Caring for Critically Ill Patients with Ebola Virus Disease
Perspectives from West Africa

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Abstract

The largest ever Ebola virus disease outbreak is ravaging West Africa. The constellation of little public health infrastructure, low levels of health literacy, limited acute care and infection prevention and control resources, densely populated areas, and a highly transmissible and lethal viral infection have led to thousands of confirmed, probable, or suspected cases thus far. Ebola virus disease is characterized by a febrile severe illness with profound gastrointestinal manifestations and is complicated by intravascular volume depletion, shock, profound electrolyte abnormalities, and organ dysfunction. Despite no proven Ebola virus–specific medical therapies, the potential effect of supportive care is great for a condition with high baseline mortality and one usually occurring in resource-constrained settings. With more personnel, basic monitoring, and supportive treatment, many of the sickest patients with Ebola virus disease do not need to die. Ebola virus disease represents an illness ready for a paradigm shift in care delivery and outcomes, and the profession of critical care medicine can and should be instrumental in helping this happen.

Keywords: Ebola; Africa; critical care; outbreak; viral hemorrhagic fever

Origins of the 2014 West Africa Ebola Virus Disease Outbreak

On March 21, 2014, the World Health Organization was notified of a rapidly evolving outbreak of Ebola virus disease (EVD) in the forested regions of southeastern Guinea that subsequently spread to the capital city, Conakry, marking the world's first EVD outbreak in a major metropolitan area (1). Since March, Ebola virus (formerly labeled Zaire Ebola virus and typically associated with mortality rates of 50–90%) has ravaged West Africa, including Guinea, Sierra Leone, Liberia, Senegal, and Nigeria (Figure 1). With 5,335 confirmed, probable, or suspected cases and 2,622 deaths thus far, this is the largest and most devastating Ebola virus outbreak in history (2).

West Africa has never before experienced an Ebola virus outbreak. Despite experience with Lassa fever, the initial challenges of EVD experienced in Guinea are emblematic of those throughout the region. The Guinean population of approximately 11,451,000 persons has a life expectancy at birth of 58 years, a gross national income of 970 international dollars, and 67 international dollars expenditure

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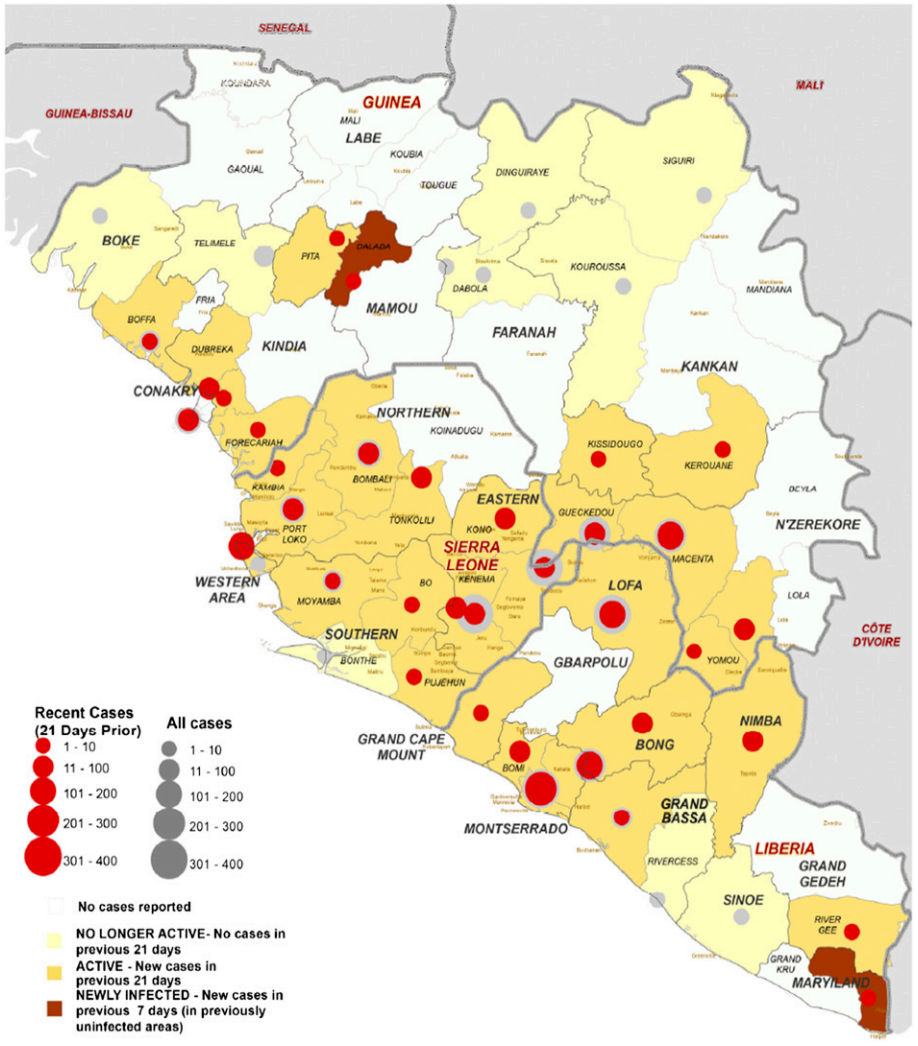

