Outbreaks of Filovirus Hemorrhagic Fever: Time to Refocus on the Patient

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In the 40 years since the recognition of filoviruses as agents of lethal human disease, there have been no specific advances in antiviral therapies or vaccines and few clinical studies on the efficacy of supportive care. On 20 September 2006, experts from 14 countries representing 68 institutions integrally involved in the response to outbreaks of filovirus hemorrhagic fever gathered at the National Microbiology Laboratory of the Public Health Agency of Canada in Winnipeg to discuss possible remedies for this grim situation, in a unique workshop entitled “Marburg and Ebola Hemorrhagic Fever: Feasibility of Prophylaxis and Therapy.” A summary of the opportunities for and challenges to improving treatment of filovirus hemorrhagic fevers is presented here.

THE PROBLEM

The filoviruses, Marburg virus and Ebola virus, have the dubious distinction of being associated with some of the highest case fatality rates—approaching 90% in many outbreaks—of any known infectious disease [1]. The impact of the lethality of filovirus infection goes far beyond the obvious grave implications for the patient. In the absence of effective vaccines and therapeutics, the response to outbreaks of filovirus hemorrhagic fever has relied solely on the classic measures of communicable disease control: contact tracing and case isolation. However, in recent years, outbreak response teams have met with increasing resistance to admission of individuals with suspected cases to isolation wards.

Only 43 (14%) of ∼300 individuals with suspected cases of Marburg hemorrhagic fever identified during the 2005 outbreak in Angola were isolated. Similarly low proportions were noted during recent outbreaks of Ebola hemorrhagic fever in Gabon and the Republic of the Congo. In some instances, resistance was violent and tragic, forcing suspension of outbreak response operations; in 2004, 4 teachers in the Republic of the Congo who were encouraging community compliance with disease control measures were accused of casting an “Ebola spell” and were stoned to death by angry villagers [2].

What accounts for such resistance to isolation and treatment? Even under the best of circumstances, admission to an isolation ward is a harrowing experience. Sick patients, some of whom may never have been admitted to a hospital, suddenly find themselves surrounded by strangely clad, unrecognizable, and often-times foreign health care workers in a potentially frightening atmosphere of sterility. Access to one’s family is, of course, limited (usually to a single patient attendant, who is also required to wear protective material and is not allowed to touch their family member). Perhaps the most daunting aspect of the whole affair is the prospect of dying and being buried by the iso-
lotion ward staff without the funeral rituals often so integral to African culture. To this highly charged environment must frequently be added the vestiges of colonial era suspicion of foreigners and present-day friction between ethnic groups.

Although acceptance of admission to an isolation ward will never be without some degree of stress for the patient, the process can be improved by redoubling our efforts to provide quality patient care. As a result not of malice but, rather, of the heavy workloads of overstretched and overstressed field teams, the danger of infection, and, perhaps, our own pessimism about the probable outcome of filovirus infection [3], we have too often focused on case isolation as a measure of transmission control, sometimes forgetting that “cases” are patients—human beings with families who need individual attention.

The shortcomings of the isolation ward experience have not gone unnoticed by populations in sub-Saharan Africa, where entry into the ward has increasingly become viewed as a death sentence. In the most highly charged scenarios, the conclusion has even been made by local populations that neglect and death in the isolation ward are intentional [4]. Such suspicions threaten to derail the entire strategy of outbreak response. After all, every “contact” is potentially a “case” who, if they do not like what they see or perceive about the prospects of isolation and care, may decide to hide from local surveillance or, of even more concern, flee to a distant site, with the catastrophic potential of filovirus introduction into new populations.

RECENT RESEARCH ADVANCES

Meanwhile, in the past decade, industrialized countries’ fears regarding bioterrorism have rendered significant funds available for research in diagnostics, vaccines, and therapeutics for the viral hemorrhagic fevers, with particular focus on the filoviruses [5]. These efforts have begun to bear fruit. Perhaps the most promising results are in vaccinology. In the past few years, a number of vaccine strategies have shown 100% efficacy in nonhuman primate models of filovirus hemorrhagic fever, including recombinant vesicular stomatitis [6, 7] and adenoviruses [8] and DNA vaccines [9]. A DNA vaccine for Ebola virus was shown to be safe and immunogenic in a phase 1 clinical trial [10].

Although somewhat less promising, some success has nevertheless been noted with therapeutics. A number of new compounds have been tested in animal models, including tissue factor inhibitors [11], monoclonal antibodies [12], small interfering RNAs [13], and phosphorodiamidate morpholino oligomers [14]. The most success to date has been achieved with a recombinant inhibitor of factor VIIa/tissue factor (r-ONAPc2) that resulted in a 33% reduction in mortality in nonhuman primate models of Ebola hemorrhagic fever when given up to 24 h after challenge [11]. A recombinant vesicular stomatitis virus–vectored vaccine also proved highly efficacious as postexposure prophylaxis in primate models of Marburg hemorrhagic fever [15]. Nevertheless, no drug has yet resuscitated a human or research animal after the onset of symptoms, and the critical thresholds of disease progression for initiation of treatment remain largely unknown.

FIRST STEPS: DOING WHAT WE ALREADY KNOW HOW TO DO BETTER

How can we translate our growing experience from outbreaks of filovirus hemorrhagic fever and recent progress in the laboratory to better treatment in the field? First and foremost, we must reemphasize the importance of care of the individual patient, putting as much effort and resources into patient care as we do into contact tracing, reducing mortality where we can, and, when we cannot, offering appropriate and compassionate palliation. The following steps are essential.

Include communications and social mobilization experts as a primary part of every outbreak response team. Up until the early 2000s, response teams were almost exclusively epidemiologically and biomedically oriented, a situation that sometimes resulted in misunderstandings or cultural clashes detrimental to outbreak control. The need to understand cultural and societal norms to communicate with the local population was largely an afterthought, to be approached after the day’s work was done. But how can villagers be convinced that entry into an isolation ward is necessary when, unbeknownst to the foreign epidemiologist, they might be more inclined to invoke sorcery or malicious intent to explain the events they observe?

The situation has been improving in recent years, with the inclusion of medical anthropologists on the outbreak teams and greater efforts to ensure that team composition is balanced between expatriate experts and members of the local community. This process must be further strengthened, ensuring that what is learned about indigenous culture and customs indeed translates to better communication with local populations. Cross-cultural understanding is necessary not only on humanitarian and practical grounds but also for the identification and engagement of local customs that may themselves actively contribute to outbreak control, particularly with regard to contact with sick persons in the household and burial practices [16].

Protect health care workers in the isolation ward. Appropriate patient care in an isolation ward can be provided only when health care workers can function without undue fear of infection or stigma of having been “tainted” by Ebola or Marburg viruses. Infection control guidelines specific to the viral hemorrhagic fevers in Africa have been developed [17] and have been shown to be effective [18, 19]. Although fatal infections have occurred in health care workers after the imple-
tachment of these guidelines, they are generally thought to be associated with breaches in protocol [3]. Nevertheless, experience has shown that some revision in personal protective equipment is necessary to ensure safety. For example, tight-fitting goggles, which immediately fog in the tropical climates where most outbreaks of filovirus hemorrhagic fever occur (and are thus often quickly abandoned), should be replaced by lightweight face shields that do not fog and prevent possible infection when health care workers inadvertently adjust goggles or masks with potentially contaminated gloves (figure 1). Face shields also allow patients a clearer view of the face of the health care worker (unidentified personnel with masked faces often present a disturbing image to patients and their families and contribute to the resistance to isolation). Each isolation ward should have an experienced and respected “infection control cop” on every shift, whose job is to not only to ensure compliance with safety guidelines but also to monitor and record transgressions and problems to make sure that we learn from each outbreak, continually collecting the evidence necessary to refine and improve our procedures for disinfection and decontamination. Especially needed are more data on the precise modes of filovirus transmission between humans, including assessing the danger from aerosols and fomites.

