Ebola Virus Disease in the Obstetric Population

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4.1 Management of Ebola Virus Disease in the Low and High Resource Setting

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4.1.1 Introduction

The clinical management of Ebola created a significant challenge during the outbreak in West Africa in 2014/15, due to the paucity of previous research conducted into the optimum treatment regimen. That left many centres, to some extent, having to 'work out' best practice as they went along, and attempting to conduct real time prospective research. Médecins Sans Frontières (MSF) [1] were the only organization to have provided relatively in depth practical guidance prior to the outbreak and this manual was the basis of further planning between the WHO, national Ministry of Health and Sanitation in Sierra Leone, and other relevant stakeholders. Additionally, guidance changed over the epidemic as experience grew. This chapter will describe four key areas in the management of Ebola in West Africa. Firstly, it outlines the most recent WHO guidance; secondly, it looks back at how Ebola was managed in differing low and high resource settings; thirdly it outlines possible and optimal options for managing complications, paying particular attention to some of the controversies faced; fourthly it describes recent and ongoing studies into potential novel therapies that may shape future practice.

There is, as yet, no specific cure for EVD and the mainstay of treatment is supportive care and managing complications, alongside ring-fence vaccination of close contacts. However, due to many tropical illnesses masquerading as Ebola, and

Table 4.1 EVD differential diagnosis[a]

Differential diagnosis (consider local epidemiology)	Specific interventions
Typhoid	Antibiotics
Malaria	Malaria RDT, antimalarials
Viral/bacterial gastroenteritis e.g. *Shigella* spp. infection	ORS, IV hydration Consider antibiotics
Cholera	ORS
Amoebic dysentery	Anti-protozoal therapy e.g. metronidazole/tinidazole
Dengue fever	Monitor for shock syndrome
Other VHFs e.g. Lassa, CCHF	Supportive, consider Ribavirin if confirmed Lassa/CCHF
HIV-related illness	VCT, further investigations when EVD excluded. Consider empirical therapy for sepsis/PCP depending on presentation
Leptospirosis	Antibiotics
Typhus/rickettsial disease	Antibiotics e.g. doxycycline
Other viral illness e.g. influenza, EBV	N/A
Other bacterial sepsis	Antibiotics, monitor and treat shock if present, inotropic support if required and available, investigate source

[a]Not exhaustive
N/A not applicable, *ORS* oral rehydration solution, *PCP* Pneumocystis pneumonia, *VCT* voluntary counselling and testing for HIV

thus requiring isolation and EVD testing, it is worth bearing these diagnoses in mind as empirical treatment for them should be considered in the undifferentiated patient (Table 4.1). This is particularly important in contexts lacking diagnostic resources, and additionally, with the current absence of a rapid diagnostic test that has been widely used or field tested. As an example, O'Shea et al. [2] reviewed 51 patients who presented with suspected EVD but tested negative, at the UK Ministry of Defense ETU at Kerrytown, Sierra Leone. Eleven had malaria (25.5%), 12 *Shigella* spp. or *E. coli*, 12 a respiratory infection and 11, an undifferentiated febrile illness supporting the need for empirical malaria and antibiotic treatment.

4.1.2 WHO Guidance 2016 [3]

The WHO released their most recent guidance on the management of Ebola in February 2016. This is recognised as the gold standard in the low-income setting, however, it is possible that the capabilities of many centres will not meet these targets. The WHO classifies the patient into three categories of severity; mild, moderate and severe. These are briefly summarised here, but for specific guidance the most up to date version of the WHO manual should be referred to.

Mild
The patient will be haemodynamically normal, able to eat and drink, have no complications nor evidence of dehydration. Empirical oral broad-spectrum antibiotics, anti-malarials and oral rehydration solution are recommended. Treatment for symptoms such as pain, fever and dyspepsia can be provided orally.

Moderate
Patients often have vomiting and diarrhoea, are weak and look dehydrated with sunken eyes and a skin pinch slow to return. Antibiotics and anti-malarials should ideally be given intravenously, however, if there are contraindications to intravenous line insertion, can be administered intramuscularly. Fluids should be given intravenously with additional oral rehydration solution.

Severe
This patient will be severely dehydrated and shocked from either dehydration, sepsis or bleeding, although haemorrhage in the West African outbreak was seen in as little as 5–10% of cases. Empirical broad-spectrum antibiotics should be administered intravenously within the first hour of presentation, along with anti-malarials, and effective intravenous fluid resuscitation is essential. Tables are provided in the WHO guidelines to calculate fluid requirements, however, as a rule of thumb an adult who is severely dehydrated or shocked would be treated with a bolus of 1L in the first 30 min. Monitoring the patient for acute fluid overload with regular vital sign measurement and fluid balance charts is required.

In ill patients, the WHO advocates testing for malaria and HIV, and measuring potassium, sodium, bicarbonate, blood glucose, creatinine, and lactate. For women of a childbearing age, a pregnancy test should be performed as a priority. If possible, magnesium, haemoglobin or hematocrit, platelet count, INR and APTT should also be tested.

In all instances management of symptoms and signs is required—these are described in the management of complications section below.

4.1.3 Practical Aspects of EVD Management in Differing Contexts

There was great variation in EVD management in practice, influenced in part by resource discrepancies, differences in case load and staffing, and disagreements in best practice that developed due to the void of evidence. Here we discuss some of the different EVD management settings, the type of care that was provided and the impact that these differences may have had on patients' outcomes.

Table 4.2 describes the variation in care across the three most affected West African countries at low and high resource centres, and those repatriated or treated within Europe and the United States. There was a wide variation in reported mortality rates. However, the heterogeneity of populations studied, demographics, geography, time period (early versus late in the outbreak), survivor bias (only

Table 4.2 Examples of management in Ebola care facilities—West African Ebola outbreak

Location/phase of outbreak	EHU/ETC/ECC	Organization	Patient characteristics	Resources/management strategy	References
Kenema, Sierra Leone EARLY Rural	Government hospital, EHU, ETC	MoH WHO	Local walk in and regional referrals. One of few ETCs available early in the outbreak, high burden area. Severe cases. High mortality (74%)	Low. Haematology and biochemistry possible. IV fluids for all patients. Antibiotics for most (93%). Anti-malarials for 55%	Schieffelin et al. [4]
Kailahun Sierra Leone EARLY Rural	EHU, ETC	MoH	Local walk in and regional referrals. Often presented late or already died in transport due to distance. Only 1 ambulance for three million population. 53% mortality	Low. No labs or IV fluids. Supportive and symptomatic care—ORS, antibiotics, anti-pyretics	Dallatomasina et al. [5]
Freetown Sierra Leone EARLY Urban	Government hospital, EHU	MoH KSLP	Local walk in and referrals. High burden area, patients with comorbidities. All confirmed cases referred to ETCs. Overall mortality—39% (unpublished data)	Low. IV fluids in some cases. Antibiotics and anti-malarials for all. Only HIV and malaria RDT possible, later in the outbreak	Lado et al. [6]
Conakry Guinea EARLY Urban	Two sites: ETC and government hospital	WHO MoH MSF	Walk ins and referrals. First ETC of outbreak. High burden. Mortality 43%	Low. POC labs for some. WHO/MSF protocolised care but poorly staffed limiting interventions. 72% IV fluids (average 1 L/24 h), all antibiotics, 18% anti-malarials	Bah et al. [7]
Hastings Sierra Leone MID Peri-urban	Military, ETC	MoH MoD (SL)	Referrals, confirmed cases only. Lower mortality (32%) reported than some concurrent studies but may be related to selection of patients (possible survivor bias). High burden area	Low. No labs. HIV and malaria RDT possible. Strict 72 h regime of IV fluids (500 mL R/L, 500 mL 5% dextrose alternating every 8 h, IV Antibiotics, IV anti-malarials, then switch to oral. NSAIDs, multivitamins, ORS and fruit juice	Ansumama et al. [8]

(continued)

Table 4.2 (continued)

Location/phase of outbreak	EHU/ETC/ECC	Organization	Patient characteristics	Resources/management strategy	References
Monrovia Liberia MID Urban	ETC	MSF	Walk ins and referrals. High burden	Low. No Labs. High patient: physician ratio (30–50:1) limited IV fluid use. Treated according to staging: clinically hypovolaemic but not in shock and self caring—antiemetic, anti-diarrhoeal, ORS; hypovolaemic, shocked and unable to self care—IV fluids; shock and organ dysfunction whose outcome would not be altered by medical intervention—no treatment	Chertow et al. [9]
Waterloo Sierra Leone MID Peri-urban	ETU	Chinese military	Referred and confirmed cases Mortality 69%, possibly from late presentations	Low. No labs. Protocolised WHO treatment given according to clinical judgement: anti-malarial, IV fluids, Antibiotics. High patient:staff ratio	Qin et al. [10]
KerrytownSierra Leone LATE Rural	EHU, ETC	Save the Children DFID	Mostly referral patients, confirmed cases. Lower mortality (37%), may be related to later phase of outbreak, patients referred earlier or survivor bias, better staff:patient ratio and improved monitoring	Medium: access to laboratory monitoring and relatively well-staffed. Treated according to staging of patient (decided by WHO and UK-MoD). Stage 1: ORS, multivitamins, antimalarial if RDT +ve, targeted electrolyte and glucose therapy. Stage 2: IV fluids 3–6 L/24 h IV antibiotics. Stage 3: sedation/anti-epileptics, vitamin K, FFP	Hunt et al. [11]
Kerrytown Sierra Leone LATE Rural	ETC	UK MoD	Referred positive cases. Health care workers only initially. Mortality 44%	High. Labs available. Monitoring-CVP line under ultrasound guidance (to reduce repeated venepuncture), catheter and bowel management	Clay et al. [12] O'shea et al. [13] Nicholson-

				system. IV fluids on all, I-O and vasopressors available. Blood products administered -FFP, cryoprecipitate, platelets, convalescent whole blood and packed red cells, tranexamic acid and vitamin K. Anti-helminths, anti-malarials and wide selection anti-microbials. Symptomatic management—analgesia, ranitidine, omeprazole	Roberts et al. [14]
US and Europe Whole outbreak	15 hospitals with isolation room in 9 countries	Local country institution	24 of 27 cases contracted in West Africa. 18 already started treatment while in WA 18.5% mortality	High. Treatment according to local protocol. Nearly all received IV fluids and, electrolye supplements. Nine received non-invasive and invasive vent, five renal replacement. Fifteen parenteral nutrition. Only 15% (4 pts) did not receive experimental interventions. Antibiotics, antimalarial, antiemetic, few anti-diarrhoeal. Also, blood, FFP, and platelet support. Of five critically ill with multiorgan failure—invasive vent and CRR, three died. Eight received vasopressors, five died. Trans cut pacing-1, none CPR	Uyeki et al. [15]

EHU Ebola Holding Unit, *ETC* Ebola Treatment Centre, *ECC* Ebola Community Centre, *WA* West Africa, *POC* point-of-care, *DFID* Department for International Development, *MoH* Ministry of Health, *WHO* World Health Organisation, *KSLP* King's Sierra Leone Partnership, *ORS* oral rehydration solution, *MSF* Médecins Sans Frontières, *RDT* rapid diagnostic test, *NSAIDs* non-steroidal anti-inflammatory drugs, *IV* intravenous, *SL*, *FFP* fresh frozen plasma, *CVP* central venous pressure, *I-O* intraosseous, *CPR* cardiopulmonary resuscitation, *vent* ventilation

patients who made it as far as hospital settings were included) most likely explain most of this variation, rather than the effect of differing management strategies. Therefore, drawing a meaningful conclusion from these mortality trends about the effect of treatment strategies is very difficult, though expanded access to staffing, therapeutic monitoring, blood product support, and critical care is almost certainly contributory to improved survival.

There was a range of the care delivered from differing facilities across the world. As aforementioned, the most recent WHO manual outlines categorizing the patients into mild, moderate and severe, however, this was not available at the start of the outbreak and many centres used their clinical judgment to determine appropriate therapy. Additionally, there was variation across laboratory testing, diagnostic abilities, clinical management and discharge criteria. This was due to multiple factors including the human resource and funding allocation, geography of the unit and specific patient factors (such as time of day they presented and agitation levels) which affected the safety of procedures.

A key component to the MOHS operational plan for country preparedness was the establishment of isolation facilities at every hospital admitting suspected, rather than just confirmed cases. EHU's such as at Connaught Hospital in Freetown provided a point of access to basic health care where unfortunately in practice the highest levels of management generally only reached intravenous lines and IV fluid and antibiotic therapy, due to resource constraints, leaving laboratory testing and closer monitoring to the ETCs. Isolation in these facilities was expected to be for less than 24 h, while waiting for blood results and transfer, however, patients were often waiting much longer due to delay in diagnostics and limited bed availability and thus received basic care for this period of time. Additionally, at the height of the outbreak when the number of suspected cases exceeded bed availability, there were many patients who were forced to wait outside hospitals, ETCs or at home, receiving only ORS, until a beds became available. It is clear now that this time window was critical for patient resuscitation and the ability to check laboratory results and correct electrolyte imbalances would have been of significant benefit.

Even once a patient reached an ETC, the level of care differed widely. For example Kenema ETC, in the East of Sierra Leone, one of the first ETCs set up by MSF and a 5 h drive away from the EHUs in Freetown was able to perform basic laboratory tests but often was so overburdened with cases that optimal management was challenging. However, in Kerrytown, Sierra Leone, where the British funded two ETC sites, one staffed by Save the Children and the other through the Ministry of Defense, patients could receive a higher level of care from onsite laboratory services measuring and correcting electrolyte imbalances and a lower patient to staff ratio allowing more time and a safer environment for monitoring and delivering intravenous fluid resuscitation. Unfortunately, epitomizing the global delay in rapid response to the outbreak, Kerrytown opened in late November 2015 providing a mere two months of care during the height of the outbreak. In addition, the UK MoD ETC at Kerrytown limited its patients through selecting only health care workers who had become infected, and with a high level of resources were able to do all

supportive interventions apart from intubation and ventilation and renal replacement therapy.

From the review conducted by Ukeyi et al. [15] on the care of 27 patients with Ebola in the US and Europe, it is clear that in all centres regular monitoring and laboratory testing were available and management was tailored to results. Five patients received renal replacement therapy, nine received non-invasive and invasive ventilation and transcutaneous pacing was conducted on one patient. None of the patients in any of the settings received cardiopulmonary resuscitation as it was deemed that once a patient had lost cardiac output, resuscitation would be futile.

4.1.4 Management and Controversies Surrounding Specific Complications (Table 4.3)

4.1.4.1 Fluids and Electrolytes

At the start of the outbreak there was reluctance to provide intravenous fluid therapy mainly due to the risk to health care workers and challenges surrounding observing patients for bleeding complications, and therefore oral rehydration solutions were relied upon. However, over the course of the outbreak there developed an understanding of the mechanisms of death from Ebola through shock, with high lactate (values reported as ranging from 4 to 10 mm/L [20]), hypoxia from late multi-organ failure, renal failure and electrolye imbalances, in particular hypokalaemia from diarrhoea. This led to a consensus that the basic principles of resuscitative supportive care should be applied with aggressive management of intravascular volume depletion, the correction of electrolytes and prevention of complications associated with shock (Hunt et al). In one well-documented case managed in a German Intensive Care setting, diarrhoeal output exceeding 8 L in 24 h was reported, with intravascular collapse, and was managed aggressively with fluid repletion (7–13 L per day). Intravascular leak did occur (pleural effusions, pericardial effusion, ascites) but overall, the treatment was successful [21]. Certainly Dallatomasinas et al. [5] noted that 95% of deaths occurred within 10 days of admission, when supportive therapy is most likely to impact survival. There still is, however, uncertainty on how much, what type and how fast, fluid should be given promoting suggestions that further research is required in these areas, to optimize simple interventions, including resuscitation with a pre-mixed Ebola specific fluid [22]. There were very few complications related to fluid overload in the West African setting, and Perner et al. [22] commented on minimal capillary leak and less hypoxaemia/ARDS than in Western sepsis, suggesting that perhaps not enough fluids were given as opposed to too much. Unfortunately, the challenges faced from high patient to staff ratios, limited time inside the unit and concerns over bleeding risks through IV cannulation, (although clinically significant gastrointestinal bleeding was reported in less than 5% [9]) meant that patients were likely not receiving optimal medication.

