial wound may increase the number of healthcare professionals and patient care environments exposed to the Ebola virus.
- For patients who are currently undergoing routine maintenance dialysis for the treatment of end-stage renal disease and EVD requiring-dialysis, placement of a catheter to initiate

dialysis may reduce the risk of future blood exposures via fistula or graft access. Temporary dialysis catheter placement in a patient with prior ESRD may prove technically challenging due to previous vascular injury from lines and fistula placement, even in the presence of ultra-sound guidance. If a temporary catheter is not placed, careful consideration will be needed to protect health care worker as accessing a graft or fistula usually is performed by a dialysis professional and may not be feasible for all clinical personnel.

- In the setting of an EVD-infected ESRD patient who is chronically receiving peritoneal dialysis (PD), consideration may be given to switching modalities and performing CRRT or IHD with placement of a temporary catheter as the virulence of peritoneal dialysate/ultrafitrate is unknown. However, potential advantages of continuing PD are that the risk of blood exposure via catheter placement is avoided, catheter patency is not likely to be an issue (as with CRRT), and the volume of effluent produced will be significantly lower than with IHD or CRRT. Physicians should consult with their local infection control and hospital policies as continuation of PD may not be feasible for a variety of reasons, including mandating exposure of additional healthcare professionals to infectious patients. The unknown infection risk from peritoneal dialysate fluid the handling of this solution may vary across institutional policies.

9. How should the nephrology care team handle the dialysate effluent/spent dialysate?

- Dialysis effluent should be sterile given the large size of intact Ebola virus and the small pore size of the filters used in dialysis. Specifically, filoviridiae are elongated fiber-like structures with smallest dimensions about 75 nanometers. The pore sizes of high-flux dialyzers are typically 3-4nm and can be expected to block transmission of the virus from blood to dialysate.
- Polymer dialysis membranes have a wide distribution of pore sizes and may not be a perfect barrier to virions or viral nucleic acids. Further, blood leaks can occur and may not be detected by the dialysis or CRRT machine. Waste dialysate or CRRT effluent should therefore be assumed to be infectious.
- The CDC ,as of October 22, 2014, suggests that untreated urine and stool from EVD patients can safely enter municipal wastewater streams by using toilets. Please refer to this CDC webpage for further information on municipal wastewater systems.
- However municipalities with combined sewer overflows (CSOs, described by the Environmental Protection Agency on this website) may require Ebola virus-contaminated wastes to be sterilized prior to disposal or forbid disposal of wastes from EVD patients altogether.
- Nephrology health professionals should, therefore, treat the effluent as potentially infectious and exercise caution in its handling and disposal. Both CDC guidelines and federal, state, and local health department recommendations will need to be ascertained and followed in the handling of dialysis effluent (as well as other infectious or potentially infectious waste).
- It is recommended that those involved in the planning of taking care of EVD patients contact their local health department so that locally-appropriate methods to handle effluent may be designated.
- Treating effluent with bleach or disinfectant may reduce the risk of transmission.

10. What type of anticoagulation, if any, should be used?

- The approach to anticoagulation for dialysis in EVD patients requires a balance between several factors: patient bleeding risk, minimization of healthcare professionals' exposure risk, and local experience/expertise.
- Maximizing filter life by reducing filter clotting events is a key consideration in the dialysis care of patients infected with EVD. By reducing filter clotting and excess filter changes,

blood transfusion requirements may be reduced for the patient. Furthermore, reducing the number of filter changes decreases health care worker exposure to infectious fluids as filter changes are a potential source of exposure.

- For critically ill EVD patients with active bleeding, it may be prudent to limit or avoid systemic anticoagulation with heparin.
- Regional citrate anticoagulation may be an effective alternative that has the advantage of prolonging CRRT circuit life without increasing bleeding risk. In one center's experience with dialysis in patients with EBV, regional citrate anticoagulation was used effectively with prolonged filter life. However, because there is a lack of standardization, at some sites a disadvantage of regional citrate anticoagulation is an increased need for ionized calcium monitoring, which will increase blood exposure for healthcare professionals. Adapting protocols to minimize lab monitoring may be a consideration to attenuate this risk, recognizing that adapting and changing protocols may lead to errors that put the patient and health care worker at risk. Centers should consider both the potential exposure risks and benefits of citrate anticoagulation based on their local protocols and experience.
- Medical centers without established citrate protocols can consider a no-anticoagulation approach and apply alternative filter-prolonging measures. These may include increasing blood flow rate (>300mL/min) and/or utilizing pre-filter replacement fluid for hemodilution.
- Once active bleeding resolves, consideration can be given to instituting heparin protocols for either CRRT or a transition to intermittent hemodialysis or SLED.

