World Health Organization

Optimized Supportive Care for Ebola Virus Disease

CLINICAL MANAGEMENT STANDARD OPERATING PROCEDURES

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Optimized supportive care for ebola virus disease: clinical management standard operating procedures

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ABBREVIATIONS AND ACRONYMS

AG	anion gap
ALIMA	The Alliance for International Medical Action
ALT	alanine transaminase
ASAQ	artesunate-amodiaquine
AST	aspartate transaminase
AVPU	alert, voice, pain, unresponsive scale
BUN	blood urea nitrogen
Ca^{2+}	calcium ions
CFR	case fatality rate
Cl^{-}	chloride ion
CRT	capillary refill time
D5/10/50	5%/10%/50% dextrose solution
D5LR	5% dextrose in lactated Ringer's
D5W	5% dextrose in water
ECG	electrocardiogram
EDCARN	WHO Emerging Diseases Clinical Assessment and Response Network
EDTA	ethylenediaminetetraacetic acid
ETU	Ebola treatment unit
EVD	Ebola virus disease
GCS	Glasgow coma scale
GI	gastrointestinal
Hb	haemoglobin
HCO_3	bicarbonate
Hct	haematocrit
HR	heart rate
IM	intramuscular
INRB	Institut National de Recherche Biomédicale (Democratic Republic of the Congo)
IO	intraosseous
IV	intravenous
JVP	jugular venous pressure
K	potassium
LNS	lipid-based nutrient supplements
Mg	magnesium
MSF	Médecins sans Frontières

Na	sodium
NS	normal saline
NSAIDs	nonsteroidal anti-inflammatory drugs
PO	per os (orally)
PPE	personal protective equipment
PT/INR	prothrombin time/international normalized ratio
ORS	oral rehydration salts
oSoC	optimized supportive care
RL	Ringer's lactate
RR	respiratory rate
SBP	systolic blood pressure
SpO_2	peripheral oxygen saturation

1. INTRODUCTION

1.1 Optimized supportive care

Ebola virus disease (EVD) is a life-threatening multisystem illness associated with fever and gastrointestinal (GI) symptoms that frequently leads to hypovolaemia, metabolic acidosis, hypoglycaemia, and multi-organ failure. The prolonged 2013–2016 EVD outbreak in West Africa allowed for an evolution of care such that by outbreak end many patients received individualized and optimized supportive care (oSoC), including volume resuscitation, symptom control, laboratory and bedside monitoring of glucose, electrolyte levels and organ dysfunction, as well as rapid detection and treatment of co-infections, potentially contributing to the downward trend in the case fatality rate (CFR).*(1,2)* However, considerable variability exists in the level of supportive care offered between Ebola treatment units (ETUs) in the same outbreak as well as across outbreaks. Building on evidence-informed guidelines created by a multidisciplinary panel of health care providers with experience in the clinical management of patients with EVD, this guidance should serve as a foundation for oSoC that should be followed to ensure both the best possible chance for survival and allow for reliable comparison of investigational therapeutic interventions as part of a randomized controlled trial.*(3)* This guideline provides recommendations for the management of adults and children.

1.2 Optimized supportive care summary

Systematic assessment and re-assessment of all EVD patients

- staffing ratio of one or more clinicians for four patients
- assessments (evaluation of each patient) performed at least three times per 24 hours
- close monitoring of patients to allow recognition of and reaction to acute changes in condition

Fluid resuscitation

- oral rehydration in patients who can drink
- parenteral administration of clinically appropriate fluids in those who are unable to drink or who have severe dehydration or shock

Electrolyte monitoring and correction

- daily biochemistry labs during acute phase of illness and haematology on admission and as needed
- appropriate and timely correction of electrolyte abnormalities

Glucose monitoring and management

- serum glucose checked at least three times a day with vital signs
- intravenous (IV) glucose management as needed

Treatment of potential co-infections

- empiric antibiotics on admission with re-assessment after 48 hours
- empiric antimalarial medication until the treatment course is finished or malaria testing is negative

Nutrition

- enteral nutrition should be provided and advanced as tolerated
- IV dextrose provided for patients that cannot take oral food and with evidence of hypoglycaemia

Symptomatic care and prevention of complications

- symptomatic care of fever, pain and nausea
- prevention of catheter associated infections and pressure ulcers

Management of complications

1.3 Daily assessment checklist

Every patient with EVD should be assessed systematically each day using the following checklist.

