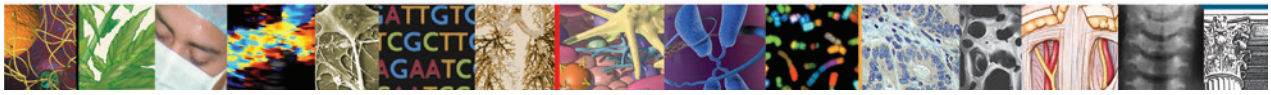

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Perspective

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Shifting the Paradigm — Applying Universal Standards of Care to Ebola Virus Disease

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As the Democratic Republic of Congo's (DRC's) 10th outbreak of Ebola virus disease (EVD) rages in this resource-limited, war-torn region, advances in the delivery of supportive care and the introduction of investigational therapies provide a glimmer of hope amid the mounting infections. In the absence of effective therapies or vaccines, EVD outbreak response has centered around the most basic of public health principles — identification and isolation of patients with suspected and confirmed EVD and tracking of all the contacts of the confirmed patients, who are then rapidly isolated if they show signs of disease. This strategy of "identify, isolate, and track" allows public health responders to curtail and eventually eliminate virus transmission in the community and has been the foundation of EVD outbreak-control efforts since the disease was first described in 1976.

Strategies for protecting susceptible communities have not always benefited patients, however. Within what were once routinely called EVD isolation units — now known as Ebola treatment units — supportive care was typically limited to the most basic measures, such as providing oral rehydration salts and acetaminophen. Unsurprisingly, case fatality ratios were high, which fueled community mistrust and resistance to broader outbreak-control efforts. The prolonged 2013–2016 EVD outbreak in West Africa allowed for an evolution of care that, by the time the outbreak was declared over, saw many patients receiving intravenous volume repletion, antibiotics, and antimalarials, potentially contributing to the downward trend in case fatality ratios.[1,2] In effect, as the epidemic waned, a new standard of care emerged, along with the important and enduring lesson that substantial progress in the clinical care of patients with EVD was not only possible but most likely essential to improving patient outcomes.

The fact that basic supportive care for patients with EVD could be debated seems incongruous with the fundamental principles of clinical care. The management of other life-threatening infections — even those for which specific treatments exist, such as influenza and bacterial sepsis — often involves a bundled approach to care

that comprises, at a minimum, adequate volume resuscitation, electrolyte monitoring and replacement, and administration of supplemental oxygen to stabilize and support essential organ functions, prevent further organ failure, and buy time while an antiinfective agent or the body's own immune system fights the pathogen. The treatment of a patient with sepsis using antibiotics alone, without consideration of other aspects of recommended care, would be considered malpractice in most settings.

At the beginning of the West African EVD epidemic, a World Health Organization (WHO) clinical expert team, together with Médecins sans Frontières (MSF) and health care providers from Guinea, achieved improved outcomes by focusing on aggressive supportive care in line with this approach, including intravenous fluid resuscitation and, when operational, electrolyte repletion directed by point-of-care laboratory testing.[1] As pragmatic as the provision of such supportive care may seem, however, it was not without challenges. As the epidemic progressed, several factors, including increasing ratios of patients to health workers, made it difficult to consistently provide this level of care. Furthermore, the limited numbers of experienced health workers and a hesitancy to perform procedures that could place workers at risk, such as insertion of intravenous catheters, also constrained universal uptake of aggressive clinical management.

In contrast, the care of patients with EVD in countries where health resources were readily available looked very different. Such patients were treated by teams of health care professionals who administered the highest levels of supportive critical care and were able to perform procedures that carried risks far greater than those associated with placing an intravenous line. Of the 27 patients with EVD who received treatment in the United States or Europe, only 5 died, corresponding to a case fatality ratio, expressed as a percentage, of 18.5% — substantially lower than the case fatality ratio of 40 to 70% reported in West Africa.[3,4] Eighty-five percent of patients in the United States and Europe also received one or more experimental therapies under expanded-access protocols; such therapies were generally unavailable to patients in West Africa. Although conclusions about the efficacy and safety of both the investigational therapies and the supportive care provided to certain patients cannot be reached outside a controlled research setting, it seems unlikely that investigational therapies alone were responsible for the difference in outcomes between patients in these settings. Rather, the provision of optimized supportive care, including adequate volume repletion, active monitoring and management of laboratory abnormalities, and mechanical organ system support, most likely had an important effect on case fatality ratios.

There are clear logistic challenges associated with bringing this level of enhanced care to places where EVD outbreaks originate, but recent innovations in treatment centers are enabling progress. In the DRC, the nongovernmental organization Alliance for International Medical Action (ALIMA) introduced to the field the CUBE system — a portable, biosecure room with transparent walls that permits continuous observation, improved accessibility, and provision of basic clinical care from the low-risk zone of the Ebola treatment unit (see photo). Similarly, MSF's laboratory tent straddles the treatment unit's low- and high-risk zones, thereby allowing staff to perform on-site laboratory testing, the results of which are critical to providing data-driven care. These innovations increase health workers' capacity to deliver supportive critical care and reflect the continued evolution toward patient-centered approaches that involve both isolation and treatment.

A natural next step in the care of patients with EVD is treatment directed against the virus itself. Whereas a minority of West African patients during the 2013–2016 epidemic received either an investigational therapy or the type of supportive care that was available to virtually every patient treated outside Africa, almost all patients in the current DRC outbreak have had improved access to both forms of treatment because of implementation of the Monitored Emergency Use of Unregistered and Investigational Interventions (MEURI) protocol.[5] Under the MEURI umbrella, the WHO clinical expert team and the Institut National de Recherche Biomédicale have partnered with ALIMA, MSF, and other groups to support the rapid scale-up of access to and safe delivery of investigational therapies, closely coupled with optimized supportive care. This experience demonstrating proof of capacity will ultimately provide an important bridge to clinical research that will enable evaluation of therapeutic efficacy and safety.

Health Workers in Beni, Democratic Republic of Congo, using the CUBE System to Monitor and Treat a Patient with EVD.

The 2013–2016 West African EVD epidemic was declared a global public health emergency and led to global recognition that emerging infectious diseases once considered "tropical" in nature must now be considered global threats that can emerge in a remote location one week and appear as new clusters of infections in even the most distant settings the next. Distance is no longer a reliable barrier to the spread of such diseases, but it has continued to determine the level of care a patient is able to receive. Within the broader context of the WHO's universal health coverage and Sustainable Development Goal initiatives, and as the treatment paradigm for patients with EVD shifts from isolation to aggressive supportive care and antiviral therapy, the global health community can build on existing momentum and work toward establishing universal standards of care in EVD management with a goal of eliminating the disparities that often dictate health care inequality.

It should no longer be acceptable to have two standards of care — one for patients in resource-constrained settings and another for those in countries where resources are more readily available. The ongoing response to EVD is teaching us that higher standards are no longer aspirational but are possible, and that during inevitable future outbreaks of EVD, no matter how remote the setting, we can provide people who are sick and suffering with the type of care that we would want to receive.

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1. Ibrahima Bah E, Lamah M-C, Fletcher T, et al. Clinical presentation of patients with Ebola virus disease in Conakry, Guinea. N Engl J Med 2015;372:40-7.
2. The PREVAIL II Writing Group. A randomized, controlled trial of ZMapp for Ebola virus infection. N Engl J Med 2016;375:1448-56.
3. Uyeki TM, Mehta AK, Davey RT Jr, et al. Clinical management of Ebola virus disease in the United States and Europe. N Engl J Med 2016;374:636-46.
4. Garske T, Cori A, Ariyarajah A, et al. Heterogeneities in the case fatality ratio in the West African Ebola outbreak 2013-2016. Philos Trans R Soc Lond B Biol Sci 2017;372(1721):20160308.
5. World Health Organization. Notes for the record: consultation on Monitored Emergency Use of Unregistered and Investigational Interventions (MEURI) for Ebola virus disease (EVD). August 27, 2018 (http://www.who.int/ebola/drc-2018/notes-for-the-record-meuri-ebola.pdf).

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