Evidence-Based Clinical Management of Ebola Virus Disease and Epidemic Viral Hemorrhagic Fevers

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KEYWORDS

• Ebola virus disease • Viral hemorrhagic fever • Clinical management
• Evidence-based care

KEY POINTS

- The mortality of Ebola virus disease remains high, and opportunities to improve supportive care remain.
- Emerging technology enables rapid diagnosis in the field and monitoring of routine laboratory parameters, which may guide clinical management.
- Supportive care encompasses fluid resuscitation and correction of electrolyte disturbances. Early use of intravenous fluids is warranted in patients unable to drink. The net effect of nonspecific adjunctive treatments, such as antibiotics and antidiarrheal agents, is uncertain, and justification for their routine use decreases as diagnostic and therapeutic capacity increases.
- Currently recommended personal protective equipment impedes clinical management. More tolerable equipment or temperature control in Ebola treatment centers would enable longer presence at the patients' bedside.
- Despite numerous Ebola and Marburg fever outbreaks in the last 50 years, there is a dearth of documented clinical and biological data beyond patients' initial presentation. Proper data collection and medical record keeping remain high priorities.

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INTRODUCTION

The deadly 2014 to 2016 outbreak of Ebola virus disease (EVD) in West Africa underscored the severity of the threat posed by viral hemorrhagic fevers.[1] New outbreaks in the Democratic Republic of the Congo in 2018 further highlighted the pervasiveness of Ebola and other viruses, such as the Marburg and Lassa viruses, in certain regions of Africa.[2,3]

Outbreaks of viral hemorrhagic fevers caused by filoviruses have been identified since 1967, but the use of clinical or biological data collected over time remains limited. Although symptoms reported by patients on admission to Ebola treatment centers (ETCs) are described in several publications, objective data required to make clinical decisions, such as body temperature, blood pressure, heart rate, respiration rate, and fluid balance, have not been systematically collected over the entire clinical course. Similarly, limited data exist on derangements of electrolytes and acid-base balance, renal and hepatic function, and blood coagulation. Epidemiologic data suggesting a very poor prognosis for viral hemorrhagic fevers must be interpreted in light of historically limited clinical evaluation and management.

The prompt recognition and management of clinical, physiologic, and laboratory abnormalities on admission to an ETC should, in theory, improve outcomes. With this objective in mind, recommendations for basic clinical management for patients with EVD were created.[4] However, important clinical questions remain, and additional research would likely help future patients with viral hemorrhagic fevers. With the exception of emerging specific anti-Ebola treatments, this article addresses different aspects of the clinical management of viral hemorrhagic fevers, particularly on filoviruses, based on scientific evidence to the extent it exists. Broader considerations, such as epidemiology and modes of transmission, are addressed when they are likely to influence clinical decisions.

EPIDEMIOLOGY

Definitions

The generic term “viral hemorrhagic fevers” designates a group of viral diseases, some of which, such as Marburg fever and EVD, typically manifest as outbreaks. The most striking example remains the 2014 to 2016 outbreak of EVD in West Africa, which was widespread and deadly.[1] Certain other viral hemorrhagic fevers, such as Lassa fever, are mostly endemic, with sporadic outbreaks or significant upsurges, such as in Nigeria in 2018.[5] Viral hemorrhagic fevers that are mostly endemic are not discussed further.

Outbreaks of Filoviruses

Marburg fever is caused by a filovirus belonging to the Filoviridae family. Marburg fever was first described in 1967 when 2 outbreaks occurred simultaneously in Germany (Marburg and Frankfurt) and in Serbia (Belgrade).[6] These initial patients were infected by monkeys (*Cercopithecus aethiops*) imported from Uganda. Since then, approximately 10 outbreaks have occurred, each one infecting between 1 and 374 patients for an approximate total of 587 cases.

EVD is also caused by a filovirus belonging to the Filoviridae family and was first described in 1976 (**Tables 1** and **2**). There are 5 known species of this virus: *Zaire ebolavirus, Sudan ebolavirus, Tai Forest ebolavirus, Bundibugyo ebolavirus*, and *Reston ebolavirus*. Before 2014, 2387 cases had been recorded in African outbreaks, with a crude overall mortality of 67%.[7] Reston virus has been introduced several times through imported macaques from the Philippines to the United States and Italy.[8]