Electrolyte disturbances are common in EVD, although electrolyte monitoring was not widely available in West African holding units and treatment centres. Case

Table 4.3 EVD complications and interventions

EVD complications		Interventions			
Complication	Notes	WHO standard	Optimal care	Controversies/unknowns	References
Respiratory problems					
Respiratory distress	Common	Consider treatable causes. Monitor saturations, provide O_2 if <90%, if available	Ventilatory support; consider fluid overload	Reluctance to offer invasive ventilation in higher resource settings is controversial as case reports support use.	[15, 16]
Circulatory problems					
Dehydration	Common, may be severe	ORS, IV fluids if severe, monitor input	Precise fluid balance monitoring	Role for CVP monitoring; Aggressive IV therapy may lead to fluid overload; Type of fluid most efficacious; Role of loperamide for severe diarrhea if no evidence of paralytic ileus	[17]
Shock	Multi-factorial, uncommonly due to haemorrhage	Reverse hypovolaemia, treat sepsis	Inotropic support if fluid resuscitation ineffective	Amiodarone trialed at one NGO Hospital	
Haemorrhage	Variable presentation, rarely the cause of shock or hypovolaemia	Consider transfusion of whole blood, containing clotting factors, vitamin K, blood transfusion, fresh frozen plasma, tranexamic acid	Monitor Hb, HCT and coagulation and provide targeted treatment	Role of Vitamin K and transexamic acid	
Anaemia	Not common	Assess clinically	Measure Hb Treat if severe	Role of transfusion, threshold to treat	

Renal problems					
Acute Kidney Injury/Renal failure	Common in severe disease; associated with mortality	Monitor urine output, avoid NSAIDs	Renal replacement therapy (RRT) may be required, optimize fluid balance, treat reversible causes e.g. hypovolaemia	Reluctance to offer RRT in higher resource settings is controversial as case reports support use.	
Acidosis	Common	Correct hypovolaemia and treat sepsis	Monitor bicarbonate, lactate, consider organ dysfunction		
Gastrointestinal problems					
Hepatitis/Liver failure	Hepatitis is common and associated with poor outcomes	Avoid concomitent hepatotoxic drugs	Monitor LFTs		
Dyspepsia +/− Gastric ulceration	Common	PPI e.g. omeprazole, ranitidine, Magnesium trisilicate		Not evidence based	
Vomiting and diarrhoea		Antiemetics e.g. Ondansetron If bloody diarrhoea—metronidazole	Test for other infective causes for which targeted treatment may be given	Role of routine broad spectrum antibiotics	[9]
Neurological syndromes					
Anxiety/ Agitation	Common	Reassurance, environmental modification, Haloperidol/ benzodiazepines if severe	Psychological support		
Convulsions	Commonly reported-consider hypoglycaemia, hyperpyrexia and electrolyte disturbance	Anticonvulsants, Dextrose, electrolyte correction	Anticonvulsants		
Encephalopathy	Common—end stage	Extra nursing care, consider sedation, consider thiamine deficiency	Consider CSF analysis		[18, 19]

(continued)

Table 4.3 (continued)

EVD complications		Interventions			
Complication	Notes	WHO standard	Optimal care	Controversies/unknowns	References
Pain	Common	Analgesia: 1st line Paracetamol, 2nd line tramadol, 3rd line morphine; avoid NSAIDS/aspirin	Analgesia	Concern about respiratory depression with morphine	
Electrolyte disturbances					
Hypokalaemia	Common	Potassium supplementation orally+/− IV, IV magnesium	Regular electrolyte monitoring and replacement	As both hyper and hypokalaemia are possible, electrolyte monitoring is increasingly considered essential	[11, 12]
Hyperkalaemia	May accompany renal failure	Insulin and dextrose if severe	Consider need for RRT	As above	
Hypoglycaemia	May be common in children	Point-of-Care glucose monitoring ORS, oral glucose, IV dextrose may be required	Regular monitoring, Dextrose supplementation of IV fluids if required, Nutritional assessment/ support		

ORS Oral rehydration salts, *IV* Intravenous, *CVP* Central venous pressure, *HCT* Hematocrit, *NSAIDS* Non steroid anti inflammatory drugs, *LFT* Liver function test, *PPI* Proton pump inhinbitors, *CSF* Central system fluid, *RRT* Renal replacement therapy

series have highlighted variable potassium requirements in EVD. In a series from Kerrytown, Sierra Leone, 33% patients had potassium abnormalities—with similar proportions having hyper- and hypokalaemia, highlighting the need for point of care monitoring to direct therapy [11]. Hyperkalaemia was associated with acute kidney injury and mortality. In the same series, hyponatraemia was also prevalent, in over 30% patients.

4.1.4.2 Intubation, Ventilation and Haemodialysis

There has been controversy over the appropriateness of intubating and ventilating patients with Ebola. In November 2014, a meeting was convened by the Chief Medical Officer of the UK, Dr. Sally Davies, to review the evidence surrounding critical care for patients with EVD. Subsequently, a statement was published concluding that there was "no evidence that addition of ventilatory or renal support would result in substantial overall benefit for patients who receive the optimum supportive care for Ebola" (Jacobs M, Beadsworth M et al. Provision of Care for Ebola. Lancet 2015, https://doi.org/10.1016/S0140-6736(14)62250-9. However, this was met with a rebuttal [16, 23] summarizing the evidence from case reports in USA and Germany, where five of eight patients who received critical care interventions made a complete recovery. Those who died had received critical care late in their illness. Additionally, the CDC and international nephrologists stated that performing haemodialysis in Ebola was safe, with no virus detected in dialysis effluent [24]. The UK's Ebola referral hospital, the Royal Free, is now prepared to perform haemodialysis and intubation. There are still no standardised guidelines for use in high income settings, however, the current recommendations are that organ support should be available but that interventions should be limited with a do not resuscitate (DNR) order place.

4.1.5 Specific Treatments

There are no specific treatments with proven efficacy for Ebola. The rapid and unpredictable onset of EVD outbreaks, together with their often remote location and hazards to health workers prove a major challenge to therapeutic trial implementation. A series of eight symptomatic patients in Kikwit, in 1995, given convalescent whole blood, was the largest reported attempt at a an Ebola therapeutic intervention study, prior to the West African Ebola outbreak [25].

However, this has been a rapidly evolving field. The scale and duration of the West African EVD outbreak, involving patients in urban and high resource settings, provided the opportunity and incentive for accelerated research into therapies and clinical trials.

Efficacy studies to date have consisted of:

1. In vitro and animal studies
2. Case reports/small case series of occasional or "compassionate" human use
3. Phase II clinical trials

Interventions have been either post-exposure prophylaxis (PEP) in asymptomatic exposed individuals, and/or treatment in symptomatic cases.

Candidate drugs that have made it into human clinical use currently fall into four categories:

1. Novel specific antiviral agents e.g. small interfering RNAs
2. Repurposed anti-infective agents, e.g. favipiravir
3. Other repurposed agents e.g. amiodarone
4. Specific immune therapies, e.g. convalescent plasma, convalescent whole blood, monoclonal antibodies such as ZMapp

In summary, an impressive effort to generate human trial data on therapeutic inventions, the results of which are summarized in Table 4.4 (taken from Brown [34]) has to date identified no clearly efficacious agent.

There was a reluctance to attempt double-blind, placebo-controlled trials, for questionable ethical and logistical reasons (see Lanini [35]—this includes a good review of clinical trials and a discussion of the ethical issues). An opportunity to collect data on the efficacy of supportive interventions e.g. threshold for IV fluids, loperamide for diarrhea, was largely missed due to inadequate human resources, and no systematic controlled studies of such were performed to our knowledge. As EVD is most likely to affect the low income setting in future, further research into interventions, such as the safety of intravenous lines, usual care versus laboratoryguided care, effectiveness of anti-diarrhoeals, empirical antibiotics and oral potassium supplements would be beneficial. Provisional plans for trials should be agreed prior to the next outbreak, to improve rapid implementation when the need arises.

This is a moving field and more trial data is likely to be available in the upcoming years. We suggest consulting the following useful resources for up-to-date information:

https://ebolaclinicaltrials.tghn.org
http://www.ukcds.org.uk/resources/ebola-research-database
http://www.who.int/medicines/ebola-treatment/emp_ebola_therapies/en/
https://clinicaltrials.gov

4.1.5.1 Novel Specific Antiviral Agents

Small interfering RNAs, have shown potential in treatment and prevention, in non-human primates and humans. TKM-100802 (by Tekmira), was fast-tracked due to encouraging animal and phase 1 data for a clinical study in Sierra Leone. However, the trial was terminated early, as demonstration of efficacy was deemed unlikely, and the product discontinued by the manufacturer [29]. Other siRNA molecules are in development with encouraging data efficacy in non-human primates (limiting symptoms, abrogating mortality—siEbola-3, see Thi [36]).

Brincidovir, a small molecule nucleotide analogue, orally available lipid conjugate of Cidofovir (Chimerix, Inc.), was used occasionally in repatriated patients and in an open-label, single arm phase II clinical trial (in Liberia) which stopped early,

Table 4.4 Summary of published evidence available for the use of novel therapeutic agents with potential anti-EVD activity

Trial (References)	Design	Sites	Patients	Enrolment dates	End point reached	Outcome
Brincindofovir [26]	Single-arm phase 2 trial	1	4	January 1, 2015 to January 31 2015	No—trial terminated	All four enrolled patients died
Favipiravir-JIKI [27]	Single-arm phase 1 trial	4	126 (540 historic controls)	December 17, 2014 to April 8, 2015	No—reported differently	Nuanced conclusions; limited tolerability
Favipiravir-Jui [28]	Single-arm phase 2 trial	1	39 (85 historic controls)	November 1, 2014 to November 10, 2014	Not applicable: reported as a retrospective clinical case series	Survival rate 56% [22/39] intervention versus 35% [30/85] controls; $P = 0.027$
TKM-Ebola [29]	Single-arm phase 2 trial	1	14 (3 cohorts, observational)	March 11, 2015 to June 15, 2015	Yes—stopped due to futility	No survival benefit
ZMapp (PREVAIL II) [30]	Randomised-controlled (non-blinded) trial	11	36 (35 controls); Guinean patients received favipiravir; unclear if matched	March 1, 2015 to November 1, 2015	No—stopped early due to low EVD case numbers	Mortality rate 37% [13/35] intervention versus 22% [8/36] controls; posterior probability = 91.2%
Convalescent plasma [31]	Non-random comparative study	1	99 (507 controls)	February 17, 2015 to August 3, 2015	No—also uncertain if neutralising antibody present	Mortality rate 38% [158/418] intervention versus 31% [26/84] controls; $P = 0.92$ after age/Cycle Threshold value (CT) adjustment
Convalescent whole blood [32]	Non-random comparative study	2	44 (25 controls who consented for the study but did not agree to the intervention)	December 2014 to April 2015	Not applicable: reported as a clinical case series	Unadjusted case fatality rate 27.9% intervention versus 44% control
Interferon β-1a [33]	Single-arm, proof-of-concept study	1	9 (21 historical controls and a further 17 historical controls matched for age and baseline viraemia)	March 26, 2015 to June 12, 2015	No—low EVD case numbers limited the trial to a pilot study	Unadjusted hazard ratio for treatment = 0.27 [95% CI 0.08–0.94]; $P = 0.039$. However, increased to 0.79 when adjusted for viral load.

ORS Oral rehydration salts, *IV* Intravenous, *CVP* Central venous pressure, *HCT* Hematocrit, *NSAIDS* Non steroid anti inflammatory drugs, *LFT* Liver function test, *PPI* Proton pump inhinbitors, *CSF* Central system fluid, *RRT* Renal replacement therapy

after allocation of only four patients, after termination of manufacturing by Chimerix [26].

4.1.5.2 Repurposed Drugs

Favapiravir (Toyama, Japan), is a broad spectrum anti-viral, approved for treatment of influenza, in Japan. A therapeutic effect was reported in Ebola virus-infected mice and supported by relatively good outcomes in some cases of occasional human use in repatriated patients (PEP and treatment). Since then two historically-controlled, open-label, single arm phase II clinical trials have been undertaken: a multi-centre study in Guinea (the JIKI trial, see Sissoko [27]) and a single-centre study in Freetown, Sierra Leone [28]. Conclusions are limited by the chosen study design and the challenges of trial implementation under the circumstances. The former, larger study did not demonstrate a treatment effect of favapiravir on mortality, whereas the latter reported survival benefit and viral load reduction in treated patients. Together these results support prioritization of a randomized placebo-controlled trial of Favapiravir, when the opportunity presents.

4.1.5.3 Specific Immune Therapies

There is some evidence (and a widely held belief) that an Ebola-specific antibody response is protective, providing the rationale for attempted treatment and prevention with Ebola virus-specific antibodies. Specific monoclonal antibodies were available but in short supply and were not easily amenable to rapid scale up. One such antibody cocktail, ZMapp, was initially used compassionately in repatriated patients and when increased supply became available, the only randomized control clinical trial was performed, in US, Guinea, Liberia and Sierra Leone. The results suggested that there was some evidence of treatment effect, and again this agent will certainly be a likely candidate for prioritization in any future outbreaks [30]. Other monoclonal antibodies, (ZMab and MIL77) were also used in selected cases as PEP [37]. Due to encouraging results during the earlier Kikwit outbreak (albeit in selected patients, see Mupapa [25]) there was considerable enthusiasm for a trial of convalescent plasma and/or whole blood from EVD survivors. Phase II trials were commenced in Guinea and Sierra Leone, but neither trial recruited enough patients, and the Guinea trial did not ascertain whether any neutralizing antibody was present [31, 32]. Additionally, a pilot study of interferon β-1a for EVD enrolled only 9 patients in the intervention arm (reference Konde et al Plos One 2017 Interferon β-1a for the treatment of Ebola virus disease: A historically controlled, singlearm proof-of-concept trial. It remains to be seen whether there are long term side effects or other consequences of therapeutic manipulation of the natural immune response to EVD.

4.1.6 Conclusion

It is difficult to assess the effect of different interventions on outcomes, due to the lack of formal studies involving rigorous prospective data collection and appropriate

controls. The epidemiology of the disease and the response changed significantly, and so historical comparisons are relatively unhelpful. We have concluded that, in the absence of evidence and the lack of opportunity to generate evidence, it should be the priority to optimize supportive therapy, including intensive care therapy when available. Other specific interventions may be used when they are readily accessible, likely to provide benefit based on extrapolation from other diseases, and very unlikely to do harm, in pragmatic studies. Other interventions, including novel drug therapies and immunotherapies should be evaluated in randomized, adequately controlled clinical trials, prior to use.

4.2 Ebola Virus Disease in the Obstetric Population

Diana Garde and Emily Headrick

4.2.1 Introduction

Care for the pregnant and postpartum patient in the context of an Ebola Virus Disease (EVD) epidemic presents unique and challenging clinical, ethical and logistical considerations. Since the first recognized epidemic of EVD in Zaire in 1976, subsequent outbreaks have occurred in Sub-Saharan Africa (SSA) [38] where access to robust maternal health care services has been limited. An EVD epidemic superimposed on an already weakened health system further exacerbates extremely poor outcomes for the obstetric population. In general, 15% of all women are expected to experience obstetric complications [39]. The 2013–2015 West African EVD epidemic is the largest to date, with approximately 27,500 cases in three countries—Guinea, Sierra Leone and Liberia. Prior to the 2013–2015 EVD epidemic, these countries demonstrated some of the worst health care indicators due to inadequate infrastructure, human resources and lack of access to basic medical resources [40–43]. In Sierra Leone, it is estimated that prior to the EVD epidemic, one in every 21 women would die in childbirth-related incidents in her lifetime, [44, p. 34] with the maternal mortality ratio at 1630 per 100,000 live births in 2010—the highest in the world [45]. In addition, all three countries fell within the lowest density of medical personnel per capita, resulting in the smallest and least-skilled healthcare workforce in the world [46]. Both the number of in-hospital deliveries and cesarean sections declined as the incidence of EVD increased [47]. Ultimately, it was predicted at the end of the epidemic in West Africa, that the greatest impact of EVD would be on maternal health due to the loss of medical staff to Ebola (physicians, midwives and nurses). By September 2015, the three countries had lost 513 medical personnel from their already significantly small workforce [48]. From that data, it was estimated that there would be an increase of at least 38% (Guinea) and as much as 111% (Liberia) in maternal mortality [49].

It has been asserted that women are at an increased risk for EVD infection, both physiologically and socioculturally. Traditionally, they are the caregivers for ill family and community members, and they responsible for burying the dead, and as such have significant potential for interaction and contact with the virus via body fluids [50]. If a woman is pregnant during an EVD epidemic, routine health care encounters for antepartum or intrapartum care places women at high risk for exposure to infected patients also seeking care. There is a higher prevalence of female medical staff, namely nurses and midwives, both inside government facilities and in the community who would then be more likely to have (knowingly and unknowingly) direct contact with positive EVD patients in an epidemic. In addition, females in SSA have historically had less authority over their reproductive health and are at higher risk of gender based violence or coercion [51]; sexual intercourse with an infected or surviving male also places women at increased risk of infection [52]. Natural immunosuppression occurring in pregnancy [53] may play a role in a higher acuity of illness observed in presenting obstetric patients with positive EVD, contributing to very poor maternal outcomes. Considering the expectation of an excess of 1.3 million pregnancies per year [54] across Guinea, Sierra Leone and Liberia, a significant number of women who had direct contact with the virus were either pregnant or postpartum.

During the 2013–2015 West African EVD epidemic, pregnant women presenting for health care services—either for routine peripartum care or in the event of obstetric complications—often met case definition for EVD (see Table 4.5).Where proactive clinical management would have been appropriate in a non-epidemic

Table 4.5 Clinical and epidemiological factors in initial EVD case definition screening

Clinical presentation	Epidemiological factors
Considerations for screening for general populations	
Early: fever, profound weakness or malaise, headache, myalgia, arthralgia, conjunctivitis, nausea or anorexia, throat pain or difficulty swallowing, abdominal or epigastric pain, diarrhea (bloody or nonbloody)	Exposure/Contact: infected animals, bushmeat or fruit also fed on by bats, healthcare workers/ traditional healers also treating EVD, items soiled or touched by positive EVD patient, deceased EVD bodies Sexual intercourse with EVD-positive male or EVD survivor
Late: confusion and irritability, hiccups, seizures, chest pain, diarrhea (watery or bloody), vomiting (with or without blood), skin rash, internal or external bleeding, shock, respiratory distress	
Additional considerations for screening obstetric population	
Vaginal bleeding of unknown origin, spontaneous abortion, premature labor and/or rupture of membranes, preterm labor, antepartum and postpartum hemorrhage, intrauterine fetal demise, stillbirth, loss of consciousness	Exposure to products of conception or deceased fetus of EVD positive patient Being a pregnant woman with history of contact with confirmed EVD patient, recent EVD survivor with an intact pregnancy, newborn of an EVD positive mother, infant breastfed by a recent EVD positive mother

WHO Library Cataloguing-in-Publication Data [55]

setting, women were often left untreated or were provided minimal intervention by frightened medical staff working in an overwhelmed, under resourced health care system in crisis. Even as the emergency response resources became more established, an unfortunate number of women were isolated based on presenting symptoms; the majority of these women ultimately tested negative for EVD, yet they languished and died in EVD isolation centers due to the limitations of obstetric interventions available in this setting. *It is in this context that clinical care for obstetric patients in an EVD setting be specifically considered.* Culture, health infrastructure, access to resources, geography and physiology are all complex forces that must be considered when managing individuals and populations alike. Treatment of the pregnant or postpartum patient who meets case definition for EVD should be offered without haste and with the highest level of quality interventions possible, while maintaining safety of healthcare workers and the community.

