Key messages from the WHO Meeting on Clinical Aspects of Ebola Virus Disease, Advancing Standards of Clinical Care

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Geneva, Switzerland

(Note: This summary is intended as an update for the general technical audience. Details of some of the information contained herein will be published later by respective investigators.)

Introduction
From the declaration of the current Ebola Virus Disease (EVD) outbreak in March 2014, WHO has been developing and promoting its Viral Haemorrhagic Fever (VHF) pocket guide8 as the standard of care for EVD. Together with their many partners, WHO has trained thousands of healthcare workers using this guide. The informal clinical review conducted by the Organization in July 2014 suggested that significant body fluid loss due to massive watery diarrhoea is the main cause of severe illness that leads to shock and other complications in EVD patients. WHO clinicians deployed to the field since have therefore been tasked to promote timely fluid resuscitation and, when possible, to monitor electrolytes and metabolic abnormalities in efforts to resuscitate patients and reduce EVD mortality.

Meeting Objectives
Reports of improved case survival in EVD patients1-3 have been published in peer-reviewed journals, all affirming the importance of early fluid repletion and other symptom management. However, different standards of clinical management have been used by the clinical partners in the field, perhaps reflecting the varied patient loads and associated clinical care demands in Ebola treatment units (ETUs) across the epidemic region over time. These differences in standard of care and sometimes time to presentation have been associated with differences in outcomes. To share information and build consensus regarding clinical standards of care for EVD, WHO sponsored a meeting in Geneva on January 26-27, 2015 to review clinical aspects of EVD, including clinical manifestations, disease evolution and complications, and case management experiences in West Africa, Europe and the United States of America. The meeting was co-hosted by Hôpital Université de Genève, under the leadership of Professor Laurent Kaiser, and supported by the Swiss Federal Office. It is expected that the application of the improved clinical standards resulting from the meeting will not only improve clinical outcomes in patients with EVD but will also provide standardized protocols to facilitate comparisons between outcomes associated with different experimental therapies.

Participants
Meeting participants were primarily the clinicians caring for EVD patients on the front lines in West Africa as well as in Europe and the United States, and included representatives of African Union Member States, NGOs, and national and international agencies. They were joined by experts in filovirus laboratory science including animal models, clinical trials, and database and information management. WHO staff from Essential Medicines and Health Products, Infection Prevention and Control (IPC), Pregnancy and Child Health and Foreign Medical Teams were also present, in addition to the Clinical Management Team.

8 Clinical Management of Patients with Viral Haemorrhagic Fever: A Pocket Guide for the Front Line Health Worker. 30 March 2014
(http://apps.who.int/iris/bitstream/10665/130883/2/WHO_HSE_PED_AIP_14.05.pdf?ua=1)
Summary of Key Messages

Epidemiologic Update. The virus causing the current outbreak is Zaire ebolavirus. The reservoir for this virus is thought to be a species of fruit bat. Various intermediate hosts, especially non-human primates, have been recognized. Like most filovirus outbreaks, the molecular epidemiologic evidence suggests that there was a single introduction into humans from a wild animal, followed exclusively by human-to-human transmission. Stopping human-to-human transmission has thus been the focus of control efforts.

The number of new cases being reported from West Africa has significantly diminished recently. While this is very good news, intense efforts at control must continue until the number reaches zero. Significant challenges remain; for example, roughly 50% of new cases are not previously recognized contacts, reflecting a lack of comprehensive surveillance and awareness of all areas and chains of transmission. Furthermore, unsafe burials and episodic resistance to contact tracing continue. The time from symptom onset to isolation, while decreasing overall, is still 5-10 days in some areas, leaving ample time for secondary transmission to occur. While significant emphasis and resources must be put on controlling transmission, at the same time, healthcare and social support of EVD survivors and their families and reestablishment and strengthening of health systems also need attention.

The ongoing outbreak has provided unprecedented opportunities for learning about the characteristics of those with EVD, disease progression and case management. The majority of cases are adults. Children represent approximately 20% of cases and, along with pregnant women, have special needs with regard to treatment as well as in the organisation of care. For example, young children will need an adult care-giver to assist with adequate intake of fluids and to provide emotional support.