Table 1
Characteristics of viral hemorrhagic fevers

Family	Filoviridae		Arenaviridae			Bunyaviridae	
Genus	Filovirus	Filovirus	Tacaribe complex	Tacaribe complex	LCMV/Lassa complex	Nairovirus	Phlebovirus
Name	Ebola	Marburg	Junin	Machupo	Lassa	Crimean-Congo	Rift Valley
Geography	Africa	Africa	South America	South America	West Africa	Africa, Central Asia, Europe, Middle East	Africa, Yemen, Saudi Arabia
Host	Bats, monkeys	Bats, monkeys	Rodents (*Mastomys natalensis*)	Rodents	Rodents	Domestic and wild vertebrates	Ruminants
Vector	No	No	No	No	No	Tics (Hyalomma)	Mosquitoes (*Aedes* spp)
Incubation time (d)	2–21	2–21	7–14	9–15	5–21	3–14	2–6
Start	Sudden	Sudden	Progressive	Progressive	Progressive	Progressive	Sudden
Characteristics	Mortality (40%–90%) outbreaks	Mortality (30%–90%) outbreaks	Encephalitis	Encephalitis	Rare thrombocytopenia Low mortality (1%–2%)	Mortality 30%–50%	Mortality <10% Ocular involvement
Antiviral therapy	None has demonstrated efficacy	None	Ribavirin	?	Ribavirin	Ribavirin ineffective	Ribavirin

Abbreviation: LCMV, lymphocytic choriomeningitis virus.
Adapted from Tattevin P, Lagathu G, Revest R, et al. Les fièvres hémorragiques virales. Rev Francophone des Laboratoires 2016;480:72; with permission.

Table 2
Ebola outbreaks

Year	Country	Ebola virus species	Number of Cases	Number of Deaths	Mortality, %
Patients treated in Africa[a]					
2014	Democratic Republic of Congo	Zaire	66	49	74
2014	Senegal	Zaire	1	0	0
2014	Mali	Zaire	8	6	75
2014	Nigeria	Zaire	20	8	40
2014–2016[b]	Sierra Leone	Zaire	14,124*	3956*	28
2014–2016[b]	Liberia	Zaire	10,675*	4809*	45
2014–2016[b]	Guinea	Zaire	3811*	2543*	67
2012	Democratic Republic of Congo	Bundibugyo	57	29	51
2012	Uganda	Sudan	7	4	57
2012	Uganda	Sudan	24	17	71
2011	Uganda	Sudan	1	1	100
2008	Democratic Republic of Congo	Zaire	32	14	44
2007	Uganda	Bundibugyo	149	37	25
2007	Democratic Republic of Congo	Zaire	264	187	71
2005	Congo	Zaire	12	10	83

2004	Sudan	Sudan	17	7	41
2003 (Nov–Dec)	Congo	Zaire	35	29	83
2003 (Jan–Apr)	Congo	Zaire	143	128	90
2001–2002	Congo	Zaire	59	44	75
2001–2002	Gabon	Zaire	65	53	82
2000	Uganda	Sudan	425	224	53
1996	South Africa (ex-Gabon)	Zaire	1	1	100
1996 (Jul–Dec)	Gabon	Zaire	60	45	75
1996 (Jan–Apr)	Gabon	Zaire	31	21	68
1995	Democratic Republic of Congo	Zaire	315	254	81
1994	Côte d'Ivoire	Taï Forest	1	0	0
1994	Gabon	Zaire	52	31	60
1979	Sudan	Sudan	34	22	65
1977	Democratic Republic of Congo	Zaire	1	1	100
1976	Sudan	Sudan	284	151	53
1976	Democratic Republic of Congo	Zaire	318	280	88
Patients treated in Europe or North America[c]					
2014–2015		Zaire	27	5	18.5

[*] The '*' indicates 'includes suspect, probable, and confirmed cases'.
[a] From World Health Organization.[6]
[b] According to the World Health Organization, these numbers underestimate the reality in proportions that cannot be estimated.
[c] From Uyeki and colleagues.[9] Of note, some of the cases reported by Uyeki and colleagues may also be counted as African cases.

During the 2014 to 2016 outbreak in West Africa, there were 28,610 in West Africa, with an overall mortality of 39.5%.[7] During the same period, 27 patients were treated in Europe or in North America (overall mortality 18.5%).[9]

Although systematically higher than in Europe and in North America, mortalities reported in Africa vary widely. The reasons for this variation are not clear. There does not appear to be a consistent secular trend, given that outbreaks occurring in the 2000s were deadlier than some that occurred in the 1970s to 1980s. Part of this variation may be attributable to the viral species. Indeed, the Zaire ebolavirus species appears to be associated with higher mortality than the Sudan or Bundibugyo species.[10] Furthermore, variations in case definitions, surveillance systems, and clinical care also likely contributed to fluctuations in mortalities. For example, reporting mortality for both suspected and confirmed cases probably dilutes the mortality. During the 2014 to 2015 outbreak in West Africa, which was caused by a single species (*Zaire ebolavirus*), and using consistent definitions for suspect, probable, and confirmed cases, mortality was higher in Guinea (67%) than in Liberia (45%) and Sierra Leone (28%).[7] Within Sierra Leone, as an example, variation in mortality was apparent; for example, 74% of confirmed cases receiving care at an ETC early in the outbreak died,[11] much higher than the overall national mortality.

A better understanding of key prognostic factors requires virological confirmation of the diagnosis and improved collection of clinical and biological data on admission and during the entire clinical evolution in the ETC.

Modes of Transmission

In all likelihood, fruit bats of the Pteropodidae family are natural Ebola virus hosts.[8] Ebola is introduced into the human population through close contact with the blood, secretions, organs, or other bodily fluids of infected animals, such as chimpanzees, gorillas, bats, monkeys, forest antelope, or porcupines. Ebola then spreads through human-to-human transmission when mucous membranes come in contact with infected blood or other bodily fluids, which may contaminate surfaces and materials. Persistence of Ebola on environmental surfaces has been demonstrated in simulated conditions,[12] but is unlikely to be relevant in ETCs, where infection prevention and control procedures are followed.[13–15] Funeral rites during which family and friends are in direct contact with the body of the deceased likely played a critical role in the transmission of the Ebola virus in West Africa in 2014 to 2016.[16–18] Although concerns about the possibility of aerosolization of Ebola have been raised,[19] there have been no documented cases of airborne transmission.

CLINICAL FEATURES

Although outbreaks of Ebola viral hemorrhagic fever have afflicted Africa since 1976, clinical and biological descriptions of early epidemics remain extremely limited. Limitations in the clinical management of patients admitted to ETCs, which were primarily designed for quarantine rather than treatment, explain the emphasis on clinical status at presentation rather than subsequent evolution. Paradoxically, a more detailed description of clinical and laboratory evolution over time has emerged from case descriptions of a small number of patients treated outside of Africa in 1967[20] and in 2014 to 2016.[9] One review has highlighted the similarity between clinical presentations of EVD and of Marburg virus disease.[21] Given the dearth of clinical data reported since then, the following description encompasses the diseases caused by both viruses.

Symptoms Reported at Presentation

Clinical descriptions enumerate nonspecific symptoms of asthenia, fever, myalgia, headaches, vomiting, diarrhea, delirium, conjunctivitis, hiccups, and dyspnea.[22,23] Data collection relies on closed questions to which patients answer yes or no, but patients' precarious clinical states and frequent language barriers limit the reliability of these questionnaires. Although the relative frequency of individual symptoms varies, hemorrhagic manifestations appear to be uncommon. For example, Dickson and colleagues[22] report hemorrhagic symptoms in only 3 of the 44 patients in their cohort.

The absence of objective vital signs data, such as blood pressure, heart rate, and respiratory rate,[21] continues to be problematic in more recent descriptions of the 2014 to 2016 outbreak.[24,25] When collected, vital signs have been reported on admission only.[22–24] Accordingly, these observations are of limited utility to inform prognosis or to provide longitudinal and personalized care. In a prospective observational study of 118 patients with EVD, Hunt and colleagues[26] define 3 disease stages of severity according to clinical features on admission. Stage 3, characterized by the presence of shock (not defined), coma, hemorrhage, or organ failure, was associated with a significantly higher risk of death, but only a small number of patients (10%) met those criteria. Vernet and colleagues[27] adopted the same approach, obtaining similar results, based on symptoms reported by 97 patients with EVD. Only bleeding was a predictor of mortality, but it essentially constituted a premortem finding.

Laboratory Data

Close monitoring of objective physical signs and biological data during hospitalization is essential for early detection of potentially lethal but correctable complications. For example, vomiting and diarrhea in patients too weak to self-rehydrate led to hypovolemia and biochemical imbalances, as documented in 27 patients treated in Europe and North America in 2016.[9] Although obtained in a starkly different context, this clinical and laboratory characterization aligns with the data derived from African outbreaks. Recently, Hunt and colleagues[26] reported the results of biochemical analyses performed with a portable point-of-care device on 118 patients admitted to the Kerry Town ETC in Sierra Leone. Analyses conducted solely on admission were used to identify prognostic factors. Among this cohort, half of the patients presented with acute kidney injury (AKI), with increased levels of blood urea and creatinine. Although urine output was not evaluated, the investigators hypothesized that hypovolemia caused by dehydration was the predominant mechanism. Hemoconcentration, diagnosed in many patients, supported this hypothesis. Rhabdomyolysis was present in 83% of patients on admission, and in 100% of nonsurviving patients, likely contributing to the risk of AKI. In this study, the prognosis was independently associated with the severity of AKI on admission. Findings from a case series (n = 16) by Cournac and colleagues[23] echo the clinical importance of rhabdomyolysis; the investigators reported elevated creatine kinase (>1000 IU/L) in 59% of patients, and the severity of rhabdomyolysis was associated with mortality.[23]

Another very common biological abnormality observed during the 2014 to 2016 outbreak, as in previous epidemics, was an increase in liver transaminases.[21] Bilirubin was most often normal or low, and there were no symptoms associated with acute hepatocellular failure.[26–28] Admission electrolytes are typically only moderately abnormal, if at all. Although hypokalemia may be expected due to severe gastrointestinal losses, and hyperkalemia may be associated with AKI and metabolic acidosis,[26,27] electrolytes have not been measured over time. Repeated monitoring

of electrolytes in critically ill patients is standard care and can be achieved even in resource-limited settings using point-of-care devices.[26,29]

DIAGNOSIS OF MARBURG AND EBOLA VIRUS INFECTIONS

The cornerstone of laboratory diagnosis of Ebola is a nucleic acid amplification test implemented by reverse transcriptase-polymerase chain reaction (RT-PCR); several kits are available and were implemented in mobile biocontainment laboratories.[30] These techniques have been limited by complexity (including the requirement for a continuous power supply), cost, and time required for specimen processing and analysis. Diagnostic properties may also degrade in new outbreak due to genomic drift.[31] More recently, a fully automated RT-PCR system (GeneXpert) showed comparable performance to standard RT-PCR, with much faster turnaround time and minimized need for specimen handling.[32] Both techniques provide an indirect measure of viral load, a strong prognostic variable,[27] by reporting the number of PCR cycles required to obtain a positive test result; the smaller the number of PCR cycles, the greater the viral load.[33]

Rapid tests that detect Ebola antigen are also available or under development and can be implemented in point-of-care testing platforms with results available in a few minutes. In addition to standard antigen capture enzyme-linked immunosorbent assay, other techniques (immunohistochemistry, lateral flow assay, fluorescent antibody) have also been developed.[30] Although antigen detection systems typically are positive 48 to 72 hours after RT-PCR, some evaluations have shown excellent sensitivity.[33,34] The antibody response to Ebola infection is too variable for use in acute diagnosis.

Although a comprehensive review of diagnostic modalities of VHF is beyond the scope of this article, this brief overview of evolving diagnostic modalities is relevant to the discussion of clinical management. Indeed, these recent advances have the potential to reduce the time to diagnosis and, therefore, the period of uncertainty during which suspect and probable cases are confined together in isolation. Moreover, early identification of cases should enable health workers to more rapidly allocate sparse resources to the patients who are most likely to benefit from them.

CLINICAL MANAGEMENT

Supportive Care

A crucial hypothesis of clinical management of viral hemorrhagic fevers is that mortality will be reduced when supportive care is delivered based on repeated evaluation of the patient's clinical, hemodynamic, and electrolyte status. Such care includes replacement for failing organs,[22,28] which "buys time" while the body's immune system forms antibody and clears the virus. Although many factors may have contributed to the lower mortality of patients repatriated to Europe and North America, it is plausible that part of this difference is attributable to the identification and effective correction of hypovolemia and biochemical disorders and use of organ-supporting care, such as renal replacement, vasopressors, and mechanical ventilation.[9] Similarly, as early as 2007, Bausch and colleagues[29] noted that during the only outbreak of Marburg fever (1967) occurring in countries (Germany and Yugoslavia) where supportive intensive care was possible, mortality was 22%, whereas it was more than 87% in Africa for the same condition several years later. Given these observations, several investigators exhort decision makers to focus on patient care, which may be achieved without jeopardizing the safety of health care providers.[29,35]

Failing to make this paradigm shift and ensure the delivery of life-sustaining therapies perpetuates the cycle of limited care, poor prognosis, and fear in the community of dying alone and untreated in an ETC. This paradigm shift occurred in certain ETCs during the 2014 to 2016 EVD outbreak in West Africa.[22,36] Supportive care interventions are not disease specific. Rather, they entail close and repeated monitoring of clinical signs (eg, heart rate, blood pressure, urine and stool output, oral intake of a sufficient quantity of oral rehydration solutions, capillary refill, mental status, respiratory rate, oxygen saturation, temperature) and laboratory disorders (eg, blood gases, sodium, potassium, blood urea nitrogen, creatinine, creatine kinase). Documentation of these physical signs and standard laboratory analyses for the entire duration of the stay in ETCs is crucial. Thus, it is impossible to dissociate quality of care from medical record keeping, and recent guidelines have also emphasized this connection.[4]

Accordingly, it is also essential to ensure that the necessary material resources and protocols are in place to collect clinical and laboratory information, record it, monitor it, and deliver care in response to correctable disorders that are detected. The availability of reliable point-of-care laboratory testing devices removed what was once an insurmountable technological barrier. However, it is conceivable that during an influx of patients, these analyses will not be possible without a considerable increase in the number of machines and of personnel dedicated to the analyses. Ideally, a fixed laboratory and dedicated staff should be able to operate adjacent to the high-risk zone with a window to the high-risk zone to receive samples, enabling the use of faster and more powerful machines that can process more samples in less time and at lower unit cost.[28]

When oral intake is insufficient, guidelines and expert opinion support parenteral fluid replacement.[4,37] Parenteral intake may require the placement of intraosseous needles in very dehydrated patients initially, followed by central venous catheters. Reluctance to install such venous access devices because of the danger to health care personnel has diminished since the recent outbreak of EVD in 2014. The feasibility and safety of installing central venous catheters in treatment centers have been reported.[22,36]

Advanced Replacement Therapy for Organ Failure

Implementation of advanced organ-supportive therapies (eg, renal replacement therapy, mechanical ventilation, vasopressor support) in areas where these interventions are not usually available is a matter of debate.[24] Until the 2014 outbreak of EVD, many did not consider this possibility due to the lack of resources in areas affected by most viral hemorrhagic fever outbreaks and because of the appalling prognosis reported in the literature, which led to claims of futility. The implementation of such techniques during the recent outbreak for patients transferred and treated in the United States or in Europe,[9] as well as in a small number of West African ETCs,[22,26,28] has led to calls for more widespread implementation.[35,38]

Associated Therapies

Antibiotics

Antibiotic therapy is advocated for patients with EVD in all expert recommendations.[4,37] Antibiotics are typically broad spectrum, such as third-generation cephalosporins or quinolones, and are intended to prevent bacterial translocation from the gut as EVD progresses. However, in the absence of the necessary laboratory facilities, this widespread practice during the 2014 to 2016 outbreak could not be supported by microbiologic evidence of bacterial infection. Such liberal use of broad-spectrum antibiotics in the context of a proven viral infection opposes efforts to use antibiotics

more sparingly to reduce antibiotic resistance.[39] For patients with confirmed EVD by PCR, the value of empiric antimicrobials without evidence of a bacterial infection should be debated. Given that many areas have yet to implement a strategy to mitigate increasing rates of antibiotic resistance,[40] failure to do so may ultimately have dire consequences. Implementation of basic bacteriology using current technology,[41] notwithstanding the need to ensure laboratory personnel safety, would allow for reliable culture and sensitivity testing in ETCs and rational deescalation of initial empiric antibiotics in patients with negative cultures.

Antimalarials

The use of rapid diagnostic tests to detect *Plasmodium falciparum* should guide the prescription of antimalarials for curative purposes, although one study suggests that even with universal administration of antimalarials to patients in ETCs, initial parasitemia is associated with improved survival.[42] A complementary approach of mass community drug administration of antimalarials as part of a universal treatment program reduced the impact of patients presenting with febrile illness due to malaria when health care capacity was severely strained during the 2014 to 2016 West African outbreak, although the effect was attenuated after a few weeks.[43]

Antiemetic and antidiarrheal medications

The rationale for the use of antiemetic and antidiarrheal medications hinges on the assumption that they reduce the loss of fluids and electrolytes, which compounds the risk of death in situations where intensive monitoring and correction of losses are not possible.[44] However, enthusiasm for these interventions is tempered by the theoretic risk of slower pathogen clearance, bacterial overgrowth, and eventually, peritoneal translocation, despite the lack of published data supporting these concerns. In contrast to strategies aimed at restoring fluid volume and electrolytes, use of antiemetic and antidiarrheal medications should be considered in the context of clinical investigations.

Recovery

During the recent outbreak of EVD, patients were considered cured once clinical signs had resolved, provided that Ebola virus PCR was negative at least 3 days after disease onset. Current recommendations for discharge in surviving patients suggest 2 negative samples.[45] However, Ebola virus remains detectable by PCR for prolonged periods in certain bodily fluids, such as sperm,[46] breast milk,[47] cerebrospinal fluid,[48] and ocular aqueous humor.[49] Recent reports suggest that EVD may be sexually transmitted more than a year after clinical recovery.[50,51] In addition, a recent report described a household cluster of cases in 2015 that was most likely related to viral persistence or recrudescent disease in a postpartum woman who was presumed to have survived EVD 1 year previously.[52] In this context, recommendations are to advise male survivors to avoid sexual intercourse or use condoms for at least 3 months initially, and for a subsequent period guided by semen testing for Ebola virus.[37,53,54] During the postoutbreak period, clinicians and public health authorities must remain vigilant to new cases.

EQUIPMENT AND LOGISTICS

Personal Protective Equipment

One of the explanations for the gaps in care during the African outbreaks is that clinicians spent insufficient time providing bedside assessment and clinical care in the ETCs. At the height of the outbreak in November 2014, Chertow and colleagues[55]

noted that direct contact between health care providers and patients in treatment centers was limited to 45 or 60 minutes, 2 or 3 times a day, due to the risk of heatstroke and dehydration associated with the personal protective equipment (PPE) worn by staff. Under these conditions, time spent with each patient did not exceed 1 to 2 minutes, on average.

Currently recommended PPE is summarized in **Table 3**, and posters of recommended donning and doffing procedures are available.[56] A principal means of transmission of infection from patient to clinician occurs during PPE removal, although this can be reduced (but not eliminated) by education efforts.[57] Simulation studies have shown moderate thermal strain with 1 hour in conventional PPE in simulated West African climate conditions.[58] In addition, simulation using Ebola PPE even in European room temperature conditions shows that providers perceive advanced medical procedures to be more complicated, more stressful, and less comfortable compared to standard protection.[59] Whether variations of PPE can make medical care for extended periods in ETCs more feasible, by increasing comfort and decreasing heat strain, while maintaining safety, requires urgent study. In addition, whether air-conditioned ETCs would allow for standard Ebola PPE to be worn for longer periods in the high-risk zone and thus for more intensive care to be delivered has not been studied, although clinical experience from one ETC in Sierra Leone the latter part of the West African outbreak suggests this to be the case (Ref.[60] and see Fig. 2 in Ref.[28]).

Data Collection and Transfer

The challenges associated with the collection and transmission of clinical data outside the high-risk zone also contributed to gaps in clinical management. Paper-based data collection materials cannot easily be removed from the high-risk zone. Approximate solutions (eg, photographs of a paper sheet held at arm's length by a health care provider) should be replaced by more reliable, long-term solutions. Buhler and colleagues[61] created an inventory of the various possible methods by surveying 40 health care providers who had been involved in prior Ebola or Marburg virus outbreaks. Among the most promising options are wired or wireless computer networks that only require one computer or mobile device inside the contaminated zone that communicates with the outside.

Functionality of Ebola Treatment Centers

ETCs serve 2 purposes: to stop transmission of Ebola in a community by isolating patients and to provide a safe environment for the provision of high-quality clinical care. To accomplish these objectives, engineering controls are needed that divide the ETC into zones and direct the flow of patients and staff (**Figs. 1** and **2**). The entire ETC is separated from the outside world while maintaining the ability of ambulatory patients to safely visit with family members across plastic mesh fences that allow for visual contact and conversation. Within the ETC, the green zone is a low-contamination risk zone with space for staff meetings, staff toilets and showers, preparation of chlorine, laundering and drying of reusable materials, pharmacy, and equipment storage. The red zone is at high risk for contamination and has space for patient care (suspected, probable, confirmed cases), patient toilets and showers, waste disposal (including sharps), management of infectious waste, and a morgue for deceased patients. Movement of patients is one way from the triage area to the suspect ward, then to the confirmed ward, and then outside the ETC after passing through a dedicated shower. Access to the red zone for clinical staff is also unidirectional; staff must enter via the PPE donning area and exit via the PPE doffing area. Staff movement is from the lowest to

Table 3
Recommended personal protective equipment for Ebola

Recommendation	Strength of Recommendation	Quality of Evidence of Effectiveness of Preventing Filovirus Transmission to Health Workers
The mucous membranes of eyes, mouth, and nose should be completely covered by PPE	Strong	High-quality evidence for protecting mucous membranes compared with no protection
Use either a face shield or goggles	Strong	Very low-quality evidence comparing face shields and goggles
Use a fluid-resistant medical or surgical mask with a structured design that does not collapse against the mouth (eg, duckbill or cup shape)	Strong	Low-quality evidence comparing medical or surgical mask with particulate respirator
Use a fluid-resistant particulate respirator during procedures that generate aerosols of body fluids	Strong	Moderate-quality evidence, when evidence on protection against other pathogens during aerosol-generating procedures is also considered
Use double gloves	Strong	Moderate-quality evidence comparing double gloves to single gloves
Nitrile gloves are preferred over latex gloves	Strong	Moderate-quality evidence on health worker tolerance of nitrile gloves compared with latex gloves
Use protective body wear in addition to regular on duty clothing (eg, surgical scrubs)	Strong	High-quality evidence for using protective body wear compared with not using protection, based on accumulated evidence from other infections with similar modes of transmission
The choice of PPE for covering clothing should be either a disposable gown and apron, or a disposable coverall and apron; the gown and the coverall should be made of fabric that has been tested for resistance to penetration by blood and other body fluids or by blood-borne pathogens	Conditional	Very low-quality evidence comparing gowns and coveralls
The choice of apron should be, in order of preference: • A disposable, waterproof apron • If disposable aprons are not available, heavy-duty, reusable waterproof aprons may be used, provided that they are appropriately cleaned and disinfected between patients	Strong	Very low-quality evidence comparing disposable and reusable aprons

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Table 3
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Recommendation	Strength of Recommendation	Quality of Evidence of Effectiveness of Preventing Filovirus Transmission to Health Workers
Use waterproof boots (eg, rubber or gum boots)	Strong	Very low-quality evidence comparing boots with closed shoes with or without shoe covers
Use a head cover that covers head and neck	Conditional	Low-quality evidence comparing head covers with no head cover
It is suggested that the head cover is separate from the gown or coverall, so that it can be removed separately	Conditional	Low-quality evidence comparing different types of head covers

From Personal protective equipment for use in a filovirus disease outbreak: rapid advice guideline. Geneva (Switzerland): World Health Organization; 2016. p. xiii; with permission.

highest risk areas, that is, starting in the suspect ward and then moving to the probable ward, confirmed ward (these 2 may be combined), and waste management area or morgue (if needed). The ETC has 4 exits: one for staff to the green zone (exit after PPE removal, hand hygiene, and cleaning and disinfection) and 3 for patients. A suspect patient who tests negative for Ebola exits after a shower but without passing through the confirmed ward; deceased patients exit through the morgue; and recovered probable and confirmed patients exit after taking a shower.

Improved ETC engineering may simultaneously enhance quality of patient care and health care worker safety. Air-conditioned ETCs may allow for more intensive clinical care while maintaining the thermal comfort of patients and clinicians. Alternatively, individual patient care rooms made of transparent plastic and air conditioned, such as the "Biosecure Emergency Care Unit for Outbreaks" developed by one non-governmental organization,[62] may allow for easier monitoring of multiple patients and delivery of some medical care by health care workers not in full PPE, who access the patient via plastic-lined portholes.

Ebola Treatment Centers Staffing and Policies

ETC operations hinge on the complementary expertise of numerous staff members. The ideal clinical team includes doctors, nurses, psychologists, and social support staff. In addition, the infection prevention and control team includes a clinical specialist, cleaners, hygienists, and a water and sanitation specialist. Support staff includes specialists in logistics, coordination, laundry, and safe burial. Additional nonclinical staff experts in epidemiology, data management, and research may also be present.

Clinicians (nurses, clinical officers, physicians) should be organized into shifts of approximately 8 hours according to context and workload, with the objective of providing clinical coverage 24 hours per day and a ratio of 1 clinician per 4 or fewer patients to enable adequate clinical contact with patients. During a shift, the number and duration of visits should be guided by patient requirements. Clinicians should always be paired in the red zone so that adherence to infection prevention and control

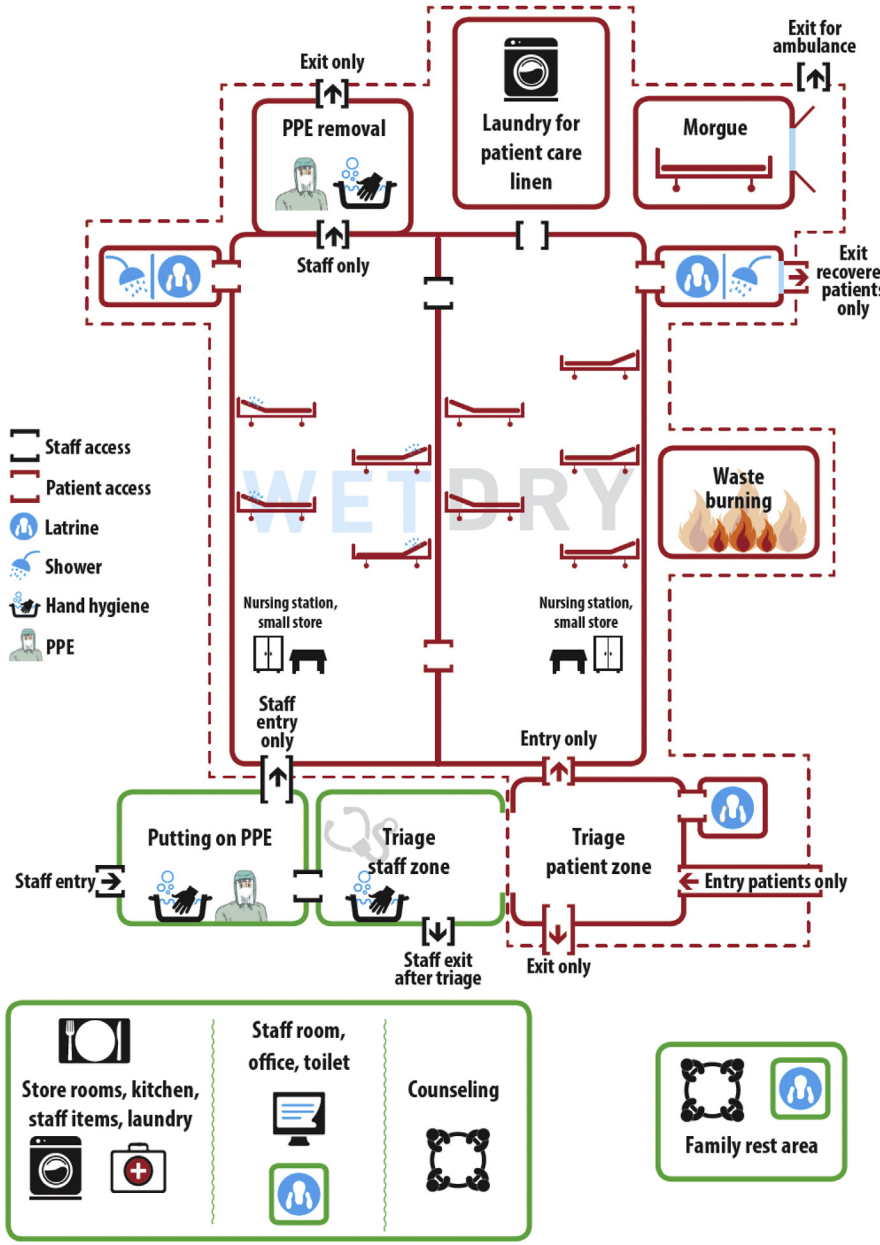

Fig. 1. Sample architecture of an ETC. (*From* Manual for the care and management of patients in Ebola care units/community care centres: interim emergency guidance. Geneva (Switzerland): World Health Organization; 2015. p. 4; with permission.)

practices is ensured and for assistance during tasks (for example, intravenous cannula insertion). Similar to a medical ward, regular rounds should take place in the green zone to conduct handover between shifts, develop plans for the day, and prioritize care for the sickest patients.

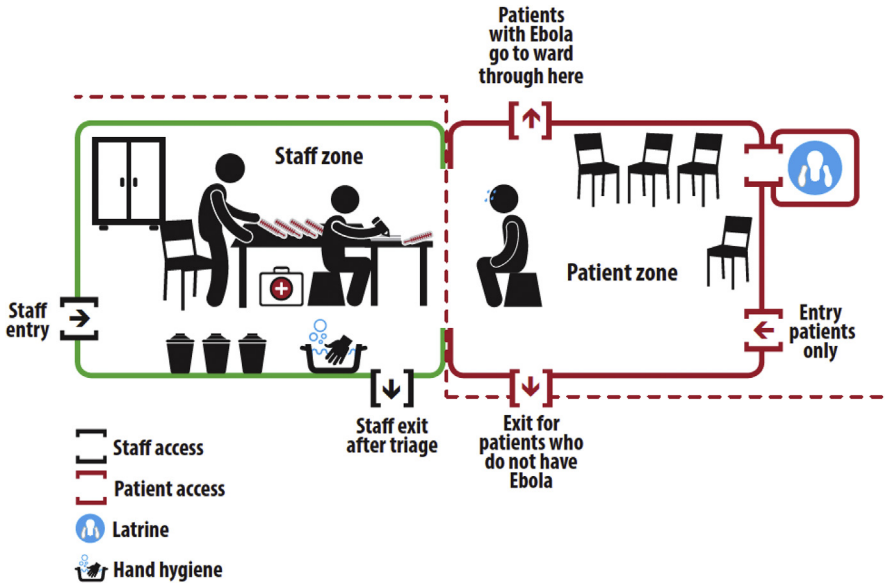

Fig. 2. Sample layout of a triage area. (*From* Manual for the care and management of patients in Ebola care units/community care centres: interim emergency guidance. Geneva (Switzerland): World Health Organization; 2015. p. 5; with permission.)

Policies should promote the safety and well-being of ETC staff, including training for the provision of supportive care, regular training on PPE donning and doffing, scheduled days off and sufficient salary so that there is no temptation to work simultaneously in non-ETC facilities, and a nonblame culture whereby sick clinicians are promptly evaluated and cared for as needed, while still receiving a salary.

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