Daily assessment checklist

Assessment	Plan
1. Is the patient at high risk of complications? a. Airway obstruction or respiratory distress? b. Tachypnea (RR > 22 or fast for age) or SpO_2 < 92%? c. Shock? Hypotension, weak or rapid pulse, cold extremities or delayed capillary refill? d. Signs of severe dehydration? e. Altered mentation or seizure? f. Oliguria or anuria, urine output < 0.5 (adult)/1.0 ml (child)/kg/hour? g. Haemorrhagic manifestations? h. Severe hypoglycaemia (glucose < 54 mg/dl or < 3 mmol/l)? i. Severe electrolyte abnormalities? j. Severe weakness with inability to ambulate or eat/drink?	❑ NOT at high risk Regular assessments – three times a day ❑ HIGH risk Increased interval of assessments: _____ ❑ Plan:_____
2. Fluid status assessment a. Able to drink normally? b. Able to drink some but not enough to correct dehydration or meet daily fluid requirements? c. Signs of sepsis or shock (HR > 90, SBP < 100, RR > 22). And for child: cold extremities, weak fast pulse, delayed capillary refill > 3 sec?	❑ Continue with oral fluids ❑ Add maintenance fluids ❑ Bolus IV fluids: _____ml
3. Laboratory assessment a. Does potassium or magnesium need to be replaced? b. Is renal failure present? i. If yes, has the patient been adequately fluid resuscitated? ii. Is a urinary catheter needed to monitor urine output?	❑ Replace potassium ❑ Replace magnesium ❑ Place a urinary catheter ❑ Use ultrasounds to assess fluid status
4. Severe hypoglycaemia a. Evidence of hypoglycaemia (glucose < 54 mg/dl or < 3 mmol/l)? i. If yes, are they symptomatic and require D50 or D10? ii. If no, are they able to eat and drink or do they require continuous infusion of D5 or D10?	❑ Euglycaemic ❑ D50 (adult) or D10 (child) for symptomatic hypoglycaemia ❑ D5 or D10 for asymptomatic hypoglycaemia
5. Treatment of potential bacterial co-infections a. Is the patient at high risk of co-infections? i. If yes, is the patient being treated with ceftriaxone? ii. If no, is the patient being treated with cefixime? b. Does the patient still need to be treated with antibiotics?	❑ Ceftriaxone ❑ Cefixime ❑ Antibiotics discontinued
6. Treatment of potential malaria a. Does the patient have signs of severe malaria? i. If yes, is the patient being treated with artesunate? ii. If no, is the patient being treated with an antimalarial medication? b. Can the antimalarials be stopped due to a negative malaria test?	❑ Artesunate ❑ Artesunate-amodiaquine (ASAQ) ❑ Malaria negative ❑ Malaria treatment completed
7. Nutrition a. Is the patient able to eat and drink? i. If yes, can maintenance fluids be stopped?	❑ Able to eat and drink ❑ NOT able to eat and drink and requires maintenance fluids
8. Prevention a. Can the IV line be removed? b. Can the urinary catheter be removed? c. Does the patient require assistance walking or can they walk on their own?	Remove IV line ❑ Yes ❑ No Remove urinary catheter ❑ Yes ❑ No Patient requires assistance walking ❑ Yes ❑ No
9. Is the patient a pregnant woman? a. Is she having an abortion? Premature birth? Has she had an incomplete abortion? If no, is the fetus viable?	Date of last menstrual period: _____ Echo: _____ Plan: _____

Notes: D dextrose; HR heart rate; RR respiratory rate; SBP systolic blood pressure; SpO_2 oxygen saturation.

2. PRINCIPLES OF PATIENT MANAGEMENT

2.1 Systematic assessment and re-assessment of all EVD patients

An initial systematic clinical assessment performed immediately after admission followed by regular re-assessments of clinical signs, symptoms and vital signs is essential to identify those patients at high risk of complications and to treat complications of EVD early.*(3)*

Identification of patients at high risk for complications

- low systolic blood pressure (SBP) in either adults or children or delayed capillary refill and cold extremities in a child
- altered mentation, delirium or seizure
- tachypnea (fast respiratory rate)
- weak or rapid pulse
- oliguria (urine output < 0.5 ml/kg/hour in adults; < 1.0 ml/kg/hour in children) or anuria
- haemorrhagic manifestations
- severe hypoglycaemia (glucose < 54 mg/dl or < 3 mmol/l)
- SpO_2 < 92%
- severe electrolyte, metabolic, acid-base abnormalities
- severe vomiting and/or diarrhoea
- severe weakness with inability to ambulate or eat/drink.