11. How long do EVD survivors remain infectious?

- The blood is infectious until there is no viral RNA, the timing of which depends on the severity of disease and the effectiveness of the immune response, but is typically less than a month. According to World Health Organization and CDC guidelines, patients with EVD may be discharged from the hospital setting under two conditions: 1) Symptoms have improved, and 2) Blood is free from the virus. At this time, the patient is considered not to be infectious.
- Studies suggest, however, that the urine and semen may remain positive for RNA for a period of 1-3 months after the blood clears. However, it is not clear if the virus can be transmitted in this period. There is a case report suggesting that Marburg virus (in the same genus of viruses and which also causes hemorrhagic fever) may be transmitted through semen.

12. If EVD survivors continue to require dialysis—HD after CRRT—are there special considerations for these patients to receive dialysis?

- When the patient improves and needs to become mobile as part of his or her recovery, an intermittent therapy may be required.
- Until the blood is clear of virus, intermittent dialysis using the same CRRT machine should be used to continue the principles of isolation.
- After the blood is clear of virus, the only special consideration is that the urine and semen may remain positive. Semen may remain positive for up to 3 months. Preliminary data suggest that the urine may remain positive for a shorter time (e.g., a week). A cautious approach seems warranted in dialysis units and isolation similar to that used for hepatitis B should be considered until better data exist.

13. How should dialysis in infants and children be managed?

- The approach to a child with EVD should be similar to that outlined for the adult population, with some exceptions for consideration listed below.

- Children with AKI, compared to adults, are more likely to receive PD. Consequently, the selection of modality in children is often a choice between PD and CRRT. However, in children with EVD, the presence of hemorrhagic gastroenteritis can potentially limit the use of PD. In addition, the infectious risk of PD effluent is unknown. It is likely that the infection risk of PD ultrafiltrate is higher than that of CRRT effluent because of presence of cellular elements in the peritoneum. If PD is implemented, center specific protocols should be implemented to guide the appropriate disposal of the PD ultrafiltrate/effluent.
- Alternatively, initiation of CRRT will lead to potential blood exposure, as discussed in previous sections. When choosing the mode of dialysis, institutions should institute best clinical practice according to the expertise in their hospital, and work to minimize risk as much as possible.
- An additional consideration related to general care of children with EVD is to address the needs of the family members, especially parents. Family members, especially parents of critically ill infants and children often feel the need to be at the bedside. Isolation of the child due to high risk of transmission of EVD obviously poses significant challenges to providing family-centered care. Development and implementation of center specific protocols to alleviate family and patient concerns will be helpful.
- Of the utmost importance in the case of a child requiring dialysis is referral of the child to a center with the expertise to perform dialysis in children, as such centers should inherently have protocols and teams in place to best care for the child and minimize risks to health care workers.

14. How should machines used in the care of patients with EVD in the isolation unit be terminally disinfected following patient discharge from the isolation unit?
Machines used for dialysis can be safely disinfected and re-used for other patients per CDC guidelines. Specific methods for disinfection should follow CDC recommendations on this matter.

The cleaning and disinfection of external machine surfaces should be performed in accordance with CDC's "Interim Guidance for Environmental Infection Control in Hospitals for Ebola Virus" and the manufacturer's instructions.

According to the CDC, general principles for EVD infection control in the hospital environment include the following:

- Use appropriate PPE
- Perform a cleaning step using a detergent
- Perform disinfection using an EPA-registered hospital disinfectant recommended for use against Ebola during the 2014 outbreak*
- Ensure all surfaces are cleaned and disinfected (including accessory equipment such as IV poles), paying particular attention to high-touch surfaces, such as control panels
    - Assure sufficient wet contact time of disinfectant according to label claims for inactivation of a non-enveloped virus

Additional considerations:

- Vaporized hydrogen peroxide and ultraviolet (UV) light applications for decontamination of isolation room surfaces (during terminal disinfection) might serve to disinfect external surfaces of dialysis machines. If UV light is used, the importance of a direct line of sight for efficient disinfection should be considered.

CDC has been in contact with some machine manufacturers and may be able to assist in providing more specific guidance for machine terminal disinfection procedures. (CDC Emergency Operations Center 770-488-7100)

Internal pathways
Standard heat or chemical disinfection procedures recommended by machine manufacturers and used routinely by dialysis providers are sufficient to inactivate Ebola virus.
Internal machine disinfection of hemodialysis machines should be performed between treatments and conducted in the isolation room.

Other internal machine components
If there is concern about the possibility of fluid contamination of internal machine components such as pressure monitors, contact the manufacturer for guidance and notify the appropriate local or state health department and CDC (CDC Emergency Operations Center 770-488-7100).

* EPA-registered disinfectant: Use a U.S. Environmental Protection Agency (EPA)-registered hospital disinfectant with a label claim of potency at least equivalent to that for a non-enveloped virus (e.g., norovirus, rotavirus, adenovirus, poliovirus).