Update on EVD pathogenesis. Animal models are useful in understanding many aspects of disease pathogenesis, but all of the available models have limitations, including the requirement for work under BSL-4 conditions. Non-human primates develop more rapid and severe illness than do humans, in part because of the routinely high virus challenge doses used, which are designed to produce 100% fatality in control animals to facilitate interpretation of the efficacy of interventions. Pathologic examination showing duodenal oedema and haemorrhage in Ebola virus-infected primates could explain the upper gastrointestinal symptoms seen in humans, although the profound diarrhea seen in human EVD is not observed in NHPs. Computed tomographic images show abdominal compartment syndrome and cerebral parenchymal ischemic lesions that are compatible with the severe abdominal pain and encephalopathy, respectively, observed in some humans with EVD.

Ebola virus infects macrophages and dendritic cells followed by viremic dissemination to multiple organs including liver, spleen, lymph nodes and adrenal glands. Clinical features are believed to relate to both systemic pro-inflammatory cytokine release in response to virus infection and virus infection and damage of multiple organs. Markers of a poor prognosis include high viral load and high aspartate aminotransferase (AST), creatinine phosphokinase (CPK) and creatinine levels. Severely ill patients tend to have several of these markers. Severe dehydration and electrolyte imbalance are prominent clinical findings for which early correction may significantly reduce mortality. Other serious clinical events include kidney failure, hepatic involvement, and acute respiratory distress syndrome (ARDS). Haemorrhage is relatively infrequent and occurs late in disease. More research is needed to better understand the pathogenesis of EVD and the cause of some of the common laboratory findings, such as elevated creatinine kinase and very high AST as compared to alanine aminotransferase (ALT) levels.
It is believed that asymptomatic persons are not infectious, an assumption supported by the findings that blood PCR tests to detect Ebola virus RNA become positive only after symptoms appear and revert to negative when the patient recovers (Figures 1 and 2). However, initial symptoms can be non-specific and fever is not always present, especially in pregnant women or older adults. There are presently no laboratory tests to reliably identify persons in the incubation period. Presence of virus in body fluids during the pre-symptomatic period is thus far not adequately studied.

![Figure 1](source.png) **Figure 1.** The classic pattern of fever, viremia and antibody production in persons infected with and surviving Ebola virus disease.

![Figure 2](source.png) **Figure 2.** Ebola virus shedding in body fluids. Colors=PCR positive. Bars=culture positive. 
*Source: Pierre Rollin/CDC*
In general, high viral loads are associated with a poor prognosis. However, initial viral loads and subsequent replication kinetics may not be useful in making treatment decisions or to predict prognosis in individual patients. Preliminary data comparing concurrent outbreaks in Kailahun, Sierra Leone and Lokolia, Democratic Republic of the Congo in July 2014, indicated significantly higher average viral RNA load in Sierra Leonean patients with EVD, despite no difference in the interval between symptom onset and collection of blood samples. This finding suggests that virus replication kinetics may differ at the two sites possibly due to differences in the infecting virus strain and/or host factors like presence of co-morbidities or genetic differences.

Serial data from EVD patients in Kailahun, Sierra Leone, from July to December 2014 found that average admission viral load diminished as the epidemic progressed, despite no differences in time to presentation. This observation has potential implications on severity of illness and case fatality ratio (CFR) that indicate the need for caution when using historical cohorts as a control group in clinical trials. Further research is needed to confirm these findings, which may relate to both virus and host factors, different routes of infection or inoculum size, as well as to more rapid access and earlier implementation of supportive care in ETUs.

Genetic evolution of the virus as the outbreak progresses continues to be assessed. However, sequence comparison from two patients evacuated to the United Kingdom from Sierra Leone in August and December indicate no major variation.

Healthcare worker infections. A total of 844 healthcare workers have been contracted EVD with an overall CFR of 60%. Investigation of the source of infection for the small number of infected expatriate workers suggests that most were acquired outside ETUs, including from exposure to sick colleagues (some of whom did not declare their illness), during the donning of personal protective equipment (PPE), and in uncontrolled environments such as triage areas where the diagnosis of EVD in presenting patients was not yet established. A limited number (N=13) of health workers with sharps injuries did not result in infection, although the denominator data are incomplete. It is unknown how many of these persons were actually exposed to Ebola virus through the injury.

Assessment (triage). Triage to quickly identify those suspected of suffering from EVD is the first step in managing a patient presenting at a clinic. However, many challenges exist, including:

- **Fever** may not be present at presentation in all patients, especially pregnant women. Furthermore, common complications of pregnancy such as vaginal bleeding and miscarriage may be incorrectly attributed to pregnancy itself rather than EVD, leading to increased possibility of secondary transmission, particularly to healthcare workers, since appropriate PPE for EVD may not be worn. Within countries with active Ebola transmission, it is best to take all IPC and PPE precautions as for EVD in all women with spontaneous abortions or bleeding and at the time of delivery.
- Despite fulfilling the case definition for EVD, children may be suffering from other treatable childhood illnesses such as acute gastroenteritis or acute respiratory illness. Isolating children suspected of having EVD in ETUs along with confirmed cases without providing treatment for these other conditions may result in excess non-EVD mortality, as well as increase their risk of acquiring Ebola virus infection in the ward.
- EVD and other endemic diseases, such as malaria and typhoid fever, may coexist. It is essential to consider this possibility and manage patients with appropriate anti-infective therapy. Where malaria is highly endemic, mass antimalarial drug administration campaigns should be considered to reduce the malaria-associated mortality and the number of patients presenting with febrile disease, which results in a significant healthcare burden.
Laboratory diagnostic capacity has improved considerably since the onset of the epidemic. However, better diagnostics at the point-of-care are needed, including tests for virus antigen\(^b\) or RNA detection, as well as biochemistry panels for electrolytes and other clinical laboratory parameters. There are several point-of-care diagnostic studies underway. Currently, initial decisions are based on triage algorithms and these need to take into consideration the aspects mentioned above, with local adaptation as appropriate.

**Treatment.** Providing safe quality care in a timely and dignified manner is essential. Observed CFRs vary considerably between ETUs, perhaps due to different standards of care offered to patients. Centres with effective fluid resuscitation strategies often report lower CFRs. Experience from different facilities utilizing IV rehydration in the affected countries shows that transmission to healthcare workers rarely occur if adequate IPC measures, including use of appropriate PPE, are taken. Hence, the ‘no touch’ policy practised in some treatment centres needs to be revised, not only because it is not evidence-based, but also because it will inevitably result in sub-standard clinical management and decreased survival. In turn, this undermines community engagement and confidence in control and treatment measures. Every effort to encourage patients to come to facilities for treatment must be made.

**Fluid resuscitation.** Mortality can be substantially reduced with intensive supportive care, particularly adequate fluid resuscitation and prevention and correction of electrolyte abnormalities. Difficulties in measuring vital signs, assessing fluid balance (inputs and outputs), and in supporting oral intake, especially in children, have been common. In the absence of adequate fluid intake, the likelihood of disease progression, even in those presenting with mild disease, may be significant. Of note, evidence for volume overload has been rare in those cared for in ETCs, in contrast to those who have received aggressive rehydration in well-resourced settings. While this may in part relate to increased vascular leakage in those surviving longer due to intensive care support, it also suggests that rehydration is inadequate in most ETUs.

Oral rehydration solution (ORS, according to the formulation recommended in the WHO Model List of Essential Medicines 2013) could be used in the initial phases of disease and in mild cases. A low threshold to initiate IV fluids (such as any vomiting or diarrhea, any sign of dehydration, or the observation of inadequate oral intake) is appropriate in both children and adults. Based on limited study, Ringer lactate is the preferred IV fluid. ORS should nevertheless be continued or restarted as soon as possible. It is also important to improve community messaging to encourage use of ORS.

Ideally, electrolyte correction should be based on monitoring laboratory values and following a set administration protocol. While hypokalemia was found in a significant proportion of expatriate patients with EVD, MSF data showed potassium levels to often be normal, with occasional hypo- or hyperkalemia. When electrolyte monitoring is not possible, consideration should be given to routine empiric oral potassium supplementation.

**Medications**

1) Symptomatic treatment

**Pain:** Paracetamol is currently the first line choice for pain management, with morphine for severe pain. Tramadol may be used if morphine is not available. However, the drug is not on the WHO Model list of essential medicines. NSAIDs and salicylates are not recommended in EVD because of risks of bleeding, gastrointestinal inflammation/ peptic ulceration, and kidney damage. Routine antipyretics for fever are not recommended.

\(^b\) WHO has since then approved a rapid antigen detection test for Zaire ebolavirus (ReBOV\(^TM\))
**Nausea and vomiting**: Ondansetron is the preferred antiemetic and may increase patient comfort and potentially improve oral feeding and gut healing. Alternatives could be chlorpromazine and metoclopramide. All are included on the WHO Model list of essential medicines.

**Delirium and agitation**: Haloperidol is recommended for adults. Diazepam can also be considered, especially for children, although agitation appears to be less frequent in this group.

**Diarrhoea**: There is debate regarding the efficacy and safety of antimoitility agents such as loperamide in EVD, especially in children. Current evidence is inadequate and some experts advise against loperamide use, in part because of concerns that diarrhea may be inflammatory in etiology and that it may increase risk of paralytic ileus and colonic dilatation.

2) **Antibiotics**

Despite the very limited data on the risk-benefit of antibiotic treatment in EVD, empiric antibiotics are very frequently given, including in most of the expatriate patients, for possible bacterial infection at time of presentation. Symptoms of EVD often mimic those due to bacterial sepsis or diarrhoea, especially in children (about 50% of children suspected to have EVD test negative), and bacterial infections may coexist with EVD. Early antibiotic administration in those with severe bacterial infection can be lifesaving, and empiric use was therefore considered appropriate in patients presenting with severe illness. Other indications for antibiotics are treatment of secondary infections and possible prevention of sepsis due to translocation of gut bacteria. There are some limited data to suggest that gut translocation has occurred in EVD, but bacterial blood culture systems and other diagnostic means to assess the frequency of bacterial infections are rarely available or feasible in EVD epidemic areas. When the clinician feels that they are indicated, the choice of antibiotics can be guided by WHO recommendations for bacterial infections with a similar clinical presentation, such as acute gastroenteritis, sepsis, or pneumonia. For critically ill patients ceftriaxone is a reasonable choice, although it does not cover some gut anaerobes. It is critical to regularly reevaluate the need and efficacy of the antibiotic, limiting treatment courses to the shortest duration possible, usually not more than 10 days, or even earlier if diarrhoea subsides (and there is thus no more risk of bacterial translocation). Selection of antibiotic-resistant bacterial pathogens is an obvious concern and so indiscriminate antibiotic use should be avoided.

3) **Malaria**

All patients with fever in malaria endemic areas need to be treated with antimalarials following national program guidance. Rapid diagnostic tests for malaria can be used if available and reliable.

4) **Anthelminthic medicines** may be added at the treating physician’s discretion, using knowledge of the prevalence of helminthic infection in the area when available. Overwhelming strongyloides infection would be the most likely condition to mimic EVD.

5) **Metronidazole** can be added for patients with bloody diarrhoea if amoebiasis is suspected, at the discretion of the treating physician.

6) **Oxygen** was considered an important part of supportive therapy. Tachypnea is common in severe EVD, but appears to be most often related to metabolic acidosis from electrolyte and fluid losses or increased lactate production, and not hypoxemia. Current logistics do not allow its wide use and ways of improving the situation need to be considered.
**Nutrition.** The need for adequate nutrition during both the acute and convalescent phases of EVD was stressed. This is of special importance in infants and children. Updated guidelines on nutrition in EVD are available from WHO and UNICEF.

**Considerations in children.** In the current outbreak about 20% of EVD patients are children under the age of 18. Case-fatality depends heavily upon age, and available data show that the CFRs are approximately 80% in children less than one year old and 60% in those less than 5 years. Special attention needs to be given to these age groups, including systematic study and research to develop evidence-based guidelines. There may be differences in the clinical presentation of children with EVD compared to adults, with bleeding and hypoglycaemia more common in children. Paediatric illness has to be better characterised.

Currently children and their parents or guardians are isolated together in many facilities because children left alone may not take fluids and medications adequately. Isolation in ETUs is especially psychologically traumatic for children. Hence there is need for a provision to group children together and for an adult to be nearby at all times. The possibility of a survivor taking on this role, employing adequate IPC measures, needs to be considered.

The clinical diagnostic criteria currently used for both children and adults are very similar to those used in other childhood illnesses, such as acute gastroenteritis or respiratory disease. Therefore, the triage criteria need to be adapted to better consider other childhood diseases in the context of EVD. A history of contact is especially important.

Children are rarely weighed on ETU admission, despite the importance of knowing the weight of a child to prevent over- or under-dosing of fluids and medicines. A simple upright weighing scale can be used for this purpose. All children need special nutritional support. Vitamin A supplementation should be provided if the child has not received Vitamin A in the past 6 months. Guidance has to be developed for micronutrients, especially for malnourished children.

The WHO fluid replacement plan A, B and C must be adapted to allow early administration of IV fluids. Children who are likely not to take ORS adequately should be started on IV fluids early. Oral potassium supplementation needs to be considered.

Choice of medicines is as discussed in the section on medicines above. A paediatric medicines drug dosage chart using weight and age must be available in all treatment facilities. Lack of child friendly formulations for many medicines used in ETUs is a concern. Child friendly drip regulators also need to be considered.

**Considerations in pregnant women.** Although there is little hard data from the current outbreak, published literature and experience from past outbreaks show a CFR of around 90% among pregnant women with EVD. Spontaneous abortions and still births are very frequent, and the CFR for live births is nearly 100%. Collective experiences during this outbreak confirm these findings, although rare cases have been noted of pregnant women surviving EVD with their baby still in utero. Healthcare workers should check for foetal heart tones in the rare pregnant women who survives and does not abort. Dead foetuses and babies that have been tested by PCR showed high viral loads and should only be handled with EVD IPC precautions, including the use of body bags for burial.

Transmission from infected pregnant women to healthcare workers has occurred in past outbreaks. Healthcare workers are often anxious about risk of Ebola virus exposure from the large volumes of blood and other body fluids present during delivery.
In one case discussed, amniotic fluid was PCR positive with high viral load for several days after the mother’s blood became PCR-negative. Virus isolation has not yet been performed on the sample, but is planned. Since intrauterine contents (foetus, amniotic fluid, and placenta) may be highly infectious, delivery of children born to mothers recovering from EVD should occur in facilities where adequate IPC, including PPE, are available, preferably in an ETU. Arrangements may need to be made to keep pregnant women who survive EVD and continue to carry live foetuses close to ETUs to facilitate safe delivery. If this is not possible, induction may need to be considered to prevent spontaneous labour and risk of Ebola virus transmission in an uncontrolled environment. However, more data are needed to fully understand the pathogenesis and risk of virus transmission in pregnant women who survive EVD with their baby still \textit{in utero}.

Invasive procedures such as Caesarean section do not appear to improve chances of survival for mother or baby and hence should be avoided. Oral misoprostol is the preferred treatment to prevent post-partum haemorrhage. Whether uterine evacuation by induction of labour improves survival of an infected pregnant woman remains uncertain.

Ebola virus has been isolated from the breast milk of pregnant women with EVD and it is therefore recommended to stop breast feeding, especially if the baby is uninfected. Formula must then be provided for the infant.

\textit{Record management.} Standardized data collection is necessary to facilitate clinical decisions and to evaluate indicators of quality of patient care and health systems operations. It will also help in research and evaluation of investigational products, including therapeutics, vaccines, and diagnostics. A list of patient and systems indicators was proposed and discussed. A user friendly data collection format will be made available soon. Systems will be made for data collation, analyses and feedback.

\textit{Discharge.} The current criteria for discharge are for a patient to be clinically stable and “dry” (i.e. without vomiting, diarrhea, or bleeding) for 2-3 days, followed by 1-2 negative blood RT-PCR laboratory results. This decision is driven more by prevailing laboratory capacities and political concerns (e.g. “abundance of caution”) than by evidence-based assessment of risk from survivors.

Patients who have recovered from EVD and have negative blood RT-PCR findings are not known to cause transmission to community or household contacts, except for the very rare possibility (suspected in one Marburg case, but yet undocumented) of male-to-female sexual transmission. Ebola virus has been isolated from the semen of survivors, including up to 82 days post disease onset (Figure 2) and from the urine 26 days after disease onset. RT-PCR results on vaginal secretions in one patient were positive on day 33 after disease onset, although infectious virus could not be isolated. Ebola virus was isolated from breast milk 15 days after disease onset. Infection through wet nursing was noted in a past Marburg virus outbreak.

The question of infectivity can be conclusively answered only through systematic longitudinal follow-up of survivors and their contacts, including testing for infectious virus (i.e. cell culture) in the various body fluids and appropriate serologic studies. Such data are not currently available and are not easy to collect. Until more conclusive evidence becomes available, abstinence or condom use are advised to prevent sexual transmission through semen for 3 months after disease onset.

\footnote{One example is ISARIC-WHO Clinical Characterisation Protocol for Severe Emerging Infection \url{https://isaric.tghn.org/articles/isaric-who-clinical-characterisation-protocol-severe-emerging-infection-master/} accessed January 2015}
Survivors of EVD. Given the scale of the current outbreak, and the approximately 30-40% survival rate in the most affected countries, there are potentially many thousands of EVD survivors, including many orphans. However, detailed registries of survivors are generally not available.

Data from small cohorts indicate that a significant number of survivors continue to have health related problems in convalescence after EVD, including persistent myalgia, arthralgia, anorexia, weight loss, alopecia, orchitis, irritability, eye problems (uveits/acuity loss), mental health effects, memory changes, and auditory problems. Many find it difficult to integrate back into society because of ill health, including psychological problems, and stigmatization. The urgent need to support convalescent patients through both community-based health clinics and psychosocial support was noted.

In order to better understand the needs of convalescent patients, systematic studies should be integrated into care provision programmes. These could include data collection of signs, symptoms and basic laboratory results; biological specimens to assess shedding of virus in semen, vaginal secretions, and other fluids; investigation of transmission during convalescence; and follow-up of patients for mental health issues.

Special attention must be made to the physical and psychological needs of children, especially orphans. This group could be followed up long-term to understand effects on growth and development.

Establishment of registries of EVD survivors will be valuable in providing care and in better understanding the issues facing EVD convalescent patients. To address the needs of EVD survivors, WHO proposes the creation of the WHO Ebola Survivors Network (WHO-ESSN). The WHO-ESSN will establish a framework for the immediate provision of the aforementioned healthcare and social services to EVD survivors, as well as for systematic data collection to better understand the pathogenesis of EVD convalescence and inform best practices for clinical management.

Experimental medicines. Updated information on experimental medicines was shared. ZMapp/ZMAb use in total of 15 patients so far indicates that it was generally well tolerated, although febrile reactions and systemic symptoms occurred in some recipients in temporal relationship to infusion. Although there may have been substantial decreases in viral loads following treatment in some recipients, it is difficult to definitively assess the contribution of any one treatment measure alone since they are almost always given in combination with multiple others, including general supportive measures. Other investigational interventions used principally in well-resourced settings in individual patients have included convalescent plasma, favipiravir, Tekmira’s nanoparticle siRNA, and brincidofovir. A planned clinical trial of brincidofovir in Sierra Leone was cancelled due insufficient case numbers.

The favipiravir clinical trial (JIKI trial) in Guinea has enrolled about 80 patients. The drug appears to be well tolerated; no serious adverse events have been reported. Efficacy data are expected from the French trial group at the WHO meeting planned in March 2015.

More information is needed, both on clinical and logistical aspects, on the use of convalescent plasma and whole blood. Use of these measures on compassionate grounds does not appear to have had major beneficial effects.

Ebola treatment centres and personnel. In many EVD treatment centres, care is provided in tents, often without adequate ventilation. In places where ambient temperatures are already high, the tents may act as ‘green houses,’ leading to unbearably high temperatures and humidity that are harmful to patients, care givers and also to medicines and equipment. Such conditions can severely
restrict the time that healthcare providers can stay in PPE. Alternatives need to be sought and could include ETU designs incorporating solar energy-based cooling systems. Another suggested design feature was the use of cameras or corridors with windows, so that staff could visually monitor patients inside the ETU from secure areas.

Adequate training of ETU staff not only in IPC measures but also in care provision, especially establishing IV access, needs to be ensured. The care aspects are improving within ETUs, affording further confidence and building of skill-sets to treating doctors and nurses.

Procurement and supply management to make available all medicines, medical devices and IPC needs, including PPE, was stressed. WHO has published EVD specific lists of essential medicines and devices and specifications on PPE to assist countries with procurement and the management of donations. These lists will be updated as soon as updated standards of care are made available.

WHO clinical standards. The standard of care as recommended by WHO is published as ‘Clinical management of patients with viral haemorrhagic fever - a pocket guide for frontline health worker’. The original guidance was revised and published in April 2014, both in English and French, in response to the current EVD outbreak, and later adapted by Sierra Leone and Liberia to incorporate country-specific needs. The generic WHO guidance book will be updated to include the clinical management advances agreed upon during the meeting.

References