Resuscitation should be initiated immediately for these patients and they should be placed in the area of the treatment unit designated for the care of the critically ill.

Staffing ratios and frequency of assessments

- For patients at high risk of complications, a staffing ratio of one clinician for up to two patients is recommended. Patients should be assessed at least every hour.
- For patients not at high risk of complications, staffing ratios of one clinician for up to four patients, with patient assessments occurring at least every 8 hours is consistent with current recommendations.*(3)*

Assessment and re-assessment components

The components to be assessed and re-assessed are: vital signs, physical examination, fluid status, laboratory monitoring, and recording and responding to change or abnormal clinical and laboratory parameters.

2.2 Vital signs

- temperature (oral, axillary or tympanic)
- heart rate (HR)
- blood pressure
- respiratory rate (RR)
- peripheral oxygen saturation (SpO_2)
- level of consciousness using the alert, voice, pain, unresponsive scale (AVPU) or Glasgow coma scale (GCS)
- point of care glucose
- body weight.

2.3 Physical examination

- general conditions:
  - » is the patient able to eat and drink without support?
  - » is the patient able to sit and walk independently?
- neurological status including mentation and pupil reactivity
- evaluation of volume status (and fluid responsiveness if sepsis or shock is suspected) (see Section 2.4 Fluid status)
- characteristics of peripheral pulse
- conjunctival colour
- signs of perfusion:
  - » child: capillary refill time (CRT) (< 3 sec = good)
  - » mentation (alert = good)
  - » urine output (> 0.5 ml/kg/hour = good in adults; > 1.0 ml/kg/hour in children)
  - » skin examination (no mottling = good)
- hepatomegaly and jaundice
- peripheral oedema
- signs of bleeding (IV sites, gums, skin [petechial], vaginal, gastrointestinal)
- pain assessment
- ambulatory status
- nutritional status (signs of acute malnutrition).

See Appendix 1. Key criteria used to assess nutrition and vital signs in children.

2.4 Fluid status

- Fluid status should be assessed on admission and at each visit or period of observation for shock and/or dehydration:
  - » shock = hypotension despite adequate fluid resuscitation and, for children: cold extremities and delayed capillary refill.
  - » dehydration = fluid loss (vomiting, diarrhoea, insensible losses etc.) greater than fluid intake.
- Fluid input and output should be monitored by recording:
  - » daily weights, especially useful in children
  - » total volume administered (oral and intravenously) and total volume out (urine, vomiting, stool)
  - » weigh nappies in uncatheterized small infants, i.e. urine and stool (ml) = wet nappy weight (g) – dry nappy weight (g).

Table 2.1 Classification of dehydration

	Mild (3–5% volume depletion)	Moderate (6–9% volume depletion)	Severe (> 10% volume depletion)
Pulse	Normal	Rapid	Rapid and weak or thready
Systolic blood pressure	Normal	Normal to low	Low
Buccal mucosa	Slightly dry	Dry	Parched
Skin turgor	Normal		Reduced
Urine output	Normal (> 0.5 ml/kg/hour adult; > 1 ml/kg/hour child)	At or below (< 0.5 ml/kg/hour adult; < 1 ml/kg/hour child x 3 hours)	Markedly reduced to anuric (< 0.5 ml/kg/hour x 3 hours)
Respiratory rate	No change	Increased	Increased
Ins and outs	Outs > ins	Outs > ins	Outs >> ins
Other	Increased thirst	Increased thirst	In infant, depressed fontanelle; cold skin

Source: Adapted from Somers (2018).*(4)*
Notes:
- A child with severe dehydration that has shock should have all three clinical signs present: delayed capillary refill > 3 seconds; cold extremities; and weak rapid pulse or hypotension for age (SBP < 70 + (age in years x 2)). These children should be treated with the shock algorithm.
- Adults with severe dehydration and shock (SBP < 90 mm Hg or other clinical signs of hypoperfusion), should be treated with the shock algorithm.