This chapter aims to achieve the following objectives, informed by previous research on EVD outbreaks and by field experiences from the 2013 to 2015 West African EVD epidemic:

- Examine the unique risks and needs of the obstetric patient in the context of the an EVD epidemic
- Review clinical management of the obstetric patient infected with EVD as well as the unconfirmed or suspect obstetric patient being managed in a Red Zone (RZ) setting
- Provide technical guidance for establishing a safe and effective setting for triage, screening, isolation and treatment of the pregnant patient and mother/baby dyads.

4.2.2 Clinical Presentation of EVD in Pregnant Women

4.2.2.1 Signs and Symptoms

One of the key challenges when evaluating a pregnant patient in the context of EVD is that symptoms suggestive of EVD infection (i.e. abdominal pain, vaginal bleeding) may mask a true obstetric emergency. Conversely, the clinical presentation of what initially appears to be an obstetric complication often confounds the accurate identification of potential EVD infection. However, EVD infection can be the precursor to obstetric complications and a patient presenting for care may in fact require appropriate interventions for both.

The basic evaluation of suspected EVD patient must consider both clinical presentation (signs and symptoms) *and* an accurate history to evaluate risk of exposure. Due to this unique overlap in symptom presentation for the pregnant patient, additional considerations for the obstetric population must be made in addition to the general screening (Table 4.5).

It is of note that not all EVD-infected patients presented with or manifested a febrile state during their illness. It is estimated that only between 66% [56] and 89% [57] of patients actually presented with fever greater than 30 °C. Likewise, patients did not regularly demonstrate coagulopathies or overt hemorrhagic symptoms [57], as is frequently assumed as a common presentation for a viral hemorrhagic fever, with only one study finding these as a presenting symptom in only 35% of patients [56]. In the 2013–2015 West African EVD epidemic, it was frequently observed that EVD-positive pregnant patients were presenting with tachypnea and tachycardia, sometimes in the absence of any other symptoms, and could be repeatedly seen "hitting the floor," or favoring a position on the floor rather than in bed. It is postulated that this behavior may be due to agitation, or to alleviate fever by lying on a cool surface, but was routinely observed among this population [55]. Although many guidelines for screening include fever and bleeding as dominant symptoms in the algorithm, suspect cases can present without either and EVD illness can be missed during initial clinical evaluation. In fact, there are multiple documented cases of pregnant women with known EVD exposure and/or infection who do not manifest these common symptoms as expected.

In these cases, the potential for an EVD positive fetus/neonate is 100%, thus increasing the risk to unsuspecting healthcare workers during routine intrapartum care [58].

The majority of obstetric complications outside of an EVD epidemic involve the following: postpartum hemorrhage (PPH), antepartum hemorrhage, obstructed labor, postpartum sepsis, complications of abortion, severe preeclampsia or eclampsia, ectopic pregnancy and ruptured uterus [39]. In 2010, approximately 440 women in SSA died each day as a result of obstetric complications, the majority from PPH [59]. In addition, the stillbirth rate in SSA is approximately 10 times higher than in developed countries at 29/1000 [60]. As such, an EVD-negative obstetric patient can easily meet current WHO case definition, resulting in the isolation and testing of a high proportion of women who are actually in need of basic obstetric care.

Given that overlap of presenting symptoms may be commonly seen in both EVD and non-EVD obstetric cases, astute clinical decision making is required to ensure that obstetric patients are not being overwhelmingly screened and disproportionately isolated for EVD when the absolute risk in the community is low. Conversely, great effort must be made to ensure that symptomatic obstetric patients are not being treated outside of isolation when the absolute risk of EVD is high. In West Africa, it was estimated that only 1.5% of the pregnant patients admitted to isolation were EVD positive; the 98.5% who were not merely needed intervention for obstetrical complications or normal delivery [61].

4.2.2.2 Epidemic Screening Case Definition

Epidemic: In an epidemic setting it can be argued that the likelihood of infection transmission or the public health risk from EVD is greater than the risk of morbidity or mortality from obstetric complications. You must first consider general screening for the basic symptoms of EVD infection, with additional symptoms to be considered for the obstetric patient (Table 4.6):

Table 4.6 Additional symptom screening criteria for the obstetric population, active EVD epidemic

General screening	Obstetrical considerations
Does the patient have: Fever and 3 or more symptoms History of contact and fever History of contact and one or more symptoms	Or, any of the following: Spontaneous abortion (SAB) Pre-labor rupture of membranes Preterm labor Ante, intra or postpartum hemorrhage Intrauterine fetal demise (IUFD) Stillbirth Neonatal death Survivor with intact pregnancy in labor or postpartum Pregnant and contact (asymptomatic)

WHO Library Cataloguing-in-Publication Data (2016) [55]

Any of these additional obstetrical complications, particularly in combination with symptoms included in routine EVD screening, should warrant isolation and polymerase chain reaction (PCR) testing. In addition, screening methods must capture any patient who presents to a healthcare facility who has recovered from EVD with an intact pregnancy and is in labor or in the immediate postpartum period. Given the absolute likelihood of viremia in products of conception from a patient who recovered from EVD while pregnant, delivery must take place in isolation.

4.2.2.3 Non-epidemic or Post-epidemic Case Definition

In a post-epidemic setting the general screening criteria changes, but the obstetric screening considerations remain largely the same. Contrary to epidemic settings, the risks of poor obstetrical outcomes are overwhelmingly thought to outweigh the risk of EVD infection or transmission of disease; strong clinical judgment should be employed.

In the general population, initial screening uses fever as a determinate for case definition. This tool is used for any acute hemorrhagic fever (Table 4.7).

Table 4.7 Additional symptom screening criteria for the obstetric population, non-epidemic/post-epidemic

Non-EVD epidemic general screening	Obstetrical considerations
Does the patient have: Persistent fever for 2+ days despite treatment? And unexplained bleeding, or Clinical suspicion	Or, are there any of the following: Spontaneous abortion (SAB) Pre-labor rupture of membranes Preterm labor Ante, intra or postpartum hemorrhage Intrauterine fetal demise (IUFD) Stillbirth Neonatal death Recent survivor with intact pregnancy in labor or postpartum Pregnant and known contact with someone with active EVD (even if patient is asymptomatic)

Clinical Guidelines/Wall Charts. Adapted from revised WHO and MSF guidelines Oct/Nov/Dec 2014/Jan/Sept–Oct 2015) Revised Oct 30, 2015

The fever must have persisted despite treatment with appropriate medications for the symptoms (i.e. treatment for presumed malaria), prescribed by a qualified medical professional. The patients meeting criteria must be isolated and PCR tested.

Pregnant women pose a challenging dilemma during the initial months after an epidemic has been declared over. Those who conceived during the epidemic could potentially carry an EVD infected fetus into a post epidemic setting given the average 40 weeks of gestation. In a post-epidemic setting however, one might argue for a higher level of scrutiny and clinical judgment prior to admission. The singular obstetric complication alone as criteria for admission for EVD testing cannot be justified given the numbers of patients that present for care for PPH, IUFD and SAB under non-epidemic conditions.

4.2.3 Establishing Triage and Screening

4.2.3.1 When to Isolate

In either an epidemic or post-epidemic setting, obstetric patients with *highly concerning* presenting symptoms should be admitted for testing in isolation, regardless of whether they fit the established criteria. Consultation and collaboration is recommended with other obstetric providers, surveillance officers, and EVD medical professionals who should be made aware of these cases.

4.2.3.2 General Principles of Triage and Screening

The evaluation and planning for a patient presenting with symptoms of EVD is wholly dependent on whether there is a declared epidemic present, or if there are definitive laboratory-confirmed positive cases in the population. Where there is any concern for EVD or other hemorrhagic fevers, triage and screening should be established at the entry point to every tier of health care facility in the affected area per guidance of government mandates or international recommendation.

4.2.3.3 Screening Upon Presentation to a Clinical Facility

During a declared epidemic or in cases where there is a high suspicion of infection, an obstetric-specific screening area should be staged at all peripheral health units, community clinics, and hospitals (i.e. anywhere obstetric patient may present). All pregnant, postpartum and lactating women should have an accurate temperature taken, and basic and obstetric-specific screening questions addressed before entry to the facility. Trained maternity nurses should complete the initial screening and evaluation to allow for experienced clinical judgment in this special population.

Ideally, screening should be operational for as many hours in a day as the facility is active. Staff should have clear protocols for documenting patient information to ensure multiple opportunities for confirmation of triage status upon entry into the health care encounter. We recommend standardized forms that can be made in duplicate or triplicate for record keeping. Staff should also have ways and means

of communication to other colleagues so as not to leave the triage post in the event of a positive screen, an emergency in triage, or need for consultations or technical/operational support. This station should have access to electricity or reliable lighting, and a source of water for hand washing stations and cleaning.

While the triage area should ideally remain a calm environment for efficient yet thorough screening, the possibility of emergent screening is eminent. Triage staff should be prepared to prioritize emergent or critical cases while adhering to screening protocol and ultimately prioritizing safety for themselves, colleagues and patients in the immediate surrounding area. Patients may present to the facility in critical condition on foot, by private car or by ambulance from another facility. If the patient is unconscious or unable to give a clear history of the present condition, immediate isolation should be the most likely triage decision. If family members or an accompanying health care worker can provide a clear history that places the patient at a lower suspicion for meeting case definition, clinical judgement can be exercised judiciously.

A secondary screening area can be used when staff determines that a patient is going to isolation, but more history taking and assessment must be made. An open window with a one-meter buffer can be placed between the staff area and patient secondary screening room. A patient can be removed immediately from the primary screening area and obstetric-specific information can then be gathered from safely behind the window. If the situation warrants, nursing staff can use the space in secondary screening to allow for observation to assist in determining if the patient meets case definition. When a patient enters the secondary screening, it should be considered a Red Zone until suspect status is otherwise ruled out, or the patient is transferred into the appropriate isolation ward and the secondary screening cleaned.

In some situations, emergent or non-emergent, a thorough screening is not feasible prior to delivery and in cases of unknown history care must be administered as if the patient meets case definition. It is beneficial to design and stock the secondary screening facility to immediately turn into a safe Red Zone in the case that a patient exhibits an emergent illness (i.e. actively bleeding, loss of consciousness) or in cases of imminent delivery. If the patient cannot be transferred into the secondary screening area, triage nurses must have the ability to close the primary screening zone from pedestrian traffic, offering privacy to the patient, room for nurses to work and separation from the general public until the emergency is resolved.

Clinical and IPC staff must have ready access to all necessary materials in the triage/secondary screening area to safely and effective care for patients requiring immediate attention. We recommend the following:

- Nurses must have a donning and doffing area and the means to handle blood borne waste or body fluids.
- Delivery kits, fluid resuscitation supplies, comprehensive PPE and medications for PPH should be maintained in the nursing area and access to a hospital bed in secondary screening is optimal for patient care.

- There should be the means for transferring a non-ambulatory patient to either isolation or to the hospital after the appropriate screening is completed, or postpartum. This may include a wheelchair or a stretcher.

4.2.3.4 Screening Within a Clinical Facility

There are known cases of pregnant women presenting to a health care facility in labor who do not meet case definition at admission, but who then develop higher-acuity symptoms during/after labor and are subsequently test positive for EVD [62, 63]. It is crucial that health care administrators, staff and supporting partners collaborate to establish and implement protocols to increase the chances of early identification, rapid isolation, adequate treatment and effective IPC in the health care facility.

Ongoing assessments must take place for the in-patient population throughout their stay in the hospital. There must be q-shift assessments completed to determine if a patient is showing signs of becoming ill or demonstrating the classical obstetric warning signs. Medical personnel must also screen neonates post-delivery q-shift, during their entire stay and discharge instructions must offered to caregivers regarding warning signs after discharge. Given the potential for a scenario in which a patient has subclinical asymptomatic infection, but passes EVD to the fetus, clinicians must be watchful for and proactive in isolating and treating as soon as symptoms arise.

4.2.4 Safely Managing Obstetric Emergencies and Deliveries in Green Zone Areas

During an active EVD epidemic, every patient must be treated as potentially infected, no matter where they may suddenly require care. While care should never be withheld from a patient requiring attention, appropriate IPC measures must be available before care is delivered. Given the rapid progression of obstetric emergencies and precipitous labors, rapid response protocols should be established.

Any area can be rapidly turned into an ad-hoc Red Zone. All first responders should be comfortable with IPC principles and with the concept of Red Zone/Green Zone, which can theoretically be established with or without physical barriers.

Multiple sets of complete PPE should be available at multiple locations in and around health care facilities and in ambulances. *Care should not be rendered without appropriate PPE and IPC materials*. We recommend delivery kits also be easily accessed or assembled for imminent deliveries. Support staff should be available to secure a perimeter around an ad-hoc Red Zone to maintain crowd control, for delivery of additional materials and medications, to establish a line of communication between ad-hoc Red Zones and surrounding areas, and to initiate the next steps of transfer into a facility once immediate care is rendered.

Hygienists/IPC support staff should don full PPE and prepare to decontaminate the ad-hoc Red Zone once the patient is stabilized and transferred.

In the event of potential exposure or contamination to others in the community, every attempt to identify potential contacts is crucial for ongoing contact tracing and surveillance. While this can be difficult when an ad hoc Red Zone must be established in a large facility, in a crowd, or involving methods of transportation, it is crucial in the midst of an outbreak.

4.2.5 Establishing an Obstetric-Specific Red Zone

The 2013–2015 West African Ebola epidemic catapulted the research and development of innovative designs for the structures and materials used to combat this virulent disease. While the relative quality of infrastructure used as Ebola Treatment Centers ranged from sticks and tarps to military grade modular isolation units to modified existing structures to multimillion dollar BSL4 biocontainment facilities at prestigious academic medical facilities in the United States, the guiding principles of infection prevention and control remain the same across sites.

The guiding principles of an Ebola Treatment Center include:

- Limited entry and exit points, for both patients, staff, materials and corpses.
- Double barriers between Red Zone and external environment.
- Flow of movement from Green Zone, to suspect case areas, to confirmed case areas, to morgue, thus reducing the risk of transmitting virus from confirmed EVD positive patients to possibly uninfected patients.
- Multiple points for decontamination between patients
- Adequate distance/barriers between patients and between "suspect" and "confirmed" wards
- Clinical principles that prioritize safety of staff, minimizing risk of contact with infected fluids.
- Around-the-clock bedside care is very difficult to realize given staffing constraints and limits of length of time in PPE. Regularly scheduled "rounds" to administer patient care is more feasible [64].

These principles remain the same for an Ebola Treatment Center serving the obstetric population. However, in our experience, we recommend the following considerations to the design and utility when caring for pregnant or laboring women in a Red Zone.

- ETCs are generally separated into suspect vs. confirmed wards, and/or "wet" versus "dry," meaning patients with active vomiting or diarrhea should be separated from those who do not to reduce the risk of transmission of high-viremia fluids. We recommend that in an Obstetric Red Zone, every attempt should be made to arrange patient beds so that actively laboring or unstable patients occupy an additional "ward," ideally one that can be visually monitored at all times. In the OB Red Zone setting, intrapartum patients are considered highest-risk in terms of potential of EVD transmission (in known positive or

unknown PCR status), but regardless of their EVD status, will require the most focused care until they are stabilized.

- It is likely that staff will not be able to provide 24 hour support in the Red Zone, but particularly when a patient is actively laboring, every attempt should be made to schedule teams of two to rotate through "Red Zone rounds" to assist with labor without interruption of bedside care. Deliveries can be precipitous, and forgoing constant bedside care in active labor increases the risk that simple complications (i.e. shoulder dystocia, PPH) result in death.
- In the event that staffing support does not allow for constant bedside care during an active labor, we highly recommend designing the OB Red Zone with multiple access points to visualize patients from the Green Zone, either through windows or utilizing camera or video recording equipment if available. Being able to visually assess the status of a patient to determine the best time to don PPE for bedside care can be crucial to improving outcomes.
- Every Red Zone should be equipped with the appropriate materials to care for the obstetric patient. There are several key items that will be necessary to have in abundance:
  - Menstrual pads and diapers (adult and infant)
  - Infant formula and feeding cups
  - Cotton sheets (or suitable substitute) to cover patient for warmth and privacy, also to anticipate multiple bed-linen changes, and several rags, towels, linens for cleaning large amounts of blood/amniotic fluid.
  - Bassinette which can serve as sleep area for neonate or set up as neonatal resuscitation surface post delivery (must have cleanable surface)
  - Suture materials, needle holder, blunt tipped scissors, speculum or retractor
  - Manual vacuum extractor or forceps
  - Individual blood pressure cuff and thermometer at each bedside, able to be sanitized.
  - Sharps container at each bedside
  - IV poles, both and short (short for patient who must be placed on the floor for safety)
  - Bell, intercom or other means of calling for assistance. This is particularly helpful for women in early stages of labor who may not require constant monitoring to alert staff that assistance is needed.
  - Wall clock to monitor contraction intervals, as well as time limits for staff in the Red Zone.
  - Scale for infant weights or for measuring maternal blood loss
  - Ready-made and easily accessible kits with necessary equipment to rapidly manage normal deliveries, postpartum hemorrhage, and eclampsia/seizures

4.2.6 Medication Formulary

The acuity and complexity of patients entering into the Red Zone is such that a standard medication protocol is warranted. Given the lack of immediate diagnostic

capacity in many settings, it is recommended that all patients receive empiric treatment of antibiotics, antiprotozoal and antimalarial medications until bacterial, amoebic or malarial infections can be definitively ruled out, or the entire course completed. Even in the case of EVD, one cannot rule out co-infection with malaria or other common infectious disease. As such, EVD suspect and positive patients should be continued on all medications unless testing confirms absence of co-infection.