**Implement aggressive supportive care and clinical monitoring.** Few systematically collected or controlled data exist on the impact of supportive care for filovirus infections. Although most experts would agree that it would be naive to expect supportive care alone to result in a drastic diminution in case fatality rates, it is notable that the only human outbreak of filovirus hemorrhagic fever (excluding isolated cases) to occur in an area where such care was possible—Marburg hemorrhagic fever in Germany and Yugoslavia in 1967—was associated with a 22% case fatality rate, compared with 87% for all cases of Marburg virus infection seen in sub-Saharan Africa since that time. Differences in virus strain, route, and dose of infection; in the underlying prevalence of immunodeficiency and co-morbid illnesses; and in genetic susceptibility may all play roles in the discrepant mortality rates noted between Europe and Africa, but few would argue that aggressive supportive care is not at least one important factor.

Although the case for being more aggressive with supportive care might seem obvious, increased risk to health care workers exposed to infectious patients and potentially fatal needlestick injuries makes this a topic of debate, but one that should be obviated by still tighter infection control practices as outlined above. Once infection control measures are reinforced, all the stops must be pulled out; some of the necessary measures should be relatively straightforward, such as close attention to fluid and electrolyte balance and greater attention to nutrition, pain control, and secondary infection [20–22]. Appropriate supportive drugs should be made available, such as intravenous fluids, potassium, blood products, antiemetics, analgesics, and pressor agents.

More energy will be required to offer the basic clinical laboratory tests necessary to guide patient care, such as blood smears for malaria and monitoring of blood cell counts, electrolytes, and chemistries. This must include devising ways to test for other common diseases that continue to occur during outbreaks of filovirus hemorrhagic fever, such as malaria and typhoid fever. Many of these laboratory tests are not routine in sub-Saharan African hospitals even under normal circumstances, and, even if they are, they are often abandoned once an outbreak of filovirus hemorrhagic fever is declared, because of the risk of laboratory infection. Clinical laboratory monitoring will require significant preparation, including the acquisition of reliable portable point-of-care systems, which are

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**Figure 1.** Tight-fitting goggles *(left)*, which traditionally have been recommended as personnel protective equipment in outbreaks of filovirus hemorrhagic fever, and a full face shield *(right)*, which has the benefits of less fogging, greater protection of the mucous membranes, and provision of a better view of the health care worker’s face.
increasingly available and affordable, and the development of special protocols for infection control of hemorrhagic fever viruses in field laboratories. Equally important will be investment in the training of technicians. Ideally, such improvements would not be confined to outbreaks of filovirus hemorrhagic fever but would be part of progressive health care development for the population at large, especially because filoviruses are just one of many problems affecting the world’s poorest populations.

WHAT IS THE ROLE OF VACCINES AND THERAPEUTICS CURRENTLY IN RESEARCH STAGES?

In one sense, the way forward is clear enough. Vaccines and therapeutics that may show promise in animal models must progress to phase 1 and 2 clinical trials in the industrialized countries where they have been developed. High-containment laboratory workers and members of outbreak response teams are likely to be the first target groups. Because different vaccines and therapeutics may have particular value in different settings (a vaccine that slowly induces immunity might be of use for laboratory and frontline health care workers but not necessarily for local populations during outbreaks), we must avoid the temptation to pursue only the first promising candidates.

Despite the sense of urgency to intervene when faced with the devastating social and economic impacts of outbreaks of filovirus hemorrhagic fever in Africa, we cannot cut corners on safety. Nevertheless, given the overwhelming human suffering, we must explore ways of safely expediting promising products to field testing and compassionate use, as well as to monitor their effectiveness—that is, to do clinical research. The sporadic nature of filovirus transmission compels us to learn all we can about clinical disease and management in the field in Africa, most often in outbreak settings. We are thus faced with the unique challenge of simultaneously implementing multifaceted outbreak control measures and conducting high-quality and ethically sound clinical research. As with any emergency (and large outbreaks of filovirus hemorrhagic fever are definitely emergencies, with all the attendant chaos), our performance will be only as good as our preparation.

The first step is to establish the infrastructure necessary for clinical research in the unique setting of outbreaks of filovirus hemorrhagic fever in sub-Saharan Africa. Although predicting where the next large outbreak will occur is difficult, some areas of central Africa, such as the Republic of the Congo and Gabon, are clearly endemic for Ebola virus and might be initially targeted, building on existing laboratories and programs when possible. The task should be facilitated by recent progress in developing mobile diagnostic laboratories [23–25]. Equally important as the physical infrastructure will be establishing the human resources and the logistical and legal framework for clinical research. Clinical investigation teams composed of both local health care workers and expatriate technical advisors must be established and trained in advance, ready to move into action with prescribed research protocols, data collection forms, and culturally appropriate methods of informed consent that have already been approved through an international ethical review process. This will require the creation of institutional review boards in some sub-Saharan African countries where they do not already exist. The legalities and complexities of any pharmaceutical company involvement and possible investigational new drug use must be hammered out. Lastly, and perhaps most importantly, efforts must be made to thoroughly communicate the research aims and realistic expected benefits to the local populations that are likely to be involved, because the consequences of even the appearance that outsiders are experimenting on vulnerable populations would be disastrous. The integration of African scientists and clinicians into each step of the developing research base will be vital to its success, along with a long-term plan to retain them, most likely entailing integration of their activities into the day-to-day efforts oriented toward more common endemic diseases. Otherwise, the wheel will have to be reinvented every time.

Initial studies might focus on evaluating the efficacy of specific elements of supportive care and clinical monitoring, such as the efficacy of various intravenous fluid formulations or pressor agents. Newer, already US Food and Drug Administration–approved therapies for severe shock (which is commonly seen in filovirus infection), such as activated protein C [26], could also be tested. Of course, not all of our observations will result in statistically significant conclusions, but the tag of being “observational” in nature should not keep us from learning and improving or from collecting the evidence necessary to interpret and test our observations.

The next step will likely be further phase 1 and 2 testing of vaccines and therapeutics deemed promising from initial studies in industrialized countries, leading, in turn, to phase 3 testing of some candidates. Concerns over small sample sizes should not necessarily preclude phase 3 trials of therapeutics found to be highly efficacious in animal studies. Ironically, in a statistical sense, the high case-fatality rates associated with the filovirus infections may make up for the small sample sizes; a randomized placebo-controlled trial of a drug expected to result in a 2-fold reduction in case-fatality rate—say, from 80% to 40%—would have 90% power to detect this difference (2-tailed \( P \ll .05 \)) with the enrollment of just 30 patients in each group (total, \( N = 60 \) patients). Given the increasing frequency and case counts of outbreaks of filovirus hemorrhagic fever in recent years (up to 425 cases of Ebola hemorrhagic fever in
Uganda in 2000–2002) [27], this sample population certainly seems achievable.

CONCLUSIONS

The control of outbreaks of filovirus hemorrhagic fever in sub-Saharan Africa ultimately hinges on the delivery of effective and compassionate care for each infected patient. By providing this, we also hope to reestablish the isolation ward as the key functional component of the overall outbreak control strategy. The good news is that there may be much to be gained just by refocusing our efforts on aggressive supportive care and clinical monitoring. The fundamental knowledge and technology to provide such care are available if the political will is there. Further down the road lie potential benefits from recent research advances, particularly in the area of vaccines. However, the success of all of these measures will require the development of physical infrastructure, human resources, and logistical and legal frameworks for clinical care and research of the filovirus-infected patient in Africa. It will be necessary to create a forum for improved communication between scientists involved in basic science and clinical research, public health response, and development to better integrate recent innovations. A broad array of partners and resources will be needed, including local investment from ministries of health in affected countries and laboratory and technical expertise from research and public health agencies and nongovernmental organizations—all under a coordinating rubric of the World Health Organization. Make no mistake; the task will be arduous, time consuming, and costly, but it promises future payoffs to populations in areas in which filoviruses are endemic, as well as to those concerned about bioterrorism or imported cases. Improving patient care, as well as understanding how we did it, is in everybody’s interests. Time to get started.

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