2.5 Laboratory monitoring

- Measure and record serum biochemistry and haematology on admission and daily during the resuscitative phase (typically the first 4 days of illness, or longer depending on the clinical condition of the patient) AND as clinically indicated.
  - » This includes Na, K, HCO_3, BUN, creatinine, AST, ALT, Mg, glucose, Hg, PT/INR, creatine kinase, Cl^-, Ca^{2+}, albumin and lactate.
- Glucose should be monitored daily as part of the biochemistry panel AND at every shift when vital signs are performed as point-of-care testing, during the early phase of the disease.
  - » In patients with symptomatic or severe hypoglycaemia (< 54 mg/dl), patients should be treated immediately (see Section 4. Hypoglycaemia) and glucose measured every 1–2 hours until stable (no evidence of hypoglycaemia x four checks over 4–8 hours and no increase in glucose administration).
- In children, measure glucose on admission and, at a minimum, every 8 hours. Measure glucose more frequently in patients with symptomatic hypoglycaemia and in neonates.
- Point of care testing for glucose (glucometer), pregnancy and malaria rapid diagnostic testing should be available.

2.6 Recording and responding to change or abnormal clinical and laboratory parameters

- Use age and size appropriate equipment to monitor vital signs.
- Observations should be recorded on an observation chart to show trends over time.
- If vital signs and physical examination fall within the normal range for age then they can be monitored again in 3–4 hours, unless there is a clinical change in the patient.
- Any clinical change must prompt recording of another full set of observations. Abnormal observations should prompt a clinical review and formulation of a treatment plan with re-evaluation after any clinical intervention to assess response.

3. FLUID RESUSCITATION

Patients with EVD often present with or develop one or more of the following: volume depletion (dehydration), sepsis, haemorrhage and/or shock.

Volume depletion or dehydration refers to volume loss from diarrhoea, vomiting, sensible loss or, rarely, haemorrhage, which typically responds well to volume repletion.

Sepsis, on the other hand, represents a dysregulated immune response to an infection associated with organ dysfunction and requires both volume resuscitation and pathogen specific therapy, including antibiotics and specific antiviral therapeutics.

Septic shock is a subset of sepsis which is complicated by hypotension refractory to fluid resuscitation and requires the use of vasopressor medication to maintain organ perfusion in addition to volume resuscitation and pathogenic specific therapy.*(5)* The treatments for dehydration, sepsis and septic shock are different and are discussed in further detail below.

3.1 Fluid resuscitation in patients with sepsis

Sepsis: management of sepsis requires early identification, management of infection and supportive care, including fluid resuscitation to maintain organ perfusion to reduce and prevent further organ injury. In EVD this requires pathogen specific treatment as well as treatment with antibiotics to treat potential bacterial co-infections and parenteral fluid resuscitation (bolus fluids) to reverse signs of volume depletion. See Fluid management in sepsis and shock algorithm box.

3.2 Fluid resuscitation in patients with shock

Hypovolaemic shock: this is a common type of shock due to large GI losses and presents with signs of dehydration. The treatment for shock is resuscitation with intravenous or intraosseous (IV/IO) fluid, given as one or multiple boluses with close monitoring of fluid responsiveness. Hypovolaemic shock differs from septic shock in that the etiology of the former is volume loss (e.g. diarrhoea) whereas sepsis results from an immune response to an infection. Both require fluid resuscitation whereas sepsis also requires treatment of the underlying infection. Adequacy of IV fluid intake refers to the volume that will correct signs of hypovolaemia (see Section 2.4 Fluid status).

Septic shock: the treatment for septic shock with or without large GI losses or haemorrhage is resuscitation with IV/IO fluids given as one or multiple boluses with close monitoring of fluid responsiveness, early empiric antibiotics, oxygen administration to maintain SpO_2 > 94% and vasopressors if needed. Importantly, vasopressors may need to be added before fluid resuscitation is completed to maintain a SBP greater than 90–100 mm Hg in adults or age-appropriate blood pressure in children. See Fluid management in sepsis and shock algorithm box.

Haemorrhagic shock: haemorrhagic shock from GI or other bleeding requires rapid identification of the source or mechanism of bleeding and replacement of blood to maintain oxygen carrying capacity. Haemorrhagic shock is a rather uncommon etiology in EVD. Treatment includes blood transfusion to maintain Hb > 7, and consideration of tranexamic acid and vitamin K. Hb and platelet counts should be followed regularly.