Clearly, it would be optimal to have an extensive medication formulary at the disposal of clinical staff in an epidemic, however the historical outbreaks occurring in low resource countries have forced makeshift pharmaceutical supply. The following are suggestions for coverage of the potential needs in isolation or treatment centers. Planning should include at minimum medications from the following categories. All medications listed are from the WHO Model List of Essential Medicines [65], unless otherwise noted. Clinical judgment must be made as to the relative benefits and risks involved and the acuity of the individual patient when choosing medications (Table 4.8).

4.2.7 Protocols

4.2.7.1 Admission

For purposes of simplicity and as a model for the ideal facility, the following will be addressed as if both suspect and confirmed cases are in isolated and treated within the same site. At admission, it must be determined where the patient should be placed within the unit based on their status. “Wet” suspect patients, or those with active bleeding, vomiting or diarrhea should be separated from “dry” suspect patients. All suspect women awaiting test results should be physically separated from probable confirmed patients. Laboring patients should be given privacy and placed inside intrapartum rooms for delivery, containment of body fluids and a higher level of care and observation. Infants should be with their mothers and not in a nursery. Bassinet sharing must be avoided.

It is critical for every patient who enters into an isolation or treatment center, that complete demographic and symptom history information be completed at the time of admission for care planning, data collection and tracking purposes. First name, last name, and birthdate should be verified and patients given a wrist name band including those three identifiers. Patient information can be entered onto a whiteboard or other central documentation record for clinical planning with the following information: bed number, name (first and last), age, birthdate, pregnancy status (pregnant and gestational age, postpartum or lactating), presenting symptoms, and date of onset of symptoms. This record can also include pregnancy outcomes that are updated in real-time (i.e. delivery date and time, gender of neonate, complications, etc.). It is advisable to have an admission book, or means of keeping patient status updated and relevant data logged. The goal is that all staff members can quickly assess and interpret the status of all patients in the ETC, as status can change rapidly.

Another whiteboard or central documentation record can also be used to track lab tests completed (date and time), when the next confirmatory tests are due and results.

Table 4.8 Recommended medication formulary for the EVD Red Zone

Medication	Considerations/Indications for Use
Name, class	BF = breastfeeding safety CI = contraindication
Anesthetic/Analgesic	
Local: Lidocaine, 2% w/epinephrine	Short procedures
Injectable: Ketamine	Palliative, short procedures
Inhalational: Nitrous Oxide	Analgesic, Palliative care
Morphine (opioid), pain relief	Severe pain, end of life
Haloperidol (Haldol), antipsychotic	Anxiety, combative behaviour BF: with caution
Tramadol[a] (opioid), pain relief	BF: acceptable
Naloxone (Narcan)	For opioid overdose
Antipyretic	
Paracetamol (Acetaminophen), antipyretic, pain relief	PO/IV
Anxiolytic	
Diazepam (Valium), benzodiazepine	BF: with caution
Allergy/Anaphylaxis	
Diphenhydramine	PO/IV Optimal for blood transfusion
Epinephrine	
Anticonvulsant	
Diazepam (Valium), benzodiazepine	BF: with caution
Magnesium Sulfate	IM, potentially IV with appropriate monitoring capacity Use per WHO recommendations Only for use in severe pre-eclampsia or eclampsia
Calcium Gluconate	IM: For Magnesium toxicity
Antibacterial	
Amoxicillin and Clavulanic Acid (Augmentin), Penicillin	BF: compatible
TMP/SMX, Sulfamethoxazole and Trimethoprim (Bactrim)	Bacterial meningitis, sepsis, Shigellosis… CI: near term gestation, BF: compatible if healthy and term, CI: neonate jaundice
Ampicillin, penicillin	Ampicillin and Gentamycin recommended for chorioamnionitis[b] BF: with caution
Cephalexin (Keflex), cephalosporin	BF: compatible
Ceftriaxone, cephalosporin	BF: compatible
Azithromycin, macrolide	Chlamydial infections, PID BF: with caution
Doxycycline, tetracycline	Chlamydial, Gonorrheal infections BF: acceptable short term
Ciprofloxacin, fluoroquinolone	

(continued)

Table 4.8 (continued)

Medication	Considerations/Indications for Use
Name, class	BF = breastfeeding safety CI = contraindication
	Typhoid BF: compatible
Gentamycin[e], aminoglycoside	Ampicillin and Gentamycin recommended for chorioamnionitis[b] Gentamycin and Clindamycin recommended for endometritis[c] BF: compatible
Clindamycin, lincosamide	CI: diarrhea, watery or bloody stool BF: acceptable, use alternate if possible
Metronidazole (Flagyl)[e], nitroimidazole	Septicemia, giardia, suspected anaerobic infection BF: with caution, if benefits outweigh the risks, use alternative if available
Silver Sulfadiazine, sulfonamide	2nd and 3rd degree burns CI: late term: kernicterus risk
Antimalarial[d]	
Clindamycin and Quinine	Recommended for first trimester, uncomplicated malaria treatment
Artemether and Lumefantrine (Coartem), or other Artemisinin-based combination therapy (ACT)	Recommended for second and third trimester uncomplicated malaria treatment, PO—must take recommended dose for full three-day course, missed doses result in ineffective treatment
Artesunate	Recommended for severe malaria in all trimesters: IV or IM (must have at least three doses 12 h apart, dosage based on weight. ACT is then necessary to complete treatment
Antifungal	
Fluconazole	PO Avoid in early pregnancy BF: acceptable
Clotrimazole	Topical, vaginal insert Topical acceptable for pregnancy and BF
Antiviral	
Acyclovir	Herpes simplex virus, Varicella BF: compatible
Corticosteroid	
Dexamethasone, Betamethasone	IM, Maternal Recommended for preterm fetal lung maturation (26–35 weeks gestation PTL)
Antihypertensive	
Methyldopa (Aldomet)	PO
Hydralazine (Apresoline)	IV
Nifedipine[a] (Adalat), calcium channel blocker	PO BF: no adverse effects noted

(continued)

Table 4.8 (continued)

Medication	Considerations/Indications for Use
Name, class	BF = breastfeeding safety CI = contraindication
Labetalol, beta blocker	PO or IV
Furosemide (Lasix), loop diuretic	PO or IV Recommended for preeclampsia/eclampsia (antepartem, intrapartum, postpartum) related pulmonary edema
Antiemetic	
Metroclopramide (Reglan), prokinetic	PO BF: acceptable Can be used as galactogogue CI: depression
Ondansatron (Zofran), serotonin 5-HT3 receptor antagonists	PO or IV BF: no adverse data
Antidiarrheal/Laxatives	
Loperimide (Immodium)	May be considered for symptom management in EVD in the absence of bacterial GI infection [17] BF: with caution
Zinc Sulfate	For acute diarrhea
Oral Rehydration Salts	PO, As needed, in large supply
Docusate Sodium, stool softener	PO
Senna, bulk forming/irritant	PO
Uterotonics	
Misoprostol	SL, intravaginally, per rectum For incomplete SAB or TAB, or PPH where oxytocin is not available
Oxytocin	IM or IV Labor induction or prevention/treatment of PPH
Ergometrine	PPH
Nifedipine (Adalat)	Can be used to delay progression of labor BF: no adverse effects noted
Neonatal medications	
Tetracycline 1% ophthalmic, Erythromycin 0.5% ophthalmic	Prophylactic
Ampicillin and Gentamycin	Neonatal septicemia
Caffeine Citrate	Apnea of prematurity
Chlorhexadine	Recommended for cord care
Vitamin K	IM, Prophylaxis for coagulopathy
Supplements/fluids	
Folic Acid	400 mcg daily—for prevention of neural tube defects [a]Can be delivered in combined prenatal vitamin if available

(continued)

Table 4.8 (continued)

Medication	Considerations/Indications for Use
Name, class	BF = breastfeeding safety CI = contraindication
Iron	120 mg elemental
Potassium Chloride	Electrolyte loss
Glucose	To reverse hypoglycemia
Water for Injection, Sodium Chloride	To reconstitute injectable/IV medications
Lactated Ringers, Normal Saline	IV fluids for resuscitation
Antiseptics	
Chlorhexadine	
Povidone Iodine	
Disinfectants	
Alcohol-based hand gel	
Chlorine for solution	

Notes
A loading dose for antibiotics should be considered when creating a protocol for the isolation or treatment center
Decisions should be made regarding the protocol for empirical treatment based on available medications and specifics of local infection prevalence
NSAIDs and aspirin should be avoided in EVD settings due to risk of coagulopathies; NSAIDS also should be avoided in third trimester of pregnancy
No recommendations are given for Tuberculosis or HIV given the longer-term considerations and need for referral. No recommendations are given for anti-helminthic treatment given the relative low acuity of those infections
[a]Not in the WHO Model List of Essential Medicines
[b]Ampicillin and Gentamycin (chorioamnioitis) Hopkins 2002 (Cochrane Review), French 2004 (Cochrane Review)
[c]Gentamycin and Clindamycin (endometritis) French 2004 (Cochrane Review), Livingston 2003, Sunyecz 1998, Mitra 1997, Del Priore 1996, Barza 1996
[d][66]
[e]http://www.acog.org/Resources-And-Publications/Committee-Opinions/Committee-on-Obstetric-Practice/Sulfonamides-Nitrofurantoin-and-Risk-of-Birth-Defects 2011

Plans can then be documented (discharge home, transfer etc.) and reviewed or changed based on incoming results.

4.2.7.2 Assessment

In order to create a care plan for individual patients, a complete head to toe assessment must be completed to the best ability of the clinician, given time and patient load constraints. Information that should be collected can be divided into two categories—objective and subjective. A clinician with experience in obstetric care should collect the objective information. The subjective information is dependent on patient consciousness, the ability of a patient to be an accurate historian or in some cases must be pieced together from family members. The clinician inside the Red

Table 4.9 Clinical assessment of the obstetric patient

Subjective	Objective
Significant health/OB history Date of onset of symptoms History of present illness Medications/herbs taken prior to admission	Vital signs Level of consciousness Edema Bleeding Hydration
Pregnant GTPAL (gravida, term, preterm, abortion, living) status Gestational age/LNMP Fetal movement	Pregnant Fundal height Fetal heart tones (if Doppler available) Fetal movement (if over 20 weeks) Ultrasound confirmation of viability, gestation, lie (if available)
Postpartum Breastfeeding History of delivery (date, infant status) Significant delivery details including complications· Location of infant if viable If infant is living, status of infant (healthy, ill)	Intrapartum Stage of labor (number of contractions, cervical dilation, effacement and descent for baseline reference) Membranes intact or ruptured, note quality of amniotic fluid Fetal status/fetal heart tones Moulding Medications administered in intrapartum period Immediate postpartum: Uterine tone Vaginal bleeding, source of bleeding Mental status

Zone is responsible for collecting gaps in history that has not been addressed before admission (Table 4.9).

All information must be documented in patient charts after each assessment in the Red Zone and on the central documentation record/whiteboard. Patients in labor should have a partograph started if over 4–6 cm dilation.

4.2.7.3 Testing Recommendations and Protocols

To date, PCR has been the testing method of choice for EVD infections. Approval for use of a Rapid Screening Test (RST) or GenExpert for EVD would allow access to results that could rule out EVD quickly. Choice of testing method must be made according to current international standards, national regulations and pharmacy board approvals.

All patients entering into the center should be PCR tested on admission. If the symptom onset is less than 72 h, then a second test is needed at or after the 72–h mark. Suspect and confirmed patients having either a spontaneous abortion or IUFD must have products of conception swabbed and tested (fetus, placenta—fetal side, associated tissue or amniotic fluid). An neonate delivered in isolation, or admitted with a suspect patient must also be tested.

A patient who is deceased prior to serum collection should have oral swabs collected prior to burial. IUFD at full term can also have oral swabs collected.

4.2.7.4 General Patient Care

Like any other EVD suspect or confirmed patient, pregnant, postpartum or lactating women must be assessed and treated based on presenting symptoms. Given the nature of fluid loss, offer appropriate replacement fluids (ORS or IV/IO) based on the severity of dehydration and level of consciousness. Consider differential diagnoses and offer antibiotic and antimalarial therapy as discussed above. Symptomatic relief must also be included in the care plan for pain, nausea, vomiting, agitation etc.

4.2.7.5 Intrapartum Care

Obstetrical care in the context of EVD has historically been limited to expected management given extremely high viral load present in amniotic fluid, blood, and placental tissue. As a result the inherent risk to health care workers it was determined to be too high for interventional care. The following were considered high risk in the past and healthcare workers were cautioned against engaging in: cesarean section, artificial rupture of membranes (AROM), episiotomy or deinfibulation of scarring related to female genital mutilation, manual vacuum aspiration, manual removal of a retained placenta, suturing, vacuum extraction, and craniotomy in the case of obstructed labor. Anticipated delivery in isolation should be managed with caution ensuring the utmost safety of staff while offering the highest level of care to the patient and her fetus. Adequate staffing numbers and skill level and immediate availability of needed delivery supplies and medications will eliminate some of the risks associated with deliveries in a limited resource setting. In serious cases where life is threatened or suffering is unmanaged, a higher level of intervention should be considered when qualified staff are present, adequate supplies are on hand and IPC measures can be adhered to. In this way, risks can be mediated and the potential for survival increased.

4.2.7.6 General Delivery Guidelines in the Red Zone

For management of all deliveries in the Red Zone, protocols must be created with respect to the local Ministry of Health clinical guidelines and WHO recommendations for OB care in limited resource settings. Additionally, the following considerations must be made to care for patients with EVD filovirus or other hemorrhagic fevers:

- An adequate intrapartum setting must be prepared before delivery to decrease the risk to staff and patients in the Red Zone. Safety must always be a priority and clinicians must not place themselves at risk in the event a lack of appropriate water, lighting, or PPE should occur.
- Red Zone staff should prepare the bedside when there is an impending delivery and have IV fluids, delivery kit, resuscitation equipment and neonate blanket and bedding at the ready.
- Staffing should be adequate for deliveries; ideally, there should be a nurse or midwife for the delivery, a nurse for the neonate and one other clinical staff member to monitor IPC and assist where needed. Presence of a hygienist is also advisable. Roles should be assigned prior to entry into the Red Zone.

- A second team in the Green Zone must be ready and able to relieve Red Zone staff when they are exiting and there must be a system of report to update status of the patient before the change of shift. If able, the exiting IPC clinician should update the incoming team before they enter.
- There must *always* be staff in the Green Zone to hand in needed medications, consult and support Red Zone clinicians. The Green Zone staff must help to monitor total time in the Red Zone and give adequate warning when doffing is required. A "sign in" whiteboard at the entrance to the Red Zone area allows for accurate monitoring of time in PPE and identification, location and duties of staff in the Red Zone.
  - It is optimal for clinical staff to visualize laboring patients from the Green Zone if there are not enough staff for round the clock care in PPE. A communication tool is also advised so that the patient can call for help if needed, or give status reports to staff.
- Elbow length gynecologic gloves are preferred for deliveries. In addition to standard PPE, a heavier and thick reusable apron is recommended for the delivering clinician to protect the front of the coverall from body fluid, and to reduce the movement of a lighter, thinner apron. Have all needed PPE in the Red Zone and readily available.
  - Treat all body fluids as potentially infected
  - Place IV before delivery if possible in anticipation of likely IVF resuscitation and to reduce risks to staff associated with an urgent/emergent IV placement.
- Fresh 0.5% chlorine must be available for immediate decontamination of soiled gloves and gown. Hands must be washed or outer gloves changes between procedures.
- Limit the number of vaginal exams during labor to the initial assessment and intermittent progress checks q 4 h if needed, or the to fewest number possible.
- A partograph and/or detailed charting and adequate care planning must be maintained so as to monitor labor progression and anticipate potential interventions for complications.
- Regularly monitor fetal heart rate or movement.
- Refrain from using fundal pressure during second stage
- A clear plastic sheet should be used as a drape during delivery to separate the clinician from the neonate and placenta. The delivering clinician is avoid sitting or standing at the end of the bed or between the legs of the laboring patient to limit contact with blood or amniotic fluid exposure.
- Limit the number of sharps in the Red Zone. Use blunt tipped scissors if available for cord cutting. Prioritize single use instruments over multi-use. If multi-use instruments are used, a system for cleaning must be employed. A rinse in 0.5% chlorine will ensure adequate decontamination. A fresh water rinse and immediate drying will delay corrosion of metal instruments. If available, an autoclave is optimal.
- Suturing should be available and employed only when adequate lighting and experienced staffing are available and only in cases where the patient is cooperative (not agitated) and there is a risk of negative outcome without intervention.
  - Blood loss and uterine tone should be monitored closely after every delivery, regardless of gestation.

- PO medications are preferred, but if needed progress to IV, IM or IO. All postpartum patients should have 10 IU of slow IV push or IM oxytocin (after confirmation of single fetus) to decrease the chances of PPH.
- If delivery of live baby (or with retained placenta), tie off and cut the cord under plastic. In cases of fetal demise, leave the cord intact, deliver the placenta and place both placenta and fetus together into a body bag, using recommended IPC measures.
- A team of postpartum clinicians should be available to monitor vitals and infant transition in the hours after delivery
  - Referral for HIV or TB testing or PMTCT services should be offered at discharge if there is a known or suspected secondary infection.

4.2.7.7 OB Complications in the Red Zone

Given the nature of a viral hemorrhagic fever superimposed on pregnancy, the likelihood of obstetric complications and coagulopathy is very high. Safety of staff members must be prioritized, however, we recommend the consideration that more interventions may be appropriately rendered to improve patient outcomes than were recommended in the 2013–2015 EVD outbreak.

- Adequate IV fluids must be on hand for volume resuscitation in high acuity cases.
- Consider induction of labor in emergent cases only; otherwise, defer induction if a suspect case is highly suspicious of having EVD. This is in an effort to reduce unnecessary exposure of staff to body fluids.
- Deinfibulation of type 3 female genital mutilation (FGM) is discouraged, but may be performed if it is considered a life saving measure. If proceeding with procedure, perform at the patient's side, under plastic sheeting and with adequate anesthesia or pain relief.
- Perform fundal massage (with support of lower uterine segment) and 40 IU of oxytocin in 1 L of IV fluids (60 gtt per minute) for initial PPH management and be prepared to offer higher levels of intervention if bleeding persists, including: external aortic compression and uterine balloon tamponade.
  - In cases of antepartum or postpartum hemorrhage, consider having an established system for basic blood typing within the unit and a process in place for collection and administration of blood products. No suspect or confirmed patient blood can leave the unit unless a process is in place to transfer to a EVD specific lab. Staff must be trained to type patient blood and to monitor for transfusion reactions. Inadequate training would disqualify a treatment center from transfusing.
- Patients who are suspect and acutely ill are often placed in situations that are life threatening while they wait for PCR results. Consider establishing a site for isolation surgery (dependent on trained personnel, equipment and adherence to IPC measures) so that patient needs can be addressed in emergencies and the option of cesarean section be made available.
- Consider administration of Nifedipine over Terbutaline (may have more serious side effects and requires higher level of monitoring) for delay of early onset preterm labor or onset of uterine hyperstimulation. Consider antepartum

corticosteroid (ACS) administration in cases where preterm delivery (26–35 weeks gestation) appears to be unavoidable.

- Proactively treat PROM or PPROM with prophylactic antibiotics.
- Do not delay treatment of hypertensive emergencies. Offer antihypertensives (PO or IV) if systolic exceeds 160 and diastolic exceeds 110 and monitor regularly. Address severe preeclampsia or eclampsia immediately with IM magnesium sulfate and continue until 24 h post-delivery or last seizure (whichever is later). The risk of fluid overload must be balanced with the propensity of EVD patients to be fluid depleted and anuric. Monitor for symptoms of pulmonary edema and defer diuretics unless severe edema [67]. Rapid delivery can resolve symptoms of eclampsia and induction or augmentation should be considered.
- In cases of IUFD, deliver as with a live infant under plastic sheeting. In many cases, symptoms of infection are present and mimic EVD, particularly if labor has been delayed or obstructed. Treat with antibiotics for chorioamnionitis and monitor. Induce or augment labor to expedite delivery if the risk of puerperal sepsis is high. Given the extremely high risk of fetal death with positive EVD mothers, pregnancies must be monitored and ultimately delivered in isolation or in an ETU. Even if the patient is recovered, her products of conception will have high viral load and must be treated as infectious waste.
- Spontaneous abortions must also be treated with suspicion and POC from suspect or positive patients treated as infectious waste.
- Vacuum delivery and episiotomy can be considered for obstructed labor when it is believed to be a life saving measure. IPC measures should be maintained at all times. Referral for cesarean should be made when available, if failed assisted delivery.
- In the case surgical intervention is needed and not available, all attempts at supportive care and potentially palliative care must be administered until lab results are returned. Transfer of a non-infected patient with confirmed negative PCR to non-isolation facility can be arranged when lab results are returned. This patient who has been identified as not having filovirus must be advocated for outside of isolation or treatment units and reassurance given to medical staff that they are uninfected and safe to be operated on.
- Confirmed EVD-positive patients with no access to surgery must stay in the treatment center until recovery and two confirmed negative results have been received. The fetus, regardless of gestation, will very likely not survive and will need to be delivered within the isolation facility.
  - Depending on the location of the epidemic, there may be access to high intervention medical care and drug therapy for neonates born from an EVD positive mother and though the fatality rate has historically been almost 100%, priority for should be given to advances in clinical care and vaccines. However, in the absence of adequate interventions, the option of therapeutic medical abortion before discharge should be offered if an EVD positive patient has an intact pregnancy, the patient lives far away from a EVD treatment center and there is a risk that she will not return for delivery (thereby risking further infection in the community).

4.2.7.8 Preparing for Care of the Neonate in the Red Zone

Given that the majority of women entering into the ETC will be EVD negative, the majority of care should mimic the expectations for infant care in a non-epidemic setting. Fetal monitoring during labor and delivery should be provided for early detection of complications and immediate care of the infant is essential to ensure optimal outcomes and reduce the risk of infant mortality.

- Immediately after delivery, vigorously stimulate and dry the neonate
- Oropharyngeal/nasopharyngeal suction only if secretions suction only if secretions are obstructing the airway; there is no need to suction a vigorous neonate, even if meconium present
- Perform basic assessment (airway, breathing, circulation) and offer resuscitation if needed
- Allow delayed cord clamping and cutting in non-emergent settings, tie and cut cord under plastic sheet to minimize contact with blood
- Clean and dry infant and allow skin to skin/kangaroo care and bonding if the mother is capable
- Assess initial APGAR score and then complete routine vital signs: respiration rate, heart rate (umbilicus or brachial pulse) and temperature q 30 min $\times$ 2 after delivery and q shift (at least with every assessment of mother thereafter). Complete newborn assessments as thoroughly as possible given time restraints in PPE and check for jaundice, tone, retractions and feeding. Stethoscopes cannot be utilized in a Red Zone.
- Ensure that the infant bassinet is covered with mosquito netting to decrease the risk of malaria infection
- Offer Vitamin K injection IM (1 mg) at birth, ophthalmic Tetracycline ointment bilaterally, and chlorhexidine cord care per WHO recommendations
- Delay washing for 24 h is possible and dress infant in weather-suitable layers (1–2 layers more than adults) to stabilize body temperature.
- Offer other treatments based on individual symptoms—consider IM antibiotic treatment for bacteremia for 3 days if concerns regarding infection

4.2.7.9 Care of the Neonate When Mother Is EVD Positive

Survival of neonates delivered to EVD positive patients in or out of an ETU is close to 100% mortality rate. At the end of the 2013–2015 West African epidemic, one documented infant of a deceased EVD positive patient survived after an intensive antibody, broad spectrum antiviral and antibiotic regimen [68]. One can assume that a neonate is exposed to filovirus in utero, during delivery or during breastfeeding (though it has appeared based on documented cases of live births that neonates seroconvert shortly after delivery with unknown data around the impact of breastfeeding [69]). Recommendations then include keeping the mother and infant as a treatment dyad and allow the mother to care for the infant if able. Communication with the mother about her EVD status and expected outcome of the neonate should occur as early as possible, with adequate psychosocial support as needed.

4.2.8 Breastfeeding

There are several factors that must be considered when reviewing recommendations for breastfeeding a neonate after delivery in an isolation setting and before maternal PCR results are obtained. In resource low areas, the risk of unsanitary water to make powder formula, the unavailability of ready to use infant formula (RUIF), the lack of hygienic means to sterilize bottles, or the prohibitive cost to families to obtain artificial feeding or animal milk products for the neonate for up to 2 years after delivery must be weighed with the immediate risk of continued breastfeeding and exposure to EVD. WHO recommends that in cases where the mother is symptomatic and awaiting results that her breastfeeding be suspended. In these cases a discussion with the patient about the risks, benefits and options must be had. Where the mother is unable to give informed consent one way or the other, family members must be brought into the conversation and clinical decisions be made also taking into account the current prevalence of infection in the community.

If the patient's result is positive, it can be assumed that the neonate will be positive. There are questions about the initiation of breastfeeding and whether the infant is already infected and would (1) benefit from any maternal antibodies, (2) will get an increased viral load through breastfeeding, or (3) be likely to die regardless of feeding. WHO recommends suspending breastfeeding and starting RUIF (ready to use infant formula) until breast milk samples test negative $\times 2$ by PCR testing after which the mother should be encouraged to initiate or resume breastfeeding exclusively for at least 6 months.

For patients who suspend breastfeeding until results are returned, interim supply can be maintained with pumping. However, all expressed milk must be treated as contaminated material and discarded per appropriate IPC protocols.

4.2.9 Neonate Considerations with Deceased EVD-Positive Mother

If the patient expires during or after delivery but prior to maternal serum testing, oral swabs of the corpse are to collected prior to burial. Collect a serum sample for PCR testing of the neonate as soon as possible , however note that the infant must be in the care of isolation facility for 21 days following delivery. A neonate can be infectious but present as being asymptomatic 3 days prior to becoming ill and even then symptoms are atypical or non-specific. Accounts of live newborns delivered to positive mothers were all documented to be deceased within the 19th day of life [69]. The 21-day cut off allows for monitoring for the entire contact exposure period.

If neonate is positive, treat per pediatric EVD protocol or arrange transfer to an appropriate treatment facility via local government regulations.

4.2.9.1 Psychosocial Support, Patient Education and Discharge Planning

The psychosocial impact of the 2013–2015 West Africa Ebola epidemic is an immeasurable burden for thousands of people. A common sentiment often expressed both from patients admitted to ETUs and health care workers alike was the dehumanization and trauma of being isolated. The human element of direct patient care was covered by multiple layers of plastic, only eyes visible behind foggy masks. While novel efforts to humanize health care workers rapidly spread by word of mouth among first responders, the experience of being cared for in an isolation center is undeniably traumatic. We strongly advocate for early and robust psychosocial resources as part of a comprehensive EVD response.

Care for the pregnant patient also requires unique psychosocial considerations. While practices may vary across cultures, childbirth is a global phenomenon laden with tradition, ritual and social norms. Universally, the laboring woman is at her strongest, and yet at her most vulnerable. Effort should be taken to understand and support the unique sociocultural norms surrounding pregnancy and birth in a way that maintains dignity in delivery while adhering to all safety and IPC protocol in the context of EVD care.

4.2.9.2 Discharge Planning and Patient Education

In times of crisis, it may be common for the quality of patient care to suffer as safety or allocation of resources is prioritized. We assert, however, that quality can be incorporated into emergency response service delivery in a way that does not jeopardize safety or waste valuable resources. Discharge planning and patient education are components of emergency response service delivery that may be neglected in the height of an emergency, but in the context of EVD, these practices can be a crucial component to breaking the chain of transmission as well as improving the overall quality of patient care beyond the ETU. The obstetric population has unique needs upon discharge from an EVD treatment or isolation facility that should be incorporated into the development and implementation of any program working with women of reproductive age.

Resources and protocols should be developed early so that staff are prepared to guide patients when they are discharged from the facility. All patients discharged from a Red Zone should receive clear instructions that they are, by default, considered possible contacts and should monitor their signs and symptoms for 21 days after discharge. Examples of unique obstetric patient pathways are summarized in Table 4.10.

Table 4.10 Discharge planning and education for the pregnant/postpartum patient

Patient	Discharge planning	Discharge teaching	Wrap-around services
Patient is EVD negative still pregnant upon discharge, with no complications	Where is the patient going after discharge? How will she get there? Is there a risk for EVD contact in their household? Where is the patient planning to receive ongoing prenatal care/ planning to deliver?	Signs and symptoms of labor, obstetric emergencies and EVD Where to present if these signs/symptoms occur in the future Recommendations for ongoing prenatal care	Psychosocial support Prenatal care/ delivery planning Nutritional support
Patient is still pregnant, EVD negative with complications (i.e. active labor, pre/eclampsia, obstructed labor, etc.)	Clinical judgement should be exercised about the safest place for the patient to deliver. If delivery is imminent at time of discharge, consider delivery if transfer of care to a tertiary facility cannot be arranged or deemed too risky Coordination with closest secondary or tertiary health care facility is paramount in the event of complications. Notify nearest facility in the event of imminent delivery or Cesarean section	The laboring patient should be consulted about the plan of care, and kept informed of changing condition. If possible, family members should also receive updated, and be available for discharge teaching while patient is in critical condition	Coordination with secondary/ tertiary level facilities Blood supply Ambulance transportation Materials for delivery (i.e. PPE, delivery kit, medication)
EVD negative patient is no longer pregnant upon discharge, or fetus not viable (i.e. SAB, IUFD)	Does the patient require close medical attention in a hospital? If so, plan for transfer of care to nearest facility Protocol for contacting patient and local surveillance authorities pending PCR results of fetus or POCs Assessment and appropriate management of patient's grief reaction at loss of pregnancy	Signs and symptoms of post-partum or post-SAB complications (i.e. puepueral infection), signs and symptoms of EVD infection[a]	Psychosocial support Transportation Access to family planning services if desired Access to health care if complications arise after discharge home

(continued)

Table 4.10 (continued)

Patient	Discharge planning	Discharge teaching	Wrap-around services
Patient is postpartum, EVD negative with infant	Does the mother and/or neonate require close medical attention in a hospital? Is the neonate stable (i.e. feeding, voiding, etc.)? Where will the patient/baby go after discharge, how will they get there? What is the family support situation? Is the home a safe environment for the dyad?	Extensive teaching should be dedicated to mother/child dyads after discharge, including newborn care, breastfeeding, vaccines, warning signs for complications both mother and baby	Coordination with newborn care provider should be arranged, if possible. Family planning Nutritional support Close follow up to ensure dyad has connected with local MCH resources
Patient is deceased, EVD negative infant is alive	Is the neonate stable or requiring close medical attention? Consider transfer to tertiary level facility where neonate can be monitored in hospital nursery. Is next of kin available and willing to assume responsibility of infant?	Extensive teaching for family members, if available, regarding newborn care, including signs and symptoms of complications, EVD Connection with local resources for ongoing support, if available	Psychosocial support for family of deceased patient Nutritional support Notify relevant authorities for child protection services for close follow up
Patient is EVD positive discharged when PCR is negative × 2	See next section, "Care for the EVD Survivor Upon Discharge and In Future Pregnancies."		

[a]Patient should be aware that these are similar presentations and may result in repeat isolation

4.2.10 Considerations for Safe and Compassionate Management for EVD Survivors with Subsequent Pregnancies

The development of clinical guidelines and practical health care delivery strategies to address the unique needs of EVD survivors presented grand challenges for the community serving Guinea, Sierra Leone and Liberia in the recovery phase of the 2013–2015 West African EVD epidemic. Even verifying the number of EVD survivors in West Africa is a daunting, occasionally political task, but estimates are currently that out of 27,500 documented cases of EVD, there are approximately 13,000 survivors [48].

To date, there are no strong data to approximate how many of those survivors have become pregnant since recovering from EVD, but it may be asserted that the pregnant EVD survivor represents the nexus of vulnerability. In 2010, *before the*

EVD epidemic, Sierra Leone had a baseline maternal mortality ratio of 1630 deaths out of every 100,000 deaths [45]; that number has almost certainly risen, with some estimates by as much as 30% simply by virtue of the decimated health care system and decreased utilization of services [70]. Combining these baseline maternal health indicators with the pervasive stigmatization and fear of pregnant EVD survivors lends an extraordinarily high risk for neglect and mistreatment of the pregnant EVD patient, despite the fact that there have been no data to show active virus in the amniotic fluid or products of conception in the subsequent pregnancies of women who survived EVD. It should be noted that the risk for stigma affecting care for EVD survivors is not limited to the West African nations where the outbreak occurred; a case study detailing management of a pregnant EVD survivor planning to deliver in the United States reports marked discomfort and concern from hospital staff despite no evidence of risk for transmission of virus [71].

Furthermore, there are limited data about subsequent pregnancy outcomes for women who became pregnant after surviving EVD, with a small cohort study in Liberia showing a slightly higher incidence of miscarriage or stillbirth in Liberian EVD survivors as compared to the overall rate in both the developed and developing world [72]. However, national data for baseline miscarriage/stillbirth rates are not available in Liberia, Sierra Leone or Guinea, making data specifically reflecting the EVD survivor population murky.

Recommendations addressing breastfeeding for EVD survivors in subsequent pregnancies were initially limited due to lack of data regarding viral persistence in breastmilk. Anecdotal evidence suggests that Ebola virus may persist for several months in breastmilk of survivors, but breastmilk was not routinely included in the major viral persistence studies conducted in the immediate post-epidemic period. There are no known cases of a breastfeeding infant presenting with EVD contracted from a lactating mother. Given the overwhelming benefit to breastfeeding, particularly in resource-poor settings, current CDC guidelines support routine breastfeeding of the neonate born to EVD survivors, with case-by-case evaluation to neonates born to suspect or confirmed EVD patients [73].

There are multiple circumstances complicating the approach to and delivery of quality care for the pregnant EVD survivor, largely due to emerging research regarding viral persistence, clinical sequelae in EVD survivors and sociologic trends of stigma and access to resources for pregnant EVD survivors in their communities.

With the data available, we support the following recommendations:

- EVD survivors presenting with subsequent pregnancy outside of a known EVD epidemic should be treated as a non-infected patient. Antepartum and intrapartum care should not be delivered with any more PPE than would be used for a non-survivor patient (universal precautions).
- Status as an EVD survivor should be considered as a relevant part the patient's history to inform any abnormal clinical presentation, and treated with astute clinical judgement. Other key components of a thorough history taking for a pregnant EVD survivor include: survivor status of the father of the baby, any recent illness/complications, social support status.

- The heightened vulnerability of a pregnant EVD survivor should inform a broader and more comprehensive approach to high-quality antepartum, intrapartum and post-partum care.

4.2.11 Conclusion

Treatment of the pregnant or postpartum patient who meets case definition for EVD is controversial and is often an ethically charged debate due to the overlap in clinical presentation of EVD and obstetric complications. The 2013–2015 West Africa Ebola epidemic illuminated the desperate need for adequate preparedness for infectious disease outbreaks in the obstetric population, with dedicated protocols, adequate training, and unique considerations for these extremely vulnerable patients. The safety and protection of the healthcare worker must be balanced with the commitment to deliver the highest degree of quality clinical intervention possible for the pregnant patient, with the theoretical risk of transmission of EVD incorporated into every aspect of clinical and care management.

We recommend that the lessons learned from the 2013–2015 West African epidemic, where an unknown, yet unfathomable number of EVD negative women and infants lost their lives in Ebola Treatment Centers due to inadequate obstetric care, be considered in the development of all future emergency preparedness and response protocols. With committed partners implementing informed protocols, safe and high-quality maternal/child health can and should be prioritized in the midst of an emergency.

4.3 Ebola Virus Disease in Children

Felicity Fitzgerald

4.3.1 Epidemiology

Nearly 8000 children were confirmed or suspected to be infected with EVD during the West African 2013–2015 outbreak, just under 25% of the total [74]. It appears that in this as with previous outbreaks, confirmed diagnoses were fewer in children than adults [75–77]. The reasons underlying this apparent sparing of children are poorly understood. Firstly, it could be that diagnoses are being missed, due to under-reporting or poor diagnostic sensitivity in children [77, 78]. It is possible that against a background of high infant mortality as with most countries affected by EVD, and fear of seeking health care during an outbreak parents did not bring their unwell children for testing [78]. Alternatively, it may be that the diagnostic tests such as both PCR (polymerase chain reaction for EVD DNA or serological testing) were less sensitive for small children [75]. For example, small children, particularly infants, are often challenging to take blood samples from so it may be that smaller samples

were sent, or that less sensitive mouth swabs were used for PCR as an alternative early in the outbreak [79].

However, the difference may be true biological sparing of children, where children are either less exposed or less vulnerable to exposure, or finally that children were more likely to have asymptomatic infection. From Glynn et al.'s study of seroprevalence of EVD Immunoglobulin G (IgG, evidence of previous infection) in households of EVD survivors, they found no evidence of asymptomatic infections in children under 12 years of age, and a slight excess of symptomatic undiagnosed infections in younger children: i.e. it appears that younger children were slightly more likely not to be taken to hospital despite symptoms [80]. Bower et al. investigated age-specific attack rates in the same cohort of EVD survivor households in Sierra Leone, and found that after adjustment for exposure type, children and adolescents aged 5–19 years were less vulnerable to infection than either younger children or adults [81].

Therefore it appears from available evidence that in the West African EVD outbreak at least, the apparent sparing of children was due to a combination of younger children not being brought for medical attention and true biological sparing in older children and adolescents, the mechanisms for which remain to be explained.

Routes of exposure are similar to adults with the additional exposure of breast milk for infants, and vertical transmission from mother to neonate (see obstetric chapter). It appears that close contact with a sick mother/primary caregiver is a key risk factor in children over and above other household or community exposures [82]. Regarding breast feeding, Ebola virus has been detected in breast milk up to 9 months post-infection [83–85]. Indeed, in one case, investigation into the death of a 9-month old infant from EVD led to the discovery of Ebola virus in the mother's breast milk although the mother had had no preceding symptoms [86]. However, Bower et al.'s study of 77 mother-child pairs (children aged < 2 years) found no excess risk from breast feeding over and above contact with a sick mother [82]. Contact with an EVD-infected mother was by far the greatest risk for the child, risk ratio (RR) compared with infections in the same household excluding mother 7.5, 95% confidence interval (CI) 1.9–28.9, $p < 0.001$) [82]. Interestingly, household crowding and sanitation had little impact on transmission risk, and none of the children included had contact with a dead body, indicating close proximity to the mother/primary caregiver as the most important causal factor in acquisition of EVD. The authors therefore agree with current WHO guidelines that asymptomatic infants and children should be separated from infected mothers to limit onward transmission [82, 87].

Regarding children themselves as sources of the virus, the data is conflicting. One modelling study based on data from 200 burials indicated that children might be "super-spreaders" of the virus, but this has not been substantiated by epidemiological data from Liberia or Sierra Leone [88]. In Liberia, a contact tracing study showed no difference between children and adults in terms of transmission, and a study of transmission chains indicated that children were less likely to pass on the virus [89, 90]. This was mirrored in Sierra Leone where children were more likely to be infected in later generations within households, rather than being the primary source

within a household [91]. It seems likely therefore that children may be less, rather than more likely to transmit the infection compared to adults.

In terms of mortality, infants are the most vulnerable, with case fatality rates (CFRs) varying between 70 and 90% [92–95]. The prognosis improves with age, such that mid-late teenagers have amongst the lowest case fatality rates. Table 4.11 shows CFRs for children in studies from both the West African and prior outbreaks by age. Risk factors for mortality are discussed further below.

4.3.2 Presentation

EVD is notoriously non-specific in presentation, particularly in children. Indeed, even fever which was key to the WHO clinical case definition in the West African outbreak was absent in 20–25% of cases in three studies [94, 96–98]. In most studies from the West African and previous outbreaks, features in children have included (in order of frequency) fever (71–99%), fatigue/weakness (64–80%), appetite loss (60–79%), vomiting (28–62%) and diarrhoea (43–60%) [94–97, 99]. Abdominal, muscle, joint and chest pain as well as headaches have been reported in 29–70%, although in younger children pain is difficult to localise and so recording of pain from various body sites has been compounded into the symptom of generalised distress, seen in 64% of a younger cohort [94]. Conjunctivitis was recorded in 13–22% and hiccoughs in 7–12% [94, 95, 99, 100]. Difficulty breathing and swallowing were seen approximately 13–20% of patients [96, 97, 99]. Bleeding from various body sites tended to be rarer in the West African outbreak in children than previous outbreaks (1–10% compared with 20%) [95, 97, 99, 101], although two cohort studies recorded bleeding in 15% [94, 96], and a large study of Guinean children recorded bleeding in 24% [100]. Interestingly, one younger cohort (children aged up to 5 years) recorded cough in up to 54% of children, although this was less frequently seen in other cohorts [94].

Blood tests have revealed dramatic leucocytosis, deranged liver and renal function alongside raised inflammatory markers (e.g. C-reactive protein) particularly in children who died [11, 95]. Hypoglycaemia, often severe, was common among both children who died (55%) and those who survived (30%) in one cohort [95]. More detailed description of electrolyte and haematological disturbances over the course of disease can be seen in Fig. 4.1 [102].

4.3.3 Disease Progression

The mean duration of incubation of EVD is shortest in younger children: estimated to be 1 week in children <1 year compared to 9.8 days in children aged 10–15 years [99]. Similarly, duration from symptom onset to death is shortest in younger children- under 6 days in those <1 year, compared with nearly 9 days in those aged 10–15 years [99]. However, care must be taken with these estimates as many children were admitted unaccompanied to treatment facilities, so data regarding

Table 4.11 Showing case fatality rates by age from West African and Ugandan outbreaks ordered by study size

Study	Country	Age range (years)	Number within age range	Case fatality rate (%)
Garske et al.[a]	Guinea, Liberia and Sierra Leone	<1	125	80
		1–4	460	78
		5–10	527	59
		11–15	626	50
Cherif[b]	Guinea	1–4	211	83
		5–9	136	65
		10–15	131	49
Fitzgerald et al.[c]	Sierra Leone	<1	20	70
		1–4	84	65
		5–10	84	94
		11–12	94	47
Smit et al.[d]	Sierra Leone and Liberia	0–4	44	89
		5–9	30	43
		10–14	32	41
Shah et al.[e]	Sierra Leone	0–2	34	77
		2–5	57	46
McElroy et al.[f]	Uganda	0–5	13	77
		6–15	16	38
Damkjaer et al.[g]	Sierra Leone	0–18	33	42
Mupere et al.[h]	Uganda	0–17	20	40

[a]Garske T, Cori A, Ariyarajah A, et al. Heterogeneities in the case fatality ratio in the West African Ebola outbreak 2013–2016. Philos Trans R Soc Lond B Biol Sci 2017; 372(1721)

[b]Cherif MS, Koonrungsesomboon N, Kasse D, et al. Ebola virus disease in children during the 2014–2015 epidemic in Guinea: a nationwide cohort study. European journal of pediatrics 2017; 176(6): 791–6

[c]Fitzgerald F, Naveed A, Wing K, et al. Ebola Virus Disease in Children, Sierra Leone, 2014–2015. Emerging infectious diseases 2016; 22(10): 1769–77

[d]Smit MA, Michelow IC, Glavis-Bloom J, Wolfman V, Levine AC. Characteristics and Outcomes of Pediatric Patients With Ebola Virus Disease Admitted to Treatment Units in Liberia and Sierra Leone: A Retrospective Cohort Study. Clin Infect Dis 2017; 64(3): 243–9

[e]Shah T, Greig J, van der Plas LM, et al. Inpatient signs and symptoms and factors associated with death in children aged 5 years and younger admitted to two Ebola management centres in Sierra Leone, 2014: a retrospective cohort study. Lancet Glob Health 2016; 4(7): e495–501

[f]McElroy AK, Erickson BR, Flietstra TD, et al. Biomarker correlates of survival in pediatric patients with Ebola virus disease. Emerging infectious diseases 2014; 20(10): 1683–90

[g]Damkjaer M, Rudolf F, Mishra S, Young A, Storgaard M. Clinical Features and Outcome of Ebola Virus Disease in Pediatric Patients: A Retrospective Case Series. The Journal of pediatrics 2017; 182: 378–81 e1

[h]Mupere E, Kaducu OF, Yoti Z. Ebola haemorrhagic fever among hospitalised children and adolescents in northern Uganda: epidemiologic and clinical observations. Afr Health Sci 2001; 1 (2): 60–5

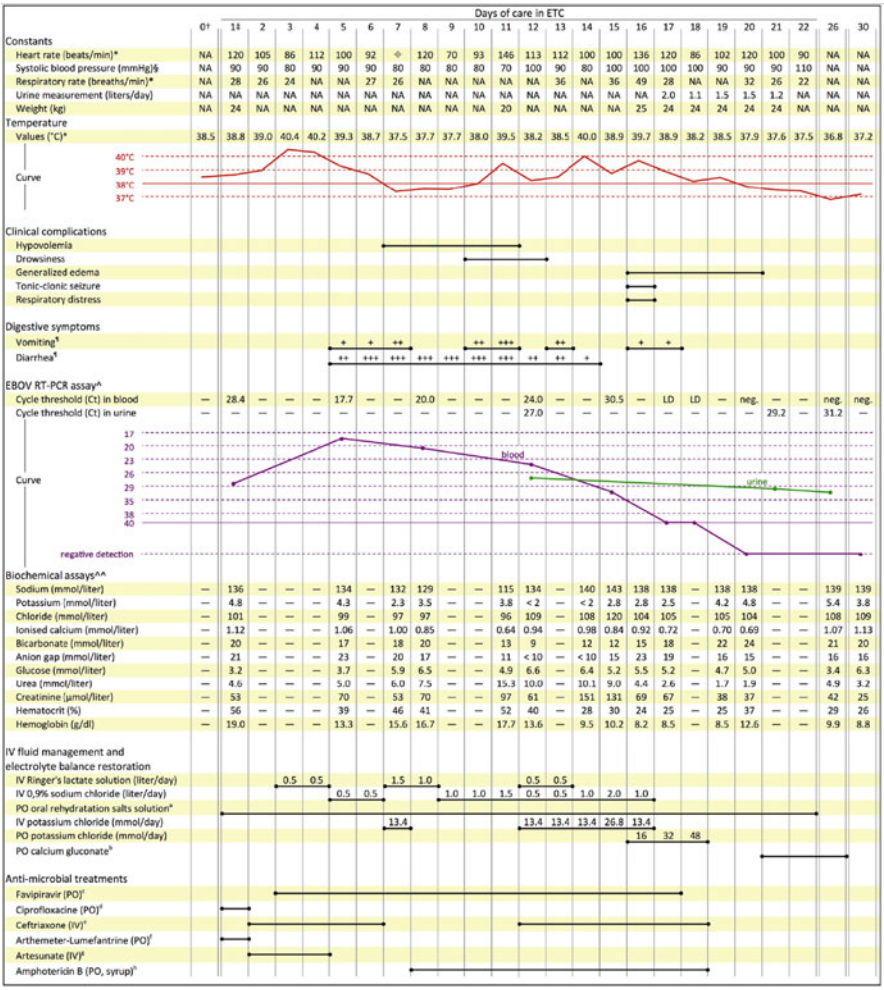

Fig. 4.1 Clinical and biological outcomes and main treatments administered to a 6 year old with EVD during care in an Ebola treatment centre [102]. *NA* not available, *LD* limit of detection. †December 25th, 2014. ‡December 26th, 2014. *Highest measurement of the day. §Lowest measurement of the day. Pulse was not perceived because of hemodynamic disorder. ¶Gastrointestinal losses were quantified at each visit of the medical team (four times per day): severe (+++), moderate (+ +), or mild (+). Severe losses: more than eight liquid stools per day (or more than four bouts of vomiting daily). Moderate losses: more than four liquid stools (or more than two bouts of vomiting per day). Mild losses: at least one liquid stool per day (or at least one bout of vomiting per day). ^Biomolecular tests employed RealStar Filovirus RT-PCR Kit 1.0 (Altona Diagnostics GmbH, Hamburg, Germany). ^^Biochemical assays employed i-STAT CHEM8+ cartridges (Abbott Point of Care Inc., Princeton, New Jersey, USA). (a) Between 0.5 and 1.0 L per day, at will. (b) 3.5 mmol per day. (c) Loading dose of 3000 mg on the first day (H0: 1200 mg, H8: 1200 mg, H16: 600 mg) then 1200 mg (600 mg twice a day) on the following days. (d) 250 mg twice per day. (e) 1 g once a day. (f) 40 mg/240 mg twice a day. (g) 120 mg (H0 60 mg, H12 60 mg) on the first day, then 60 mg per day on the following days. (h) 500 mg twice a day. Reproduced under Creative Commons Licence from Pallich et al. [102]

symptom duration may be unreliable particularly in younger children. Duration between symptom onset to attendance was 4 days [94]. Time from presentation at a treatment facility to death can also be short (a median of 3 days in one study) so there is a small window for intervention [95].

Features at admission that are consistently associated independently with mortality across several studies include younger age and a high viral load (low cycle threshold (CT) with a viral polymerase chain reaction) as with mixed age cohorts [92, 95–97, 99, 100, 103, 104]. Shah et al. record a hazard ratio of 9.2 (95% confidence interval 3.8–22.5) for death with a CT value <25 at admission [94]. However, in interpreting viral CT values, discrepancies between laboratories and assays used should be borne in mind, as there is currently no universally used assay. Bleeding at admission and diarrhoea have also been reported to be associated with an increased risk of death [95, 97]. Finally, in mixed age cohorts, concomitant infection with malaria has also been significantly associated with mortality [104].

During admission, development of bleeding, shortness of breath and diarrhoea at any point are all independently associated with mortality, as well as tachycardia within the first week of admission [103]. Dysphagia was more common those who died and in Shah et al.'s younger cohort (children under 5 years), hiccoughs, confusion and bleeding were only present in children who died [94]. For those patients who recovered, there was a period of defervescence over 7–10 days [103]. No children died after day 13 of admission in one study [96]. Median duration of admission those who survived varies between 2 and 3 weeks [95, 97]. Palich et al. have thoroughly documented the progress of a 6 year old with severe EVD managed at a treatment centre with facilities of laboratory monitoring and intravenous fluid and electrolyte replacement. Figure 4.1 summarises the clinical features and interventions received for this child. Timing of gastrointestinal and neurological symptoms can be seen along with electrolyte disturbances and interventions.

Late complications during admission include tonic-clonic seizures, which can be prolonged and severe [95, 102]. In at least two cases, children were left with severe disabilities after a prolonged seizure including blindness and paraplegia [95] (Howlett et al. in review). In Bower et al.'s study of late deaths within a cohort of 151 EVD survivors, one 6 year old and one 17 year old died after discharge from an Ebola treatment centre [92]. The 6 year old had symptoms consistent with tuberculosis, although also had a post-mortem mouth swab that was borderline positive for Ebola virus [92]. The 17 year old died 5 weeks after discharge with weight loss, night sweats and dysphagia with a post-mortem swab negative for Ebola virus [92]. It appears that true recrudescence of virus as has been seen in adult patients may be very rare although possible [18, 105].

4.3.4 Suspect Ebola Virus Disease Case Definition in Children

As can be seen by both the breadth of symptoms exhibited by children with EVD, the variations in frequency of symptoms between cohorts even within the West African outbreak, and the non-specificity of these symptoms against a backdrop of high

Table 4.12 Scores for each of the variable included in the Paediatric Ebola Predictive score

Variable	Coefficient (95% CI) from multivariable model	p-value	Integer score value
Positive contact	2.21 (1.58–2.83)	<0.001	+2
Conjunctivitis	1.34 (0.62–2.05)	<0.001	+2
Age 2+ years	1.06 (0.37–1.75)	0.003	+2
Fever	0.99 (−0.66–2.63)	0.241	+1
Anorexia	0.59 (−0.18–1.35)	0.133	+1
Male gender	0.49 (−0.11–1.08)	0.111	+1
Abdominal pain	0.42 (−0.23–1.08)	0.205	+1
Diarrhoea	0.40 (−0.21–1.01)	0.197	+1
Difficulty breathing	−0.57 (−1.39–0.24)	0.168	−1
Difficulty swallowing	−0.59 (−1.39–0.19)	0.138	−1
Headache	−0.63 (−1.29–0.35)	0.063	−1
Skin rash	−1.00 (−2.13–0.14)	0.085	−2

malaria prevalence and other childhood illnesses, the clinical case definition for EVD is key. A sensitive and specific clinical case definition for EVD in children would allow rapid access to appropriate treatment for children with EVD, crucial when early mortality is so high, and also protect children without EVD (with a different illness) from exposure to EVD while awaiting laboratory test confirmation. To date there has been only one attempt at deriving a paediatric-specific case definition using multicentre data on over 1000 children from the West African outbreak, and this case definition has not yet been validated on wider datasets [106]. It also does not include malaria rapid diagnostic test results which have been shown to be an important discriminator in a mixed age study [107]. However, these limitations aside, the paediatric Ebola predictive score (PEP) score derived had excellent discrimination (area under receiver operating characteristics curve (AUROC) = 0.8). The scores for each clinical feature within the score are shown in Table 4.12, along with the coefficient from the multivariable model used to derive them and associated p values. As the score has not yet been externally validated, it is presented here for information rather than recommendation for use. It is envisaged that the PEP score could be used together with EVD rapid diagnostic tests, several of which were trialled during the outbreak, to expedite rapid accurate diagnosis of EVD [108, 109].

4.3.5 Management

In the stressful environment of an EVD outbreak, the needs of children can be overlooked. Certain considerations should be planned for in advance to ensure

adequate care for children. These considerations include both clinical, nutritional and pastoral care of children admitted with EVD.

4.3.5.1 Assessment and Investigations

Initial assessment for emergency clinical signs should take place using the Emergency Triage and Assessment Treatment (ETAT) algorithm for children [110]. Assessment for dehydration is key. Weighing can be a challenge in facilities with limited resources, so we would suggest using a set of scales within a ziplock plastic bag (or similar) to promote easy cleaning, prevent contamination and prolong the lifespan of the scales when being cleaned with high concentration chlorine. Signs of severe or moderate dehydration should be assessed clinically on admission and at least daily (preferably more frequently during the gastrointestinal phases of disease) during admission as per guidelines in the WHO pocket book of hospital care for children [110]. Pain and distress is common in children with EVD and should be specifically assessed for and treated both at initial admission and on reassessment.

Blood should be taken for EVD PCR as per WHO recommendations for exposure prone procedures, ideally by at least two staff [9]. This is particularly important for children who need to be held still during phlebotomy. A malarial RDT should be performed if possible in high prevalence areas, as coinfection is not infrequent [107, 111]. A glucose test should also be performed as a priority if feasible.

4.3.5.2 Clinical Management

Any initial emergency clinical features noted during ETAT assessment should be managed as per the relevant treatment algorithm. Placing a laminated version of the algorithm on the wall in triage will prove useful for treating clinicians. Fever should be managed with antipyretics dosed as per weight/age, and again a laminated list of age/weight appropriate commonly used medications will prove useful for clinical staff both in and outside the "Red Zone".

Adequate hydration is a mainstay of therapy for those with both mild and severe EVD. All children should be offered oral rehydration solution and be supported to drink it, either by a caregiver or a dedicated staff member as they may be too weak to drink it themselves [112]. If the child is severely dehydrated or malnourished, or unable to tolerate oral fluids, intravenous fluid resuscitation and maintenance will be needed. This should be carried out according to the presence/absence of shock, severe malnutrition and severe anaemia according to the detailed protocols in the WHO Pocket guide to Clinical Management of patients with viral haemorrhagic fever. These include recommendations for the volume and rate of fluid replacement and are not reproduced here in the interests of space, but we recommend that laminated versions of the fluid replacement protocols be available both in the "Red Zone" and outside where fluids and medications are prepared and prescribed [79]. In brief, the three signs of shock considered are: cold extremities, weak **AND** fast pulse and a capillary refill time of over 3 s; severe anaemia is diagnosed with a haematocrit <15 or a haemoglobin less than 5 g/dL; and severe acute malnutrition is diagnosed with a MUAC of <115 mm [79].

Although in the context of large gastrointestinal fluid losses, the benefits of intravenous fluid resuscitation is unequivocal and recommended by the WHO, fluid resuscitation should ideally be carried out with input/output monitoring and using a paediatric giving set [79]. Aggressive fluid resuscitation in African children with signs of severe infection (excluding gastrointestinal infections) is not proven to be safe, so every effort should be made to monitor both the volume of fluid given and the clinical impact on the child [113]. Ongoing assessment of hydration status is therefore key, and should be planned for in daily staffing allocations. If possible, electrolytes should also be monitored and abnormalities corrected, as large derangements in sodium, potassium and calcium have all been seen in children with EVD [95, 102]. Hypoglycaemia has been demonstrated to be common in children with EVD and should be monitored for as a priority if feasible, but if monitoring is not feasible, glucose should be given intravenously empirically in the case of seizure, coma or lethargy [95]. Five percent dextrose should be used in all maintenance fluids [79]. For persistent vomiting, ondansetron (or if unavailable, promethazine, though with care to monitor for extra pyramidal side effects) may limit symptoms and permit oral intake [79].

If a malarial RDT is not available or the result is positive, children should receive a weight- or age- appropriate dose of artesunate combination therapy (ACT) or intravenous/intramuscular artesunate if there are signs of severe malaria for at least hours followed by a 3 day course of oral ACT [79].

Owing to the overlap of symptoms of EVD with sepsis, it is both the WHO and our recommendation that all children under 5 years of age admitted with suspect EVD should be treated with empirical antibiotics on admission. WHO guidelines are that all under 5 s should receive intravenous or intramuscular broad spectrum antibiotics (e.g. ceftriaxone), although evidence is limited as to whether in relatively well younger children parentral antimicrobials will provide a benefit over enteral [95]. For older children, the decision to start antibiotics lies with the treating clinician as evidence is lacking, but the local prevalence of other common childhood illnesses such as pneumonia and gastroenteritis should be taken into consideration. If used locally, the empirical treatment guidelines laid out in the WHO Pocket book of Hospital Care for Children and the Integrated Management of Neonatal and Childhood illness should be utilised [110]. All those receiving antiretroviral or antituberculous therapy should continue it, and restart as soon as possible if treatment is interrupted.

Pain and distress has been noted frequently in children with EVD (see section on clinical features at presentation and disease progression) and should be managed expectantly with age/weight appropriate doses of simple analgesia (paracetamol), or opiates (tramadol followed by morphine if available) if there is ongoing pain or distress in younger children. Dysphagia has been noted to be associated with retrosternal chest pain in adults, and should be managed in children with

Management of bleeding can include transfusion of packed red cells or components (e.g. fresh frozen plasma if required), and particularly for malnourished children supplementation of vitamin K (enterally or parentrally) should be considered. However evidence is limited, particularly as regards antifibrinolytics [79].

Other empirical management for shortnesss of breath (oxygen via nasal cannulae if available); seizures (glucose if hypoglycaemic or monitoring unavailable and benzodiazepines); confusion (reassurance, possibly sedation if agitation severe) should be given as needed/available depending on context. In the unfamiliar and frightening environment of the treatment centre, reassurance from staff or other caregivers cannot be overemphasised as a crucial therapeutic intervention.

4.3.5.3 Nutrition

Given the gastrointestinal symptoms of EVD and the background prevalence of malnutrition in the countries EVD has affected, assessment for malnutrition at admission is advisable. WHO guidelines are that a mid-upper arm circumference (MUAC) should be checked and oedema assessed for at a minimum if it not feasible to assess anthropometry in more detail [87]. As weight of children is key both in assessing hydration and nutritional status, we would suggest checking weight on admission in addition to MUAC and presence/absence of oedema. As above, scales could be kept within a ziplock plastic bag to protect from high concentration chlorine and ease of decontamination after use.

If severe acute malnutrition is present, fluid resuscitation should be given according to WHO guidelines using smaller volumes and ReSoMal™ as opposed to standard oral rehydration salts [79].

For asymptomatic breastfed infants whose mother is unwell with EVD, current recommendations based on available evidence are to separate the mother and infant and use replacement ready to use infant formula [82, 87]. If the infant also has signs/symptoms of EVD, or a confirmed diagnosis, the current guidelines are that the benefits of continuing breastfeeding are likely to outweigh the risks and so breastfeeding should be continued if the mother is well enough to do so [87].

4.3.5.4 Pastoral Care

The challenges of caring for unwell, frightened children within a "Red Zone" have been well documented during the West African outbreak [94, 96, 112, 114, 115]. This problem is amplified as many children were admitted unaccompanied by a caregiver (up to 40% in one study [95]), either because family members had already succumbed to disease or because fear of nosocomial infection prevented either relatives from wishing to enter the "Red Zone" or unit policies forbade the admission of asymptomatic caregivers. Apart from the risk of nosocomial infection between suspect EVD patients posed by unaccompanied children (who were difficult to keep in their allocated bed space); there were also the hazards of sharps bins and high concentration chlorine within the Red Zone. Units developed different practices to mitigate these risks. One treatment centre had a nursing round specifically dedicated to paediatric care 8 times a day, to manage intravenous infusions and ensure that unaccompanied small children were fed 8 times daily with therapeutic milk [96].

Other units started to develop protocols to employ survivors (believed to be at low risk of re-infection with EVD) to care for unaccompanied children, but none, to our knowledge put the protocols into practice before the end of the West African outbreak. The possibility of either dedicated paediatric clinicians or a specific

paediatric area with risks e.g. sharps and chlorine buckets minimised have both been discussed, and were put into limited practice towards the end of the West African outbreak. One study collected data post-discharge from caregivers admitted to Ebola Holding Units with children who subsequently tested negative for EVD [116]. It was possible to contact approximately 25% of caregivers admitted, and of those 125 contacted, none were subsequently readmitted with EVD. For the overwhelming majority of those who it was not possible to contact, this was due to a lack of contact details. This indicates that it may not be as dangerous as anticipated to admit asymptomatic caregivers with their children, although this should be done in the context of very clear instructions about hand hygiene and strict isolation between patients.

In the event that admitting caregivers with children is not possible or not felt to be safe, alternative mechanisms for managing the pastoral care needs of children have included using stretches of clear plastic sheeting between "Red" and "Green" Zones to enable frequent communication with staff/relatives outside with children inside (Heldermann T., personal communication); or frequent ward rounds of dedicated clinical staff as above.

Post discharge, consideration should be given to the mental health and developmental impact on children who, though they may have made a full physical recovery, have endured the traumatic experience of disease, separation from family, treatment within a facility and often witnessing sickness and death of parents and other close family members [84].

Finally, the long term plight of Ebola orphans should be considered. The West African outbreak resulted in an estimated 9600 Ebola orphans across the three countries which bore the brunt [117]. Although these children comprise a small proportion of the total number of orphans across the three countries, (1.4% of 711,600), whether they themselves were infected with EVD or not, they are likely to be the victims of considerable stigma and may not be welcomed into fostering families as other orphans might be [117].

References

1. Sprecher A. Filovirus haemorrhagic fever guidelines. Brussels: Médecins Sans Frontières; 2013.
2. O'Shea MK, Clay KA, Craig DG, et al. Diagnosis of febrile illnesses other than Ebola virus disease at an Ebola treatment unit in Sierra Leone. Clin Infect Dis. 2015;61(5):795–8.
3. WHO. Clinical management of patients with viral haemhorrhagic fever. Geneva: WHO; 2016.
4. Schieffelin JS, Shaffer JG, Goba A, et al. Clinical illness and outcomes in patients with Ebola in Sierra Leone. N Engl J Med. 2014;371:2092–100.
5. Dallatomasina S, Crestani R, Sylvester Squire J, et al. Ebola outbreak in rural West Africa: epidemiology, clinical features and outcomes. Trop Med Int Health. 2015;20(4):448–54.
6. Lado M, Walker NF, Baker P, et al. Clinical features of patients isolated for suspected Ebola virus disease at Connaught Hospital, Freetown, Sierra Leone: a retrospective cohort study. Lancet Infect Dis. 2015;15(9):1024–33.
7. Bah EI, Lamah MC, Fletcher T, et al. Clinical presentation of patients with Ebola virus disease in Conakry, Guinea. N Engl J Med. 2015;372(1):40–7.

8. Ansumana R, Jacobsen KH, Sahr F, et al. Ebola in Freetown area, Sierra Leone—a case study of 581 patients. N Engl J Med. 2015;372(6):587–8.
9. Chertow DS, Kleine C, Edwards JK, Scaini R, Giuliani R, Sprecher A. Ebola virus disease in West Africa—clinical manifestations and management. N Engl J Med. 2014;371(22):2054–7.
10. Qin E, Bi J, Zhao M, et al. Clinical features of patients with Ebola virus disease in Sierra Leone. Clin Infect Dis. 2015;61(4):491–5.
11. Hunt L, Gupta-Wright A, Simms V, et al. Clinical presentation, biochemical, and haematological parameters and their association with outcome in patients with Ebola virus disease: an observational cohort study. Lancet Infect Dis. 2015;15(11):1292–9.
12. Clay KA, Johnston AM, Moore A, O'Shea MK. Targeted electrolyte replacement in patients with Ebola virus disease. Clin Infect Dis. 2015;61(6):1030–1.
13. O'Shea MK, Clay KA, Craig DG, et al. A health care worker with Ebola virus disease and adverse prognostic factors treated in Sierra Leone. Am J Trop Med Hyg. 2016;94(4):829–32.
14. Nicholson-Roberts T, Fletcher T, Rees P, et al. Ebola virus disease managed with blood product replacement and point of care tests in Sierra Leone. QJM. 2015;108(7):571–2.
15. Uyeki TM, Mehta AK, Davey RT Jr, et al. Clinical management of Ebola virus disease in the United States and Europe. N Engl J Med. 2016;374(7):636–46.
16. Brown C, Krueuls B, Baker P, Baker T, Boyles T, Lado M, Johnson O. Ebola and provision of critical care. Lancet. 2015;385(9976):1392.
17. Chertow DS, Uyeki TM, DuPont HL. Loperamide therapy for voluminous diarrhea in Ebola virus disease. J Infect Dis. 2015;211(7):1036–7.
18. Howlett P, Brown C, Helderman T, et al. Ebola virus disease complicated by late-onset encephalitis and polyarthritis, Sierra Leone. Emerg Infect Dis. 2016;22(1):150–2.
19. Sagui E, Janvier F, Baize S, et al. Severe Ebola virus infection with encephalopathy: evidence for direct virus involvement. Clin Infect Dis. 2015;61(10):1627–8.
20. Fowler RA, Fletcher T, Fischer WA 2nd, et al. Caring for critically ill patients with Ebola virus disease. Perspectives from West Africa. Am J Respir Crit Care Med. 2014;190(7):733–7.
21. Kreuels B, Witchmann D, Emmerich P, et al. A case of severe Ebola virus infection complicated by gram-negative septicemia. N Engl J Med. 2014;371(25):2394–401.
22. Perner A, Fowler RA, Bellomo R, Roberts I. Ebola care and research protocols. Intensive Care Med. 2015;41(1):111–4.
23. Murthy S, Ebola Clinical Care authors group. Ebola and provision of critical care. Lancet. 2015;385(9976):1392–3.
24. Büttner S, Koch B, Dolnik O, et al. Extracorporeal virus elimination for the treatment of severe Ebola virus disease—first experience with lectin affinity plasmapheresis. Blood Purif. 2014;38 (3–4):286–91.
25. Mupapa K, Massamba M, Kibadi K, et al. Treatment of Ebola hemorrhagic fever with blood transfusions from convalescent patients. International Scientific and Technical Committee. J Infect Dis. 1999;179(Suppl 1):S18–23.
26. Dunning J, Kennedy SB, Antierens A, et al. Experimental treatment of Ebola virus disease with Brincidofovir. PLoS One. 2016;11(9):e0162199.
27. Sissoko D, Laouenan C, Folkesson E, et al. Experimental treatment with Favipiravir for Ebola virus disease (the JIKI trial): a historically controlled, single-arm proof-of-concept trial in Guinea. PLoS Med. 2016;13(3):e1001967.
28. Bai CQ, Mu JS, Kargbo D, et al. Clinical and virological characteristics of Ebola virus disease patients treated With Favipiravir (T-705)-Sierra Leone, 2014. Clin Infect Dis. 2016;63 (10):1288–94.
29. Dunning J, Sahr F, Rojek A, et al. Experimental treatment of Ebola virus disease with TKM-130803: a single-arm phase 2 clinical trial. PLoS Med. 2016;13(4):e1001997.
30. PREVAIL II Writing Group Multi-National PREVAIL II Study Team. A randomized, controlled trial of ZMapp for Ebola virus infection. N Engl J Med. 2016;375:1448–56.
31. van Griensven J, Edwards T, de Lamballerie X, et al. Evaluation of convalescent plasma for Ebola virus disease in Guinea. N Engl J Med. 2016;374:33–42.

32. Sahr F, Ansumana R, Massaquoi TA, Idriss BR, Sesay FR, Lamin JM, et al. Evaluation of convalescent whole blood for treating Ebola Virus Disease in Freetown, Sierra Leone. J Infect. 2017;74(3):302–9.
33. Konde MK, Baker DP, Traore FA, Sow MS, Camara A, Barry AA, et al. Interferon beta-1a for the treatment of Ebola virus disease: a historically controlled, single-arm proof-of-concept trial. PLoS One 2017;12(2):e0169255.
34. Brown CS, Houlihan CF, Lado M, Mounter N, Youkee D. What do we know about controlling Ebola virus disease outbreaks? Retrovirology. 2017;8:1–12.
35. Lanini S, Zumla A, Ioannidis JP, et al. Are adaptive randomised trials or non-randomised studies the best way to address the Ebola outbreak in west Africa? Lancet Infect Dis. 2015;15 (6):738–45.
36. Thi EP, Mire CE, Lee AC, et al. Lipid nanoparticle siRNA treatment of Ebola-virus-Makona-infected nonhuman primates. Nature. 2015;521(7552):362–5.
37. Jacobs M, Aarons E, Bhagani S, et al. Post-exposure prophylaxis against Ebola virus disease with experimental antiviral agents: a case-series of health-care workers. Lancet Infect Dis. 2015;15(11):1300–4.
38. Centers for Disease Control and Prevention. Outbreaks chronology: Ebola virus disease, Ebola hemorrhagic fever. CDC; 2015. Retrieved from http://www.cdc.gov/vhf/ebola/outbreaks/history/chronology.html
39. WHO, UNFPA, UNICEF, AMDD. Monitoring emergency obstetric care, 164; 2009. Retrieved from http://apps.who.int/iris/bitstream/10665/44121/1/9789241547734_eng.pdf
40. World Health Organization. GHO, By category, Maternal mortality – data by country. Global Health Observatory data repository: maternal mortality data by country. World Health Organization; 2016a.
41. World Health Organization. WHO, Guinea. WHO. World Health Organization; 2016b. Retrieved from http://www.who.int/countries/gin/en/
42. World Health Organization. WHO, Liberia. WHO. World Health Organization; 2016c. Retrieved from http://www.who.int/countries/lbr/en/
43. World Health Organization. WHO, Sierra Leone. WHO. World Health Organization; 2016d. Retrieved from http://www.who.int/countries/sle/en/
44. Estimates by WHO, UNICEF, UNFPA, World Bank Group and the United Nations Population Division, Trends in Maternal Mortality: 1990 to 2015. Retrieved from http://apps.who.int/iris/bitstream/10665/112682/2/9789241507226_eng.pdf
45. Maternal Mortality Estimation Interagency Group. Maternal mortality 1990–2015, Sierra Leone. 2016. http://www.who.int/gho/maternal_health/countries/sle.pdf. Retrieved 2 Apr 2016.
46. World Health Organization. Density of doctors, nurses and midwives in the 49 priority countries; 2010.
47. Brolin Ribacke KJ, van Duinen AJ, Nordenstedt H, Höijer J, Molnes R, Froseth TW, et al. The impact of the West Africa Ebola outbreak on obstetric health care in Sierra Leone. PLoS One. 2016;11(2):e0150080. https://doi.org/10.1371/journal.pone.0150080
48. World Health Organization. Ebola Situation Report – 23 September 2015, Ebola; 2015. Retrieved from http://apps.who.int/ebola/current-situation/ebola-situation-report-23-september-2015
49. Evans DK, Goldstein M, Popova A. Health-care worker mortality and the legacy of the Ebola epidemic. Lancet Glob Health. 2015;3(8):e439–40. https://doi.org/10.1016/S2214-109X(15)00065-0
50. Diggins J, Mills E. The pathology of inequality: gender and Ebola in West Africa. IDS; 2015. Retrieved from http://opendocs.ids.ac.uk/opendocs/handle/123456789/5856
51. Gerntholtz L, Gibbs A, Willan S. The African Women's Protocol: bringing attention to reproductive rights and the MDGs. PLoS Med. 2011;8(4):e1000429. https://doi.org/10.1371/journal.pmed.1000429.
52. Sow, M. S., Etard, J.-F., Baize, S., Magassouba, N., Faye, O., Msellati, P., et al. New evidence of long-lasting persistence of Ebola virus genetic material in semen of survivors. J Infect Dis. 2016;jiw078. https://doi.org/10.1093/infdis/jiw078

53. Mcmichael A, Simon AK, Hollander GA. Evolution of the immune system in humans from infancy to old age. Proc Biol Sci. 2015;282(1821):20143085. https://doi.org/10.1098/rspb.2014.3085.
54. UNFPA. The state of the world's midwifery 2014; 2014. Retrieved from http://www.unfpa.org/sites/default/files/pub-pdf/EN_SoWMy2014_complete.pdf
55. WHO Library Cataloguing-in-Publication Data. Clinical management of patients with viral haemorrhagic fever. A pocket guide for front-line health workers; 2016. Retrieved from http://apps.who.int/iris/bitstream/10665/205570/1/9789241549608_eng.pdf?ua=1
56. Haaskjold YL, Bolkan HA, Krogh KØ, Jongopi J, Lundeby KM, Mellesmo S, Blomberg B. Clinical features of and risk factors for fatal Ebola virus disease, Moyamba District, Sierra Leone, December 2014–February 2015. Emerg Infect Dis. 2016;*22*(9):1537–44. https://doi.org/10.3201/eid2209.151621.
57. Schieffelin JS, Shaffer JG, Goba A, Gbakie M, Gire SK, Colubri A, Garry RF. Clinical illness and outcomes in patients with Ebola in Sierra Leone. N Engl J Med. 2014;371(22):2092–100. https://doi.org/10.1056/NEJMoa1411680.
58. Bower H, Grass JE, Veltus E, Brault A, Campbell S, Basile AJ, et al. Delivery of an Ebola virus-positive stillborn infant in a rural community health center, Sierra Leone, 2015. Am J Trop Med Hyg. 2016;94(2):417–9. https://doi.org/10.4269/ajtmh.15-0619.
59. Mpemba F, Kampo S, Zhang X. Towards 2015: post-partum haemorrhage in sub-Saharan Africa still on the rise. J Clin Nurs. 2014;23(5–6):774–83. https://doi.org/10.1111/jocn.12126.
60. World Health Organization. WHO | Stillbirths. 2016e. http://www.who.int/maternal_child_adolescent/epidemiology/stillbirth/en/. Retrieved 25 Sept 2016.
61. Deaver JE, Siempre Salud A, Alta C, Wayne Cohen PR, Cohen WR. Ebola virus screening during pregnancy in West Africa: unintended consequences. J Perinat Med. 2015;43(6):649–55. https://doi.org/10.1515/jpm-2015-0118.
62. Akerlund E, Prescott J, Tampellini L. Shedding of Ebola virus in an asymptomatic pregnant woman. N Engl J Med. 2015;372(25):2467–9. https://doi.org/10.1056/NEJMc1503275.
63. Caluwaerts S, Lagrou D. Guidance paper Ebola Treatment Centre (ETC): Pregnant & lactating women. Table of content. 2014. Retrieved from https://www.rcog.org.uk/globalassets/documents/news/etc-preg-guidance-paper.pdf.
64. World Health Organization. WHO/OMS. Setting up an Ebola Treatment Center (ETC); 2016e. https://extranet.who.int/ebolafmt/sites/default/files/ETC_considerations_for_set_up.pdf
65. World Health Organization. WHO model list of essential medicines 19th list WHO model list of essential medicines (April 2015) Explanatory notes. 2015c. Retrieved from http://www.who.int/medicines/publications/essentialmedicines/en/.
66. World Health Organization. Guidelines for the treatment of malaria. 3rd ed. 2015b. Retrieved from http://apps.who.int/iris/bitstream/10665/162441/1/9789241549127_eng.pdf.
67. MacLennan K, O'Brien K, Macnab WR. Core topics in obstetric anaesthesia. Cambridge University Press; 2015.
68. Dörnemann J, Burzio C, Ronsse A, Sprecher A, De Clerck H, Van Herp M, et al. First newborn baby to receive experimental therapies survives Ebola virus disease. J Infect Dis. 2017;jiw493. https://doi.org/10.1093/infdis/jiw493.
69. Nelson JM, Griese SE, Goodman AB, Peacock G. Live neonates born to mothers with Ebola virus disease: a review of the literature. J Perinatol. 2016;36(6):411–4. https://doi.org/10.1038/jp.2015.189.
70. Streifel C. How did Ebola impact maternal/child health in Liberia and Sierra Leone? Center for Strategic and International Studies; 2015. https://csis-prod.s3.amazonaws.com/s3fs-public/legacy_files/files/publication/151019_Streifel_EbolaLiberiaSierraLeone_Web.pdf
71. Kamali A, Jamieson DJ, Kpaduwa J, Schrier S, Kim M, Green NM, et al. Pregnancy, labor, and delivery after Ebola virus disease and implications for infection control in obstetric services, United States. Emerg Infect Dis. 2016;22(7):1156–61. https://doi.org/10.3201/eid2207.160269.
72. Fallah MP, et al. Pregnancy outcomes in Liberian women who conceived after recovery from Ebola virus disease. Lancet Glob Health. 2016;4(10):e678–9.

73. Centers for Disease Control and Prevention. Recommendations for breastfeeding/infant feeding in the context of Ebola virus disease; 2016. https://www.cdc.gov/vhf/ebola/hcp/recommendations-breastfeeding-infant-feeding-ebola.html
74. Garske T, Cori A, Ariyarajah A, et al. Heterogeneities in the case fatality ratio in the West African Ebola outbreak 2013–2016. Philos Trans R Soc Lond B Biol Sci. 2017; 372(1721).
75. Glynn JR. Age-specific incidence of Ebola virus disease. Lancet. 2015;386(9992):432.
76. Dowell SF, Mukunu R, Ksiazek TG, Khan AS, Rollin PE, Peters CJ. Transmission of Ebola hemorrhagic fever: a study of risk factors in family members, Kikwit, Democratic Republic of the Congo, 1995. Commission de Lutte contre les Epidemies a Kikwit. J Infect Dis. 1999;179 (Suppl 1):S87–91.
77. Dowell SF. Ebola hemorrhagic fever: why were children spared? Pediatr Infect Dis J. 1996;15 (3):189–91.
78. Helleringer S, Noymer A, Clark SJ, McCormick T. Did Ebola relatively spare children? Lancet. 2015;386(10002):1442–3.
79. World Health Organization. Clinical management of patients with viral haemorrhagic fever: a pocket guide for front-line health workers. Geneva: World Health Organisation; 2016.
80. Glynn JR, Bower H, Johnson S, et al. Asymptomatic infection and unrecognised Ebola virus disease in Ebola-affected households in Sierra Leone: a cross-sectional study using a new non-invasive assay for antibodies to Ebola virus. Lancet Infect Dis. 2017;17(6):645–53.
81. Bower H, Johnson S, Bangura MS, et al. Exposure-specific and age-specific attack rates for Ebola virus disease in Ebola-affected households, Sierra Leone. Emerg Infect Dis. 2016;22 (8):1403–11.
82. Bower H, Johnson S, Bangura MS, et al. Effects of mother's illness and breastfeeding on risk of Ebola virus disease in a cohort of very young children. PLoS Negl Trop Dis. 2016;10(4): e0004622.
83. Nordenstedt H, Bah EI, de la Vega MA, et al. Ebola virus in breast milk in an Ebola virus-positive mother with twin babies, Guinea, 2015. Emerg Infect Dis. 2016;22(4):759–60.
84. Vetter P, Kaiser L, Schibler M, Ciglenecki I, Bausch DG. Sequelae of Ebola virus disease: the emergency within the emergency. Lancet Infect Dis. 2016;16(6):e82–91.
85. World Health Organization. Clinical care for survivors of Ebola virus disease 22 January 2016. World Health Organization, Geneva; 2016.
86. Sissoko D, Keita M, Diallo B, et al. Ebola virus persistence in breast milk after no reported illness: a likely source of virus transmission from mother to child. Clin Infect Dis. 2017;64 (4):513–6.
87. WHO. Nutritional Care of children and adults with Ebola virus disease in treatment centres; 2015.
88. Lau MS, Dalziel BD, Funk S, et al. Spatial and temporal dynamics of superspreading events in the 2014–2015 West Africa Ebola epidemic. Proc Natl Acad Sci USA. 2017;114(9):2337–42.
89. Skrip LA, Fallah MP, Gaffney SG, et al. Characterizing risk of Ebola transmission based on frequency and type of case-contact exposures. Philos Trans R Soc Lond B Biol Sci. 2017; 372 (1721).
90. Lindblade KA, Kateh F, Nagbe TK, et al. Decreased Ebola transmission after rapid response to outbreaks in remote areas, Liberia, 2014. Emerg Infect Dis. 2015;21(10):1800–7.
91. Glynn JR, Bower H, Johnson S, Turay C, Sesay D, Mansaray SH, Kamara O, Kamara AJ, Bangura MS, Checchi F. Variability in intrahousehold transmission of Ebola virus, and estimation of the household secondary attack rate. J Infect Dis. 2018;217(2):232–7. https://doi.org/10.1093/infdis/jix579.
92. Bower H, Smout E, Bangura MS, et al. Deaths, late deaths, and role of infecting dose in Ebola virus disease in Sierra Leone: retrospective cohort study. BMJ. 2016;353:i2403.
93. Ebola Response WHO, Team A-AJ, Ariyarajah A, et al. Ebola virus disease among male and female persons in West Africa. N Engl J Med. 2016;374(1):96–8.
94. Shah T, Greig J, van der Plas LM, et al. Inpatient signs and symptoms and factors associated with death in children aged 5 years and younger admitted to two Ebola management centres in Sierra Leone, 2014: a retrospective cohort study. Lancet Glob Health. 2016;4(7):e495–501.

95. Fitzgerald F, Naveed A, Wing K, et al. Ebola virus disease in children, Sierra Leone, 2014–2015. Emerg Infect Dis. 2016;22(10):1769–77.
96. Damkjaer M, Rudolf F, Mishra S, Young A, Storgaard M. Clinical features and outcome of Ebola virus disease in pediatric patients: a retrospective case series. J Pediatr. 2017;182:378–81.e1.
97. Smit MA, Michelow IC, Glavis-Bloom J, Wolfman V, Levine AC. Characteristics and outcomes of pediatric patients with Ebola virus disease admitted to treatment units in Liberia and Sierra Leone: a retrospective cohort study. Clin Infect Dis. 2017;64(3):243–9.
98. World Health Organization. Clinical management of patients in the Ebola treatment Centres and other Care Centres in Sierra Leone: A Pocket Guide. Interim emergency guidelines. Sierra Leone adaptation; 2014.
99. WHO Ebola Response Team, Agua-Agum J, Ariyarajah A, et al. Ebola virus disease among children in West Africa. N Engl J Med. 2015;372(13):1274–7.
100. Cherif MS, Koonrungsesomboon N, Kasse D, et al. Ebola virus disease in children during the 2014–2015 epidemic in Guinea: a nationwide cohort study. Eur J Pediatr. 2017;176(6):791–6.
101. Mupere E, Kaducu OF, Yoti Z. Ebola haemorrhagic fever among hospitalised children and adolescents in northern Uganda: epidemiologic and clinical observations. Afr Health Sci. 2001;1(2):60–5.
102. Palich R, Gala JL, Petitjean F, et al. A 6-year-old child with severe Ebola virus disease: laboratory-guided clinical care in an Ebola treatment center in Guinea. PLoS Negl Trop Dis. 2016;10(3):e0004393.
103. Skrable K, Roshania R, Mallow M, Wolfman V, Siakor M, Levine AC. The natural history of acute Ebola virus disease among patients managed in five Ebola treatment units in West Africa: a retrospective cohort study. PLoS Negl Trop Dis. 2017;11(7):e0005700.
104. Hartley MA, Young A, Tran AM, et al. Predicting Ebola severity: a clinical prioritization score for Ebola virus disease. PLoS Negl Trop Dis. 2017;11(2):e0005265.
105. Jacobs M, Rodger A, Bell DJ, et al. Late Ebola virus relapse causing meningoencephalitis: a case report. Lancet. 2016;388(10043):498–503.
106. Fitzgerald F, Wing K, Naveed A, Gbessay M, Ross J, Checchi F, Youkee D, Jalloh MB, Baion DE, Mustapha A, Jah H, Lako S, Oza S, Boufkhed S, Feury R, Bielicki J, Williamson E, Gibb DM, Klein N, Sahr F, Yeung S. Development of a Pediatric Ebola Predictive Score, Sierra Leone. Emerg Infect Dis. 2018;24(2):311–9.
107. Hartley MA, Young A, Tran AM, et al. Predicting Ebola infection: a malaria-sensitive triage score for Ebola virus disease. PLoS Negl Trop Dis. 2017;11(2):e0005356.
108. Walker NF, Brown CS, Youkee D, et al. Evaluation of a point-of-care blood test for identification of Ebola virus disease at Ebola holding units, Western Area, Sierra Leone, January to February 2015. Euro Surveill. 2015;20(12).
109. Broadhurst MJ, Brooks TJ, Pollock NR. Diagnosis of Ebola virus disease: past, present, and future. Clin Microbiol Rev. 2016;29(4):773–93.
110. World Health Organization. Pocket book of hospital care for children: guidelines for the management of common childhood illnesses. In: . Geneva: World Health Organization. p. 2013.
111. Barry M, Traore FA, Sako FB, et al. Ebola outbreak in Conakry, Guinea: epidemiological, clinical, and outcome features. Med Mal Infect. 2014;44(11–12):491–4.
112. Fitzgerald F, Awonuga W, Shah T, Youkee D. Ebola response in Sierra Leone: the impact on children. J Infect. 2016;72:S6–S12.
113. Maitland K, Kiguli S, Opoka RO, et al. Mortality after fluid bolus in African children with severe infection. N Engl J Med. 2011;364(26):2483–95.
114. Trehan I, Kelly T, Marsh RH, George PM, Callahan CW. Moving towards a more aggressive and comprehensive model of care for children with Ebola. J Pediatr. 2016;170:28–33.e7.
115. Aswani V. Being a pediatrician in an Ebola epidemic. Pediatrics. 2015.
116. Fitzgerald F, Wing K, Naveed A, Gbessay M, Ross JCG, Checchi F, Youkee D, Jalloh MB, Baion D, Mustapha A, Jah H, Lako S, Oza S, Boufkhed S, Feury R, Bielicki J, Williamson E, Gibb DM, Klein N, Sahr F, Yeung S. Risk in the "Red Zone": outcomes for children admitted to Ebola holding units in Sierra Leone without Ebola virus disease. Clin Infect Dis. 2017;65(1):162–5. https://doi.org/10.1093/cid/cix223.
117. Evans DK, Popova A. West African Ebola crisis and orphans. Lancet. 2015;385(9972):945–6.