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Ebola virus disease: An update on current prevention and management strategies

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ABSTRACT

Ebola virus disease (EVD) is characterised by systemic viral replication, immuno-suppression, abnormal inflammatory responses, large volume fluid and electrolyte losses, and high mortality in under-resourced settings. There are various therapeutic strategies targeting EVD including vaccines utilizing different antigen delivery methods, antibody-based therapies and antiviral drugs. These therapies remain experimental, but received attention following their use particularly in cases treated outside West Africa during the 2014–15 outbreak, in which 20 (80%) out of 25 patients survived. Emerging data from current trials look promising and are undergoing further study, however optimised supportive care remains the key to reducing mortality from EVD.

Contents

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1. Introduction

Zaire ebolavirus (EBOV), *Sudan ebolavirus* (SUDV), *Bundibugyo ebolavirus* (BDBV), *Taï Forest ebolavirus* (TAFV), and the only Asian species *Reston ebolavirus* (RESTV) [1]. The first three of these have previously caused large outbreaks in the Democratic Republic of Congo, Sudan, Gabon, Republic of Congo, and Uganda [2]. The most recent and largest outbreak involving over 28,000 cases in West Africa was caused by a variant strain of EBOV with an estimated overall case fatality rate of around 40% [3].

EVD is primarily a diarrheal illness that requires copious amounts of fluid and electrolyte replacement [4]. Failure to address such requirements contributes to mortality and thus an intensive level of support is required to optimize outcomes. This is challenging in resource limited settings.

There were no approved therapeutics to treat Ebola virus disease (EVD) during the 2014–15 outbreak, that devastated three West African countries [5]. A small number of cases were treated with putative therapeutics in the U.S and Europe before formalised clinical trials were established late in the outbreak [6]. Potentially, an effective therapeutic available in large quantities could not only treat individual cases but halt outbreaks.

1.1. Practicalities of clinical trials for Ebola virus disease

Although a number of experimental vaccines and antivirals against Ebola virus had been developed prior to the large EVD outbreak in West Africa in 2014-15, phase II/III field studies did not get underway until late in the epidemic [6]. Consequently, some studies will now have insufficient recruitment to establish efficacy [40]. This highlights the unique difficulties encountered in conducting clinical trials in the midst of a health emergency, particularly in resource poor settings. Nevertheless, for a disease such as EVD, which has such a high mortality and no proven directed therapy, it is imperative that an integral part of the international response be to facilitate clinical trials of therapeutic agents.

International agencies setting up treatment centres must be willing to recruit patients into clinical trials, and have structures in place to manage the ethical and medico-legal requirements to facilitate their conduct [6]. Ethical considerations around the design of clinical trials in such settings can be complex, and it has been argued that randomized, placebo controlled designs are not ideal as they may lead to withholding of potentially beneficial treatment (albeit experimental) from those with a condition that otherwise has a very poor outcome [6]. Using historical controls can circumvent this issue, but calls into question the robustness of the study outcomes. Adaptive trial designs where ongoing planned interim monitoring of the outcome data can be used to alter the trial design after commencement to maximize the potential benefit to study participants while maintaining statistical reliability, have also been advocated for such studies [55]. Other challenges to conducting clinical trials in such settings are the need for study personnel to enter the "red zone" of Ebola treatment centres (ETCs) to consent patients, thereby risking exposure to Ebola themselves, obtaining consent from very unwell patients for complex studies when next of kin are unable to be present at the bedside, and co-ordinating and expediting the ethical review process between multiple governmental and non-governmental healthcare organisations and research institutions. [55] Consent procedures can be further complicated by the cultural and linguistic barriers.

This paper will review proposed therapeutics (including vaccines, antibody based therapies, and small molecules) – many of which have only been tested in vivo on rodents or non-human primates (NHPs) [2].