Fluid management in sepsis and shock algorithm

General principles

1. A patient with severe dehydration, septic, hypovolaemic or haemorrhagic shock, needs rapid fluid bolus. In emergency situations, parenteral fluids can be given through an IV or IO line.
   - » Shock in child: delayed capillary refill > 3 seconds, cold extremities, weak rapid pulse or hypotension for age (SBP < 70 + (age in years x 2)).
   - » Shock in adult: SBP < 90 mm HG, mean arterial blood pressure < 65 mm Hg or other clinical signs of hypoperfusion.

2. Use isotonic crystalloid fluid for fluid resuscitation; 0.9% saline or Ringer's lactate (RL) solution. Certain conditions may require selected fluids:
   - » In patients with hyponatraemia the use of 0.9% saline is preferred (see Section 5.5 Hyponatraemia).
   - » Hypotonic fluids should not be used for resuscitation; these include plain dextrose solutions, 0.45% and 0.18% saline solutions.
   - » Dextrose containing fluids should not be delivered as a bolus as they can be hypotonic (D5W) and they can also cause spikes and drops in the glucose level.

3. In adults, bolus with 500 ml up to 30 ml/kg or until normalization of signs of perfusion.
   - » Re-assess signs of perfusion after each bolus, if signs of poor perfusion persist, then repeat bolus and re-assess.
   - » Each bolus is 500–1000 ml.

4. In well-nourished children bolus 10–20 ml/kg as initial bolus over 30–60 minutes (use lower dose for malnourished children).
   - » The child should be re-assessed at the completion of infusion and during subsequent hours to check for any deterioration. If the child is still in shock, consider giving a further infusion of 10 ml/kg over 30 minutes. If shock has resolved, provide fluids to maintain normal hydration status only (maintenance fluids).

5. Caution in children: rapid fluid therapy may be harmful if there is severe dehydration, anaemia (Hb < 50 g/l) or severe malnutrition.

6. If shock persists, despite fluid loading, then vasopressors may be added to maintain perfusion (see Section 3.3 Vasopressors).

7. If, at any time, there are signs of fluid overload, such as pulmonary oedema, or cardiac failure, the infusion of fluids should be stopped, and no further IV infusion of fluids should be given until the signs resolve.

Crystalloid fluid	Na mmol/l	K mmol/l	Cl mmol/l
Ringer's lactate	131	4	109
0.9% saline	154	0	154

3.3 Vasopressors

Vasopressors are necessary when patients remain in shock despite adequate volume resuscitation (30 ml/kg in first 3 hours in adults or 40–60 ml/kg in the first 2 hours in children), and:*(5)*

- there are indications of fluid overload
- there is no response to crystalloid resuscitation.

The use of vasopressors should NOT be delayed while assessing response to fluid bolus as it is essential to maintain organ perfusion. Vasopressors can be started during fluid resuscitation and weaned as a patient responds to volume resuscitation to maintain SBP > 90–100 mm Hg in adults (or MAP > 65 mm Hg), and age-appropriate blood pressure and perfusion markers in children.

- For adults, noradrenaline is the first-line vasopressor for shock.
- For children, epinephrine is first-line vasopressor for shock. The alternative is noradrenaline.

General considerations for the delivery of vasopressors

- Large vein access (16–18 gauge catheter) or IO line or central venous catheter.
- Appropriate dilution in selected carrier and precise delivery mechanism, such as infusion pumps.
  - » **For adults:** noradrenaline 4 mg = 4 ml of 1:1000; adrenaline 4 mg = 4 ml of 1:1000 (80 mcg/ml concentration)
    - add 4 ml to 46 ml of D5W to make 50 ml
    - place in syringe driver
    - 0.1 mcg/kg/min is the starting dose. Usual maintenance dose 0.25–0.5 mcg/kg/min. Maximum dose 0.5–0.75 mcg/kg/min.
  - » **For children:** use more diluted solutions because the volumes infused are lower, especially for children under 30 kg. Adrenaline 1 mg = 1 ml of 1:1000; noradrenaline 1 mg = 1 ml of 1:1000
    - add 1 ml to 49 ml of D5W to obtain 50 ml (20 mcg/ml concentration)
    - place in a syringe driver
    - 0.1 mcg/kg/min at initial flow rate for adrenaline and norepinephrine. Usual maintenance dose 0.25–0.5 mcg/kg/min. Maximum dose 0.5–0.75 mcg/kg/min.
- Close haemodynamic monitoring.
- Adequate staffing to provide close monitoring.
- Close monitoring of IV site to ensure no signs of extravasation. If signs of extravasation, administer 5–10 ml of phentolamine diluted in 10 ml of of 0.9% saline subcutaneously at site.
- Use lowest dose necessary to achieve perfusion target. Check markers of perfusion every 30 minutes.