Figure 1. Locations of confirmed cases of Ebola virus disease in West Africa, August 7, 2014. Reproduced with permission from Reference 21.

on health *per capita* per year (3). In West Africa, the stark and undeniable reality is that baseline public health and acute care resources are severely limited (3, 4). Rural residents travel long distances for basic healthcare needs. In Guinea's largest public hospital, the intensive care units have no piped oxygen and no mechanical ventilators. Basic infection prevention and control is plagued by an unstable supply of running water and insufficient personal protective equipment, which facilitates spread of communicable diseases such as Ebola. The constellation of limited public health infrastructure, low levels of health literacy, few acute care and infection prevention and control resources, densely populated areas, a mobile population, and a highly transmissible and lethal viral infection have created a perfect storm underlying this outbreak. We offer the following insights from the perspective of clinicians who have assisted in the treatment of patients with EVD throughout West Africa during this outbreak.

Public Health Challenges in Responding to EVD

Ebola virus outbreaks occur at relatively frequent intervals (two dozen outbreaks over the past 30 yr). They occur most commonly in central Africa but are often confined to rural areas with limited external transmission (5). The natural reservoirs include bats, with primates and possible other mammalian species regarded as the susceptible end hosts. An Ebola virus outbreak amid an increasingly mobile population to densely populated areas with large numbers of inhabitants per household is an enormous public health challenge. In addition to family-based transmission, urban outbreaks provide access to hospitals and often paradoxically lead to nosocomial amplification of transmission chains. In China and the Hong Kong Special Administrative Region, Singapore, and Toronto, the critical care community learned firsthand about the ease of nosocomial spread of another virus—severe acute respiratory syndrome (SARS) (6). Possibly the most humbling lesson was the effectiveness of transmission when infectious patients are admitted to hospitals with inadequate infection prevention and control practices. We also learned the perils of letting down our guard too early in an outbreak (6); it only takes one new patient to set off a new chain of transmission. The 2014 West Africa Ebola outbreak has proven these to be generalizable outbreak lessons, with many healthcare worker infections and deaths and multiple epidemiological waves of transmission (2).

It is difficult to respond with perfect intensity and timing to outbreaks of new and evolving pathogens such as SARS, Middle Eastern respiratory syndrome, influenza, or Ebola because the "sweet spot" is very thin. Robust responses, as for the 2009 pandemic, are met with criticism of excess resource mobilization at best and pandering to pharmaceutical company interest at worst (7). However, under constant financial constraints, most health care systems evolve to a state of little or no excess capacity: any excess demand can either be just met, or the system is overwhelmed. In West Africa, a lack of baseline capacity, a lack of sentinel surveillance, and a lack of accessible and reliable diagnostics lead to late recognition and delayed responses. The local, national, and international health system response to this outbreak has been characterized by some as too slow and with too little mobilization of support on the ground.

Clinical and Pathophysiological Features of EVD

Ebola, like, Marburg, is an RNA filovirus that is usually transmitted through direct mucus membrane or percutaneous exposure to infected body fluids (typically

stool, vomit, or blood) (8, 9). Monocytes, macrophages, and dendritic cells help to disseminate the virus to lymph nodes, followed by hematogenous spread to the liver and spleen. Beginning as a febrile illness, often with fatigue and myalgias, the most prominent feature in this outbreak has been of progressive gastrointestinal symptoms: anorexia, nausea, and abdominal discomfort followed by vomiting and diarrhea that lead to intravascular volume depletion and complications including profound electrolyte disorders, hypoperfusion, and shock. The "hemorrhage" of viral hemorrhagic fever is a late manifestation, usually occurring as gastrointestinal bleeding, but occurs only in a minority of patients; hence the adoption of a more contemporary name, Ebola virus disease.

Point-of-care or other laboratory testing inside the treatment facility, once available, transforms the appreciation of illness pathophysiology. Hemoglobin levels were almost never profoundly low, and hypoxia by pulse oximetry was only impaired in the terminal phases of multisystem organ failure. Hypoperfusion is ubiquitous and frequently evidenced by metabolic lactic acidosis (ranging from 4 to 10 mmol/L among many patients with clinical suspicion), diarrhea-associated profound hypokalemia (sometimes <2 mmol/L), and very common renal insufficiency. Hepatocellular injury marked by aminotransaminase elevation was very common.

Although there may be pathophysiological similarities between Ebola infection and bacterial sepsis with a systemic inflammatory response, there is much less clinically recognizable capillary leak syndrome and little compromise of oxygenation or ventilation, which often accompanies bacterial sepsis–related critical illness. Although endothelial infection and injury have previously been postulated as part of the pathophysiology of Ebola infection, there is scant direct evidence of this, resonating with the observed clinical differences between bacterial and Ebola sepsis (8); however, there is much to learn.

Supportive and Specific Treatments of EVD

The early clinical response to EVD outbreaks is often limited. Patients usually present for care late in their illness course, and there are often precious few personnel, little equipment, and no specific therapy to offer. In Guinea, for many days, although we had an isolation facility (Figure 2) and the ability to diagnosis infection with international laboratory support of RT-PCR, there were no beds and no monitoring mechanism to check blood pressure, fluid balance, basic potentially life-threatening biochemical abnormalities, or oxygenation. Thankfully we had the most important aspects of supportive care—oral rehydration and intravenous fluids—when patients could not maintain oral intake. Beds and mosquito nets eventually arrived. Antibiotics for empiric treatment of ongoing fever and gastrointestinal symptoms, malaria rapid antigen assessment and antimalarials, potassium, and antiemetic agents were donated or scavenged along with automated blood pressure cuffs, thermometers, and oxymeters.

Despite no proven EVD-specific medical therapies, the potential effectiveness of supportive care is great for a condition with high baseline mortality and one usually occurring in resource-constrained settings. Many patients have concomitant malaria infection, which can be treated and may influence outcomes. The influence of secondary or complicating bacterial infections is uncertain; however, empiric treatment for enteric pathogens is part of most clinical treatment protocols (5, 10) for patients entering the severe gastrointestinal phase of illness, even though the importance of gastrointestinal bacterial translocation is uncertain.

The most important aspect of supportive care is aggressive prevention of intravascular volume depletion, correcting profound electrolyte abnormalities, and preventing the complications of shock. This is an underlying tenant of critical care medicine and one that can and should be applied in both resource-constrained and resource-rich settings (11). Optimal supportive care is sometimes not possible due to a lack of personnel and limitation on time spent at the bedside due to the challenges of personal protective equipment. In West Africa, this involves placing and replacing intravenous and occasional intraosseous catheters and delivering fluid boluses during the periods that you are on the ward. Patients are mostly unmonitored and frequently remove intravenous access, and there is little ability to safely or with sterility place and maintain central venous access. In resource-rich settings, maintaining intravenous access with peripherally or centrally inserted catheters and increased opportunity for nursing care will help deliver treatment. Aggressive correction of electrolyte depletion and acid–base derangements is critical to avoid life-threatening metabolic complications. In West African treatment centers, routine biochemistry is sometimes possible but is infrequently deployed as part of the international laboratory response; therefore, such abnormalities are often unappreciated and untreated. For patients who develop multisystem failure, oxygenation, ventilation, and hemodynamic support are generally unavailable. However, lending strong support to the argument of greater supportive care leading to better outcomes is the experience with Marburg hemorrhagic fever, with case fatality rates in Africa typically 70 to 85%, compared with the 1967 outbreak in Germany and the former Yugoslavia, which had mortality rates of 20 to 25% (8). With improved supportive care, we can improve outcomes for EVD.

Although critical care units in developed countries have become expert at "sterilizing" critical illness and death, this is often impossible in West African Ebola treatment centers. Whole families arrive at treatment facilities, but when parents die, Ebola orphans remain; some children or babies are transported to the facility without any knowledge of who the parents are or were. Diarrhea and vomiting are ever present, and keeping patients and the environment clean is often impossible. Patients who die in the night are usually discovered the following morning. Symptom control with narcotics and benzodiazepines is often our best end-of-life therapy. All of these challenges could be improved with more personnel and a greater ability to monitor and treat patients.

The Importance and Challenges of Personal Protective Equipment

Adherence to transmission- and evidence-informed infection prevention and control procedures is a critically important aspect of clinical care. Appropriate use of standard and contact precautions along with personal protective equipment, including gloves,

Figure 2. Conakry, Guinea Ebola virus treatment facility.

a disposable impermeable gown and apron, and facial protection with a face shield or goggles and a mask, are effective at protecting healthcare workers from coming into contact with infectious body fluids (12). Although there is a distinct lack of respiratory involvement, additional precautions may be warranted if droplet or aerosol-generating procedures are performed; however, procedures such as intubation and ventilation are not practical options in most West African outbreak locations.

Adoption of personal protective equipment that is not based on known modes of transmission poses challenges to patient care and possibly even risk to healthcare providers. In the treatment facilities, personal protective equipment unfortunately limits human interaction and hides facial expressions that normally convey empathy and build patient–clinician connections. Temperatures exceeding 45°C inside impervious equipment manufactured to guard against penetration of virus at higher than possibly attainable atmospheric pressures lead to rapid build-up of liters of sweat and conspire against the time needed to deliver fluids and medications, to insert intravascular catheters, and to talk with patients in the midst of the most stressful experience in their life (13). Determining the appropriate personal protective equipment on the basis of known mechanisms of transmission is necessary to ensure healthcare worker safety and to enable, as opposed to limit, care and care duration for infected patients.

Sociocultural Context of Clinical Care

There are many challenges in delivering best care that are well upstream of treatment centers. Social mobilization and public health education in the setting of high mortality and community mistrust is difficult but is vitally important to gaining acceptance of the illness and the necessity for care. A disproportionate influx of international personnel with an often unique geo-social-ethnic culture contributes to communication challenges. This is evidenced during outreach to community members with suspected EVD that is occasionally met with strong resistance from family and neighbors of symptomatic patients. When most patients historically do not leave the treatment facility alive, early resistance is easy to understand. Yet, with ongoing community-based work, this initial mistrust often gives way to acceptance and profound appreciation for international staff and foreign medical teams.

The Imperative to Improve Clinical Outcomes of EVD

The current weighted case fatality rate of nearly 70% for all Ebola virus outbreaks is an unacceptable outcome (5). In addition to improving local, national, and international response with personnel and supportive care, epidemiology, contact tracing, and social mobilization, we must also consider observational and experimental research as a core component of an EVD outbreak response. Although improving the care of infected patients takes precedence, we must concurrently improve our research response by implementing observational studies, biological sampling protocols, and interventional studies that have been developed, vetted, funded, and then approved in the jurisdictions likely to be affected (14). If we attempt to initiate clinical research only during the outbreak, it rarely occurs. Although the history of critical care therapeutic advances teaches us that the greatest benefit to patients is likely to emerge from consistent application of a system of critical care focused upon timely recognition, early resuscitation, supportive care, and prevention of complications, without the prior approval for research, promising interventions such as vaccination, convalescent plasma, or monoclonal antibodies will remain untested and unavailable (8, 15–17). A lack of history of research acceptance in many jurisdictions is another challenge; however, not engaging these challenges before the next outbreak represents an irresponsible approach to improving medical care. We need to fundamentally change the model of clinical research development and funding for outbreaks and pandemics from reaction to research-ready preparedness.

Despite often overwhelming challenges in an Ebola virus outbreak, there is hope. Teamwork emerges among the national healthcare workers, the Ministry of Health, Médicines Sans Frontières, the Red Cross, the World Health Organization, and many others. Nurses and doctors, initially shaken and frightened to see their colleagues falling ill, come back to work to try and help them recover. Deep mutual respect and professional friendships emerge between West African and international staff in treatment facilities and the community that will provide mechanisms to improve care well after this outbreak is over.

Although the primary goal during any outbreak is to stop it as quickly as possible, discharging increasing numbers of cured patients to their community provides affirmation that supportive and specific acute care should play an increasing role in delivering care to critically ill patients, irrespective of the presence of an intensive care unit. It is our belief that many of the sickest patients with EVD do not need to die. We need to demystify EVD as a near-certain killer from the middle of Africa and one for which little can be done and instead apply the basic principles of critical

care (*see* box, How Critical Care Medicine Can Improve the Outcomes of Ebola Virus Infection). We need to change the nomenclature of our care from "isolation centers" to "treatment centers." This can be done safely with adequate attention to infection prevention and control. Even without specific medical therapy, a combination of earlier presentation to care, personnel, and more aggressive volume and electrolyte repletion to prevent intravascular volume depletion and its complications and the addition of basic laboratory resources to track patients' metabolic response to therapy is very likely to improve survival as it has for virtually all other forms of critical illness (18–20). EVD represents an illness ready for a paradigm shift in care delivery and outcomes, and the profession of critical care medicine can and should be instrumental in making this happen.

How Critical Care Medicine Can Improve the Outcomes of Ebola Virus Infection

- Demystify Ebola virus disease by reconsidering it as one of the many examples of transmissible infection-related critical illnesses that benefit from goal-directed supportive and specific intensive care.
- Recognize that the predominant Ebola virus disease clinical syndrome is gastrointestinal—nausea, vomiting, and diarrhea—and can lead to profound intravascular volume depletion and metabolic abnormalities and require prevention and treatment.
- Appreciate the important role for basic biochemistry and laboratory markers to diagnose metabolic abnormalities and guide the response to therapy.
- Advocate that these therapies truly can and should be available to all patients in resource-constrained and resource-rich environments.
- Understand that the fundamental skills of critical care clinicians represent the fundamental needs of patients with Ebola virus disease.
- Anticipate that with better supportive care, the outcomes of infection will improve. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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