2. Vaccines against Ebola virus disease

Vaccines are a potential cornerstone for limiting or fully preventing an EVD outbreak. There are numerous vaccine trials including two leading candidates in phase 3 trials (Table 1) rVSV-EBOV vaccines (recombinant vesicular stomatitis virus vector) and ChAd3-ZEBOV (adenovirus vector) [7,8]. Other potential candidates have been described elsewhere [9].

2.1. Recombinant vesicular stomatitis virus vector vaccines

When vesicular stomatitis virus was used in antigen delivery in NHPs, 50% protection was observed which was still effective up to thirty minutes post acquiring infection [7]. Recently, the interim results of a cluster randomized phase III trial of rVSV-EBOV in Guinea have been published [10]. The difficult logistics of conducting such a trial were mitigated effectively by a ring vaccination strategy, where adult contacts and contacts of contacts of patients with EVD were included. Clusters of participants were randomized 1:1 into immediate versus delayed (21 days) vaccination. Out of 2014 participants from 48 clusters in the immediate group, there were no EVD cases after 10 days post vaccination, compared to 16 cases occurring in the delayed group of 2380 participants allocated to 42 clusters. Only one case had a febrile illness associated with the vaccine, which resolved without sequelae. Although the study did not provide measures of antibody titres, it concluded that it might take up to 6 days for the vaccine to provide protection.

Prior phase 1 trials of rVSV-EBOV vaccine, including patients from various sites in the U.S, Africa and Europe, found a high number of adverse events in 90% of the study population [11,12]. The majority of events were reported as mild or moderate, appeared and subsided early ($\leq$24 h), and were alleviated with simple analgesics. Rapid onset and transient haematological changes were observed in all participants including transient leukocytopenia and lymphocytopenia. By 4 weeks, all vaccine doses produced EBOV-glycoprotein specific antibodies, although it could not be concluded whether higher vaccine doses would be required for optimal protection.

Table 1
Experimental: treatment approaches evaluated for efficacy against Ebola virus disease in mammals.

Approach	Target/mechanism of action	Demonstrated Efficacy			Comments	Ref.
		Rodent	NHP	Human		
Vaccines						
Plasmid DNA based vaccine VRC-EBODNA023-00-VP	DNA immunisation with boosting adenoviral vector	–	Y	Phase I (Uganda)	Process takes 6 months to provide protection in NHP	[37]
Accelerated vaccine of plasmid DNA based vaccine: ChAd-EBOV, Ad5-EBOV, cAd3-EBOV (GSK) and Ad26 and MVA-EBOV (J&J)	Adenoviral vector delivers DNA encoding Ebola GP MVA used as a second dose booster	Y –	Y Y	Phase I (UK, U.S, China, Mali, Uganda, Switzerland) Phase II/III*: Liberia Phase I*: UK, II/III* US	Process takes 28 days to provide pre-exposure protection in NHP. Potential for outbreaks. Booster induces longer term protective immunity *NCT02509494 *NCT02240875, NCT02598388	[16,46,47]
rGP nanoparticle (Novavax)	Recombinant Ebola GP admistered with a saponin based adjuvant (Matrix-M)	–	–	Phase I: Australia	Requires 2 injections	[48]
rVSV-EBOV (Merck), rVSVΔG-EBOV	VSV delivers Antigen	–	Y	Phase I (Kenya, U.S, Switzerland) STRIVE: Phase II/III Randomized trial in HCWs (Sierra Leone), PREVAIL: Phase II (Liberia). Ca Suffit: Phase III (Guinea)	Up to thirty minutes post infection (protection against Ebola −50%, Marburg 100%) 33% protection after 48 h, in NHP Geneva phase I trial halted for safety concerns. Less side effects with the newer strains. Potentially could provide protection after 6 days of vaccinations in humans. No booster required. Duration of protective antibodies unknown	[7,11–13,10,21]
Antibody based therapies						
IgG/IgM from convalescent patients	Virus neutralisation	–	–	Case series, INTERCEPT Phase I and Phase II/III (Guinea, Sierra Leone, Liberia)	Widely used during 2014-15 outbreak. No significant mortality benefit in 99 transfused patients. Two consecutive transfusions of 200–250 ml plasma from separate concalescent donors	[26,28]
Purified IgG	As above	–	Y	Y	48 h protection post infection (100%) in NPH	[49]
Cocktail of 3 x mouse monoclonal antibodies-ZMab	Targets GP to neutralize the virus (m1H3, m2G4, m4G7)	–	Y	Cases	100% effective at 24 h 50% @ 48 h	[31]
Cocktail combined with adenovirus vectored interferon-alpha	As above	–	Y	–	72 h post infection 75–100%	[32]

Table 1 (*Continued*)

Approach	Target/mechanism of action	Demonstrated Efficacy			Comments	Ref.
		Rodent	NHP	Human		
Cocktail of 3 x humanised monoclonal antibodies (MB-003) ZMapp and MIL-77 (China)	(c13C6, h13F9, c6D8) A combination of chimeric mAB c13C6 from MB-003 and 2 chimeric mABs (c2G4 and c4G7) from ZMab. MIL-77 is produced by CHO cells rather than tobacco plants	– –	Y Y	Cases, Phase I/II trial (multi-centre) Liberia, Sierra Leone, U.S Phase I*	Protection 100% at 1 h, 67% at 24/48 h. 43% survival at 120 h post infection and development of viraemia and fever in NHP. 50 mg/Kg/day for 3 days *NCT02389192	[30,50,4,51,68]
Drugs or small molecules						
TKM-Ebola Tekmira	Small interfering RNA cocktail against VP24, VP35, and L protein. Encapsulated in stable nucleic acid lipid particles (SNALP)	–	Y	Phase I-suspended (partial lift by FDA). Phase II: Sierra Leone Cases	IV preparation 100% protection 30 mins post exposure in NHP. Phase II trial halted in Sierra Leone. 7 daily infusions: Day1: 0.3 mg/Kg, Day2: 0.4 mg/Kg, then Days3-7: 0.5 mg/Kg	[37]
PMOs (AVI-6002)	Blocks mRNA transcription	–	Y	Phase I PEP	62.5% protection within 30 mins in NHP	[38]
Favipiravir	Pyrazine carboxamide derivative. Selective inhibition of viral RNA dependent RNA polymerase.	Y	–	Cases Phase III (U.S) Licensed in Japan for flu. JIKI Phase II trial in Guinea	Rapid viral clearance, used up to day 6 post infection- mice. Received by most European cases. Preliminary results from JIKI trial indicate effectiveness in cases with low viral load. Day0: 6000 mg then Days1-9: 2400 mg. Activity being studied in semen NCT02739477	[34–36]
Brincidofovir (CMX001)	Nucleotide analogue. Broad spectrum antiviral.	–	–	Cases Phase II (halted in January 2015)	Developed for CMV, BK viruses. Trial in Liberia halted due to reduction in new cases. Loading dose: 200 mg then 100 mg twice weekly for total of 5 doses	[40,41]
BCX4430	Adenosine analogue (PO/IM). Incorporation into viral RNA causing chain termination	–	Y	–	100% protection of NHP at 48 h post infection (Marburg virus), also thought to have anti-EVD activity.	[32,39]

PO: oral route, IM: Intramuscular route, NHP: Non-human primates, GP: Glycoprotein, VP: Viral protein, VSV: Vesicular stomatitis virus, CHO: Chinese Hamster Ovarian cells mAB: monoclonal antibodies PMOs: Phosphorodiamidate morpholino oligomers, PEP: Post-exposure prophylaxis, FDA: Food and drug agency, MVA: Modified Vaccinia Ankara, GSK:GlaxoSmithKline, J&J: Johnson & Johnson,
*Ongoing trials as per http://clinicaltrials.gov (at the time of writing)
Note: Military vaccines (Russia, U.S.A and China) were not included in the table given unavailability of publications in scientific journals.

Two further attenuated forms of rVSV: rVSVN4CT1GP1 and rVSVN1CT1GP3 were studied by Mire et al. [13], following concerns of developing arthritis in some participants in prior trials [11]. None of the vaccinated experimental animals (n = 8) showed any signs of severe illness when exposed to lethal challenge of EBOV.

The advantages of the rVSV vaccine platforms include a shorter time to achieve protecting antibodies by inducing humoral immunity which is key to survival in experimental subjects [8,14]. This renders them favorable in outbreak settings. The relatively low pre-existing immunity to VSV in various populations is an added value [15]. Duration of protective immunity, however, remains unknown.

2.2. Adenovirus vector vaccines

To date there are no published phase III trials describing adenovirus vector vaccines. In a phase 1 double-blinded, placebo controlled trial of an adenovirus type-5 vector-based Ebola vaccine conducted in China [16], 120 adults received a vaccine matching the glycoprotein of the 2014 EBOV. The study demonstrated significant increase in Glycoprotein-specific antibody titres at both day 14 and day 28 ($p < 0{\cdot}0001$) and the treatment was well tolerated. The generalisability of this study however is limited given the variable prevalence of baseline adenovirus type-5 neutralizing antibody in different African populations [16].

There are concerns regarding adenovirus- linked vaccination given previous failures in HIV trials, which were stopped early [17]. The vaccine may reduce suppressive regulatory cells [18]. As such, given high rates of HIV prevalence in Africa, if vaccination was to continue with an adenovirus vector vaccine, it has been suggested that HIV education and prophylaxis should be included in the vaccination regimen [19].

In comparison to rVSV-EBOV, ChAd3-EBOV vaccines strongly induce cellular immunogenicity, which could provide longer duration of vaccine efficacy [20]. ChAd3-EBOV can potentially be boosted by a modified vaccinia Ankara (MVA) strain to produce higher and longer lasting antibody titres. [21] This advantage favours their use in pre-outbreak settings or in health care workers.

2.3. Vaccine use post exposure to ebola virus

Following needle stick injury, rVSV-ZEBOV vaccine has been used in a 44 year old US physician caring for patients in an Ebola treatment unit in Sierra Leone [22]. Forty-three hours after exposure the vaccine was administered and the patient evacuated to the US. Similar to a previous case where vaccination was administered after laboratory exposure [23], The patient had a clinical syndrome consistent with vaccination response. He developed antibodies to Ebola virus glycoprotein (a vaccine component), but not to Ebola virus VP40, which would be indicative of natural infection.

2.4. Other antigen and vaccine delivery methods

Cytomegalovirus (CMV) based vaccination has also been studied in rodents [24]. A single dose of CMV expressing a CD8T cell epitope from nucleoprotein of Ebola Virus (designated MCMV/ZEBOV-NPCTL) induced durable CD8 + T cell immunity for at least 33 weeks. No EBOV disease was observed in vaccinated mice when challenged. These mice did however show loss of weight, suggesting protection may be only partial.

The intranasal route has also been suggested as a potentially effective vaccine delivery method [25]. This method has the potential to increase acceptance, especially in populations distrustful of Western medicine. Intranasal vaccines target the mucosal sites at which Ebola is contracted, minimise the need for specialised health care workers in resource deplete settings and reduce cost. They also decrease storage requirements, minimise medical waste and reduce the need for populations to travel to be vaccinated.

3. Antibody based therapies

Human survivors of EBOV tend to mount early, vigorous, and long standing neutralizing antibodies (NAbs) that can bind to EBOV structural envelop glycoprotein (GP) [52]. Identification of such NAbs and their mechanism of activity has been essential in the development of immunotherapies and vaccines against EBOV. The breadth of protection of such NAbs is variable and still undergoing study [53].

3.1. Convalescent blood products

Convalescent blood products have been used during Ebola outbreaks under the pretext that they contain NAbs against EBOV [26]. In one of the earliest landmark studies, from the Kikwit outbreak in 1995, whole blood transfusions were donated by five convalescent patients, to eight patients with EVD. Five of the six patients tested demonstrated negative tests for EBOV antigens by day 4 after receiving their transfusions. The mortality rate for this patient group was 12.5% (1 in 8), which was smaller than the 80% overall mortality for the outbreak. Whether these results can be generalized is unknown, as the study was limited by its small number of patients and lack of controls. Additionally, the intervention was undertaken during the late phase of the epidemic when health resources were greatly improved. There have also been suggestions that at the end of an EBOV epidemic, the virus may become less infectious and less virulent [27]. A more recent, larger, and better designed study that included 99 patients from Guinea did not show a statistically significant survival benefit in receiving up to 500 ml of convalescent plasma [28]. Paediatric patients younger than 5 years of age appeared to benefit from the transfusions, however a conclusion could not be made due to the low numbers. The study was conducted towards the end of the outbreak, when mortality rates were less than 20%. Due to logistics, the convalescent plasma NAbs levels were not tested, but this reflected real life settings. It has been suggested that convalescent blood products after 9 months from recovery might contain higher levels of NAbs and hence be more protective [29]. At least 8 patients treated outside Africa have reportedly received convalescent serum, 7 of whom survived. [3,41–5]

3.2. Monoclonal antibody combinations (ZMapp, MB-003, and ZMab)

A single antibody may not be able to neutralize every single viral particle, and hence a cocktail of antibodies may be required. Neutralising antibodies from convalescent blood can be produced in vitro in the form of cocktails of monoclonal antibodies (mAbs) against EBOV glycoprotein (GP). For example, ZMapp is a cocktail of 3 chimeric mAbs (c13C6, c2G4 and c4G7), ZMab a cocktail of mouse mAbs (m1H3, m2G4, m4G7), and MB003 a cocktail of human-mouse chimeric mAbs (c13C6, h13F6, c6D8) (Table 1). Four out of six patients treated outside Africa have reportedly received ZMapp and survived. [3,41–5] Details of those therapies, including timing and doses of serum or antibody cocktails remain unpublished. Compared to vaccines that require longer time to induce protection, antibody-based-therapies can potentially offer protection immediately after EBOV exposure for up to 120 h in animal models [30] (Table 1). Their major drawbacks however are a lack of availability and a significantly declining efficacy when given later in the course of experimental infection.

Qiu et al. investigated the administration of ZMAb [31]. All four NHPs (100%) receiving the cocktail at 24 h post EBOV challenge sur-

vived whilst two (50%) survived in the 48-h group. Of note one of the non-survivors carried an escape mutant with mutations in EBOV-GP (amino acids 275 and 508). EBOV-GP IgM and IgG were present up till day 28. ZMAb half-life is still unknown and as such timing of treatment and dosing still require further investigation. Two patients with EVD in the latest outbreak in Sierra Leone, who were treated in Europe, received ZMAb and survived [45,56].

In a previous study utilizing NHPs, co-administration of mAb and adenovirus-vectored interferon-a (Ad-IFN) demonstrated effectiveness if provided following the third day of infection [32]. Seven of eight NHPs survived challenge with signs of mild disease. In a further design to test for an extension of the potential treatment window, NHPs were treated with Ad-IFN 24 h after challenge and ZMAb at 96 h after challenge. Two of four NHPs survived infection. [32]

The delayed administration of MB-003, manufactured in the tobacco plant Nicotiana benthamiana, was investigated for efficacy in NHPs [30]. Treatment was initiated at 120 h after infection with EBOV, with further administration of MB-003 at 170 and 250 h post exposure. Only 3 of 7 NHPs survived, and all controls died.

3.3. Other antibody based therapies

The phosphatidylserine-targeting antibody (PGN401, bavituximab), an antibody previously demonstrated to have broad-spectrum antiviral activity, was shown in an in vitro trial to bind and recognise Ebola virus and Ebola virus infected cells [33]. This may also be a future treatment modality.

The above studies may be limited in their generalisability to human subjects. The cohort numbers were low, which would also limit the power to detect rare adverse outcomes of treatment administration.

4. Drugs and small molecules

4.1. Favipiravir

The pyrazinecarboxamide derivative T-705 (favipiravir) is licensed in Japan for the treatment of influenza not responding to conventional therapies [34]. It has antiviral activity against other negative stranded RNA viruses, and has been used in the European centres that treated EVD in the last outbreak (Table 1). It induced rapid Ebola viral clearance in a rodent model when administered as late as day 6 following inoculation with Ebola virus, in addition to a 100% survival rate compared to controls (100% fatality rate). Results from the JIKI trial in Guinea led by the French Institute of Health and Medical Research (INSERM) suggest a non-significant lower mortality in those with low viral loads as indicated by an EBOV RT-PCR cycle to threshold (CT) of >20 (20% vs 30% in historic controls) but not in those with high viral loads (CT < 20), with a 91% mortality rate in those treated with favipiravir vs 85% in historic controls [35]. The anti-EVD regimen used in adults was 6000 mg on day 0, followed by 2400 mg/d from day 1 to day 9, whereas doses in children were adjusted to body weight [36].

4.2. Phosphorodiamidate morpholino oligomers and small interfering RNAs

Molecules such as phosphorodiamidate morpholino oligomers (PMOs), and small interfering RNAs (siRNAs) have shown efficacy in reducing mortality when administered to NHPs up to 1 h after exposure [37,38]. AVI 6002 is a combination of positively charged phosphorodiamidate morpholino oligomers (PMOs) designed to target mRNA sequences of VP24 and VP35 in EBOV. It is currently undergoing phase I clinical trials for EBOV post exposure treatment. In a study in 2010, AVI-6002 was given intravenously to NHP's initiated 30–60 min post EBOV exposure at varying doses for up to 14 days [38]. The results of the study demonstrated that 60% of NHPs given doses of 28 mg/kg and 40 mg/kg survived with 100 times greater suppression of mean viral load at the peak of plasma viraemia compared to controls. Phase I safety trials have shown AVI 6002 to be well tolerated in healthy adult subjects. TKM-Ebola (formerly Tekmira), is a combination of small interfering RNAs (siRNAs) formulated in stable nucleic acid lipid particles was developed by Tekmira Pharmaceutical Corp. The combination of siRNAs targeting the EBOV L polymerase, VP 24 & 35, was given to 7 NHPs at 30 min post exposure to EBOV and either 3 or 6 further doses at various intervals after [37]. Six of the 7 NHPs were protected from EBOV infection with good tolerance of the drug. During its phase I clinical trial, the U.S Food and Drug Administration placed a hold on the drug due to safety concerns in regards to high cytokine levels [57]. This was partially lifted during the outbreak, and subsequently used in two patients who were treated in the U.S [58]. Furthermore, it is also being designed to target the Guinea variant of EBOV and was planned to enter human clinical evaluation in Guinea in emergency situations [57].

4.3. Brincidofovir CMX001

CMX001 (Brincidofovir) is a prodrug of cidofovir and is an effective anti-DNA antiviral medication by inhibiting viral replication secondary to selectively inhibiting viral DNA polymerases [39]. It is currently undergoing Phase III clinical trials for use against adenovirus and cytomegalovirus. In vitro tests have demonstrated efficacy against EBOV although the mechanism of action is unclear [39]. As a result, Brincidofovir has been used in emergency situations in patients infected with EBOV and was undergoing Phase II clinical trials, which were unfortunately halted due to lack of new cases. Brincidofovir was experimentally used to treat one of the first patients to be transferred to the U.S [41].

4.4. BCX443

The adenosine analogue, BCX443, when given 48 h after infection via intramuscular injection demonstrated 100% protection from Marburg virus in a nonhuman primate model (Table 1), and could potentially be used for EVD [40]. BCX4430 inhibits viral RNA polymerase activity indirectly through non-obligate RNA chain termination. It has shown efficacy in pre-exposure treatment of EBOV in vitro and in small animal models. In a rodent model, it demonstrated protection against lethal EBOV challenge receiving BD oral and IM administration for nine days [40]. BCX4430 is planned for further animal studies.

5. Supportive care

In the absence of any available directed therapy, the mainstay of management in EVD has been supportive care. This includes rehydration, electrolyte replacement, supplemental oxygen, treatment of concomitant infections, blood products, antipyretics, anti-emetics and anti-diarrhoeal agents, nutritional support and psychologic care. The level of sophistication of these interventions varies from basic oral rehydration therapy without laboratory investigations in the most resource poor settings, through to invasive fluid, electrolyte and blood product management, mechanical ventilation, and haemodialysis with full laboratory and radiology support in intensive care units in developed countries [42]. Even within countries most affected by EVD, the level of supportive care varied widely [59,60]. Whether increasing sophistication of supportive care is associated with improved outcomes is not proven, however, one could not dispute this intuitively. In an observational study, Cotte et al. compared the use of central venous catheters to

Box 1: Tips in resource limited settings

- Early administration of anti-emetics and anti-diarrhoeal agents
- Test and treat concurrent infections such as malaria
- Healthcare worker training and education in principles and practice of infection control, sharps management, and occupational safety in an ETC setting
- Dedicated staff health clinics given higher mortality rates among healthcare workers. [62]
- Early involvement of patients and their carers with ongoing education and psychologic care
- Establish a survivor network for potential training and recruitment
- Use of technology and minimisation of paper work: example, mobile phones and dedicated computers
- Early coordination between all actors

peripheral venous catheters for IV access in patients treated at an Ebola Treatment Unit in Conakry in 2015. Central catheters were associated with longer line survival times and a higher ratio of volume of fluid infused to that which was prescribed [61].

5.1. Authors' remarks

Case management varied widely due to a variety of reasons. In one major centre in Liberia, during the peak of the outbreak, the case numbers overwhelmed the ETC capacity that a decision was made to "close the doors", and a palliative approach was followed due to high rates of mortality (reaching 80%) [Box 1]. In a different setting, the case load was lower. Patients with confirmed EVD were admitted to air conditioned tents, each containing two beds. Observations included temperature, blood pressure, pulse, oxygen saturations, respiratory rate, conscious state (AVPU) and level of hydration. Frequency of observation was between 12th hourly up to 4th hourly or more frequently, depending on the stage of disease. Fluid balance was recorded, and urinary catheterisation and rectal tubes (Flexiseal Faecal Management System) were utilised as needed. Closed circuit cameras allowed continuous remote visual observation of patients from the staff station outside the 'red zone'. Peripheral venous access was established when necessary for intravenous hydration; central venous access was also utilised for patients with advanced disease. Ultrasonography was utilised to aid placement of central venous catheters, and also to assess fluid volume status by observing inferior vena cava filling.

Point of care pathology testing was utilised within the red zone, using iSTAT™ devices (analytes tested included sodium, potassium, chloride, ionised calcium, glucose, urea, bicarbonate, creatinine, haematocrit, haemoglobin, anion gap, pH, PCO2, pO2, lactate, base excess, prothrombin time, INR), glucometers, and immunochromographic testing for malaria and beta-HCG.

An onsite laboratory performed PCR testing for Ebola virus, as well as rapid diagnostic tests for Dengue and HIV. In the laboratory, biochemistry testing was available using the Piccolo™ platform. Analytes assayed on the Piccolo™ included albumin, urea, calcium, creatinine, glucose, potassium, sodium, amylase, alanine transaminase, aspartate transaminate, creatinine kinase, C-reactive protein, bilirubin, lactate, chloride, magnesium, phosphate and bicarbonate. Haemtology testing was performed on the Hemochron™ platform and included a full blood count with white cell differential and coagulation testing. Blood cultures were performed using the BacT/Alert™ system. The Biofire filmarray™ platform was also utilised for multiplex PCR testing of respiratory and faecal pathogens, and to detect bacteria from positive blood cultures.

Pathology testing was performed at least daily in the initial phase of management, and as required in the convalescent phase. In advanced disease point of care testing in the red zone was utilised as clinically necessary for more frequent pathology monitoring.

5.2. Mental health

In our experience, psychosocial support and health promotion (PSHP) are integral to the care of patients with EVD. In West Africa, many ETCs were supported by dedicated PSHP teams, responsible for counselling relatives of those admitted with EVD, coordinating "fence line" visits, linking up family members admitted to different ETCs, coordinating safe and dignified burials and allowing family members the possibility of viewing the face of the deceased, across the fence line separating red zone from the ETC boundary. PSHP personnel were critical in facilitating access to social support programs for survivors (food packages, survivor clinics, survivor networks) and providing education and counselling, including safe sexual practices, in EVD survivors. They provided an essential point of contact for many survivors who experienced discrimination in the aftermath of their disease.

Mental health of healthcare workers (HCWs) must also not be neglected. Many returning volunteers experienced stigmatisation. The names of those HCWs who contracted the illness were publicised [63]. Employers could play a role in mitigating the sensationalism driven by media by counselling families prior to an individual's return.

6. Follow-up

With around 10,000 survivors of this disease now across West Africa, there is an increasing demand for the medical management of complications related to EVD in this survivor cohort. Most notably ocular complications, chronic pain – especially arthralgias, cognitive, post traumatic stress syndrome and hearing deficits [64]. The emerging knowledge regarding immune privileged sites (e.g, eye, semen, cerebrospinal fluid) where the virus can remain sequestered, highlights the importance of ongoing follow-up and monitoring of these patients for late effects [65]. Such clinics are now being established in countries that have experienced high and intense transmission.

7. Discussion

There is evidence that current vaccines might have the potential to halt an outbreak, if a ring vaccination strategy is followed [10]. Both candidate vaccines seem to be well tolerated, however, we still do not have data on the duration of their protection or safety in subjects with underlying disease or medical conditions. There are also no data regarding their safety in paediatric or pregnant populations.

Supportive strategies and blood products have been commonly used, and there is accumulating evidence towards their benefit [61]. Intravenous (IV) fluid and electrolyte replacement are potentially challenging in certain contexts due to the lack of infrastructure for sharps management. Their use could be gradually introduced depending on the capacity of the etc. EVD patients can experience difficulties with absconding, denial and combativeness and it is not uncommon for patients to remove their lines, especially when not observed.

Other clinical supportive measures can include the use of antipyretics and anxiolytics for symptom control when needed. Identifying and treating concurrent infections such as malaria was shown to reduce mortality [54].

The orally administered therapeutics seem promising, especially if given early when the viral load is still low. [35] Concomitant administration of anti-emetics might be essential. Given the nature of increased volume losses in EVD, absorption of oral medications might become an issue. To date there are no intravenous formulations for those orally administered drugs.

8. Conclusion

Clinics to follow-up on the survivors to establish the natural history of EVD and its long term sequelae is an apparently straight forward opportunity for us to learn.

It is to the credit of WHO to establish a research and development blueprint for action to prevent epidemics by accelerating availability of vaccines, effective tests, and medicines at a large scale [66]. Indeed, there is a pipeline of interesting molecules that potentially could target EBOV [69]. We hope this will be a significant effort towards an evolving leadership in emergency research, and in particular facilitating clinical trials in outbreaks. An external investigation following the outbreak has created an opportunity for WHO "to re-establish its pre-eminence as the guardian of global public health" [67].

It remains unfortunate that an outbreak involving 28,000 people over more than a year has passed and the opportunity to evaluate so many putative therapeutics has been missed. While some therapeutics were used on human subjects for the first time, we still cannot make conclusions on their safety or effectiveness. Clinicians and outbreak responders look forward to the day that well designed and practical clinical trials can be seamlessly rolled out in parallel with clinical efforts.

Conflict of interest statement

The authors declare no conflicts of interests

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