3.3.1 Treatment of hypovolaemia from dehydration/volume loss

Patients without shock but with ongoing fluid losses (mild-moderate dehydration – see Section 2.4 Fluid status)

Plan B: Treatment of patient with some dehydration using oral rehydration salts (ORS)

WHO ORS contain: glucose 13.5 g/l, sodium chloride 2.6 g/l, potassium chloride 1.5 g/l, trisodium citrate dihydrate 2.9 g/l, (total osmolarity of 245 mOsm/l).

For adult patients unable to drink sufficient volumes of liquids to maintain hydration status, it is recommended to give IV fluids.

- In adults, it is recommended to alternate between 0.9% saline and Ringer's lactate.
- In children, use Ringer's lactate if available but monitor the serum electrolytes regularly.

Counsel the patient:

- drink extra water or ORS
- continue eating
- provide assistance with drinking if needed.

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1. Determine amount of ORS to give during first 4 hours:

To determine the approximate amount of ORS required (ml), multiply the patient's weight (kg) by 75.

Recommended volume of ORS within the first 4 hours to treat dehydration						
Weight of patient	< 5 kg	5–8 kg	8–11 kg	11–16 kg	16–30 kg	> 30 kg
Volume of ORS	200–400 ml	400–600 ml	600–800 ml	800–1200 ml	1200–2200 ml	2200–4000 ml

- Use the patient's age if you do not know the weight (estimated weight 1–10 years = (age in years + 4) x 2).
- If the patient wants more ORS, give more.
- Give the recommended amount of ORS over a 4-hour period.
- If the patient is weak or vomits give frequent small sips from a cup.
- After a vomit, wait 10 minutes then continue ORS but more slowly.
- Consider treating with an anti-emetic and continuing with ORS.
- The volume of oral ORS in the timeframe recommended above is often challenging and patients with moderate volume depletion/dehydration often require supplementary IV fluids.

2. After 4 hours or each clinical round:

- Re-assess the patient and classify for dehydration.
- Select the appropriate plan to continue treatment.
- Begin feeding the patient in the clinic.

Source: Adapted from WHO (2016).*(6)*

Patients without shock but with severe dehydration (see Section 2.4 Fluid status)

Plan C: Treatment of patient with severe dehydration

Start IV fluid therapy with 0.9% saline with dextrose or Ringer's lactate with dextrose (see also Appendix 2).

If patient can drink, give ORS by sips while IV is being set up. Check the weight of the child or adult.

1. Determine amount of IV fluid to be given: 100 ml/kg.

2. Determine rate of fluid to be given based on age: infant < 1 year or child > 1 year.

Recommended volume of IV fluid and type to treat severe dehydration			
Age	First fluid bolus, 30 ml/kg	Second fluid bolus, 70 ml/kg	Fluid composition
Infants < 12 months	1 hour*	5 hours	RL with 10% dextrose or NS with 10% dextrose
12 months to 5 years	30 minutes*	2.5 hours	RL with 5% dextrose or NS with 10% dextrose

- * Repeat once if pulse if weak radial pulse.
- Re-assess child every 15–30 minutes. If hydration status not improving, give fluids more rapidly.
- Give child ORS as soon as the child can drink.
- If the patient is weak or vomits give frequent small sips from a cup.
- Re-classify dehydration at each evaluation and select the appropriate plan to continue treatment.

Notes: NS normal saline; RL Ringer's lactate.
Source: Adapted from WHO (2016).*(6)*

3.4 Daily fluid therapy

Total fluid intake = daily maintenance fluid + replacement fluid for ongoing losses

3.4.1 Daily maintenance fluids for adults and children

See the Clinician's pocket reference.*(7)*

To estimate fluid requirement for adults and children:

- **100 ml/kg/day for first 10 kg (1 litre)**
- **50 ml/kg/day for second 10 kg (1.5 litre)**
- **20 ml/kg/day for weight above 20 kg.**

Adults: typically, an afebrile adult requires 25–30 ml/kg/day of fluid intake (1.5 to 2 litres per day for an average size adult). For normal adults the **minimum** obligate water requirement is approximately 1600 ml/day which yields 500 ml of urine (if temperature and renal concentrating ability is normal).*(8)*

- For a febrile patient, this should be adjusted to account for insensible losses, which are approximately 2.5 ml/kg/day for each degree greater than 37°C.

- Oral intake is generally preferred to meet the daily maintenance fluid requirements but is typically challenging in the acutely ill EVD patient and should be supplemented with IV infusions as necessary.
- Re-assess any patient receiving IV maintenance on a regular basis to avoid volume overload manifested by:
  » lower extremity oedema
  » increased oxygen requirement or respiratory rate
  » elevated jugular venous distention and/or pressure
  » child: hepatomegaly.

Children: for children, glucose requirements are approximately 5–7 mg/kg/min of glucose to limit hypoglycaemia. Fluid and electrolyte repletion, including potassium repletion, should be based on daily laboratory values and an isotonic fluid should be used as maintenance to avoid hyponatraemia.

3.4.2 Daily replacement fluid for ongoing losses

Volume of replacement fluid = volume loss (urine + stool + vomit + blood loss) + insensible loss

Replacement fluid for ongoing losses can be composed of both oral and parenteral rehydration.

Oral rehydration: oral fluid therapy, using ORS, is recommended for patients that can tolerate oral fluids. Patients who are too ill to drink oral rehydration independently will require active assistance from health care providers and/or IV fluids. Even if a patient is unable to take adequate volumes of fluid orally, oral intake of any amount should be encouraged. If a patient's oral intake is limited by nausea and vomiting, anti-emetic therapy can help. Adequacy of oral fluid intake refers to the volume that will prevent or correct signs of hypovolaemia/dehydration (see Section 2.4 Fluid status).

- Enteral fluids via nasogastric tube can be used in those with adequate GI motility, and with mild to moderate volume depletion, and tolerance of a nasogastric tube with sufficient provider technical skill to insert safely.*(3)*

	Na^+ mmol/l	K^+ mmol/l	Cl^- mmol/l	Bicarbonate mmol/l	Glucose g/l	Magnesium mmol/l
WHO ORS	90	20	80	30	111	-

Parenteral rehydration: parenteral administration of crystalloid fluid is recommended for patients who are unable to drink or who are unable to drink sufficient volumes to maintain normal hydration status, i.e. volume losses are larger than oral volume intake.*(3)* The benefits of parenteral rehydration include the ability to augment preload and cardiac output with bolus fluids and not having to rely on uncertain intestinal absorption, but it requires close monitoring for volume responsiveness and volume overload. At each assessment, evaluate if the patient still requires continuous IV fluids and stop once the patient is able drink sufficient volumes to maintain a normal hydration status. Adequacy of IV fluid intake refers to the volume that will prevent or correct signs of hypovolaemia (see Section 2.4 Fluid status).

Parenteral (IV) rehydration can be given as a bolus for resuscitation (i.e. limited amounts over a very short period of time – 30 minutes to 1 hour in shocked states) or as slower infusion to reverse dehydration (i.e. over several hours) or continuous for patients that cannot maintain euvolaemia by oral route.

Crystalloid fluids used for resuscitation and maintenance should be isotonic and include either normal saline (NS, 0.9% NaCl) or Ringer's lactate. Hypotonic fluids (D5W) should not be used as maintenance fluids for risk of precipitating hyponatraemia.

Bolus fluids should be used to correct signs of shock in adults and children. This is preferred over continuous fluids given their effects on cardiac output.

Continuous fluids can be used for patients who cannot maintain euvolaemia with oral hydration, and for those needing dextrose containing fluids to maintain adequate blood sugar levels.

General considerations

- In general, maintenance fluid should be delivered orally (ORS are preferred over water especially when the patient has diarrhoea; ORS can be made more palatable with the addition of juice).
- If the patient is unable to take orals or not able to keep up with losses, then use IV fluids.
- If the patient requires continuous glucose infusion, add D50 to NS (NaCl 0.9%) or RL if the patient is not able to eat. Deliver as a continuous infusion to avoid spikes and drops in glucose levels.

Signs of shock should be managed with bolus isotonic fluids such as 0.9% saline or Ringer's lactate. See Fluid management in sepsis and shock algorithm box and Appendix 3.

	Na mmol/l	K mmol/l	Cl mmol/l	D50
Ringer's lactate	130	4	109	50 g/100 ml
0.9% saline	154	0	154	50 g/100 ml

4. HYPOGLYCAEMIA

Hypoglycaemia is frequently seen in patients with EVD (especially infants and children) and should be managed to avoid complications, including altered mentation, seizure and death. Symptoms of hypoglycaemia include nervousness, tremulousness, tachycardia, altered mentation and diaphoresis, all of which are triggered by a compensatory adrenergic response to the hypoglycaemia.

Hypoglycaemia is defined as < 3 mmol/l or < 54 mg/dl in adults and children in the context of EVD. If suspect hypoglycaemia but unable to measure glucose, give empiric therapy with dextrose.

Acute management:

- D50 contains 25 g of glucose in 50 ml
- D10 contains 10 g of glucose in 100 ml
- D5 contains 5 g of glucose in 100 ml.

For **adult patients** with evidence of symptomatic hypoglycaemia and altered mentation or seizure:

- Emergent treatment with one ampoule D50 (25 g) and re-check glucose in 15 minutes. A second ampoule of glucose may be required within 1 hour of treatment.
- Patients should also receive a continuous infusion of dextrose. Options include:
  - » Add 50 g of dextrose (100 ml of D50) to 900 ml of 0.9% saline or Ringer's lactate as maintenance fluid; or
  - » Use D10W at 50 ml/hour to correct glucose in a 60 kg adult.
  - » Adjust rate sufficiently to maintain blood glucose > 80 mg/dl, with hourly glucose checks until four stable glucose levels, after which glucose monitoring can be decreased in frequency to every 4 hours.
  - » Sodium and potassium levels should be monitored given the volume of free water in D10.

For **paediatric patients**, use D10 to treat hypoglycaemia. Do not use D50, which can lead to rebound hypoglycaemia.

- Neonates and children: slow IV push bolus of 2–5 ml/kg of 10% glucose.
- The bolus should be administered slowly (2–3 ml/min) to avoid acute hyperglycaemia, which can cause rebound hypoglycaemia.
- After the bolus, maintain dextrose infusion 4–6 mg/kg/min or 5 g/kg/day.
- Re-check glucose 15 minutes after correcting.
- Repeat dose of 2 ml/kg if glucose remains low and increase dextrose infusion.

For patients with evidence of hypoglycaemia WITHOUT altered mentation or seizure:

- Patients should be encouraged to eat and drink to maintain glucose levels.
- If unable to do so, then an infusion of D10 at a rate sufficient to maintain blood glucose or, if maintenance fluid being used, add 50% dextrose to that fluid.

D5W should not be used to treat symptomatic hypoglycaemia as the concentration of glucose is too low to have an impact on serum glucose and the volume of free water could lead to hyponatraemia.

5. ELECTROLYTE MANAGEMENT

The following topics are covered in this section: hypokalaemia, hyperkalaemia, hypomagnesemia, hypocalcaemia, hyponatraemia, hypernatraemia.*(6)*

5.1 Hypokalaemia

Hypokalaemia is a dangerous complication that is associated with arrhythmias and/or death, but repletion must also be done carefully.

- When tolerated (not vomiting) oral potassium should be used.
- **Never give potassium IV as bolus.**
- **Adults:** the maximum rate of IV potassium through a peripheral IV line is 10 mmol/hour. The maximal concentration is 10 mmol per 100 ml.
  - » If a central venous catheter is in place, it can give up to 20–40 mmol/hour, administered as 20–40 mmol in 1 litre NS while on a cardiac monitor.
- **Children:** the maximum IV infusion rate is 0.5 mmol/kg/hour through a peripheral IV or central line.
  - » The maximum concentration of IV potassium through a peripheral line in children is 10 mmol/l.
- It is preferable to infuse potassium using an electric syringe pump to ensure rate.
- Every 0.1 mmol reduction in serum requires approximately 10 mmol KCl repletion in adult patients.
- Every 1 g of potassium in a 10 ml ampoule is equivalent to 13.4 mmol or 13.4 mEq of potassium.

Potassium level	Adult dosing
3.3–3.5	40 mmol oral dose. Re-check serum K level and repeat dose if needed.
2.5–3.2	60–80 mmol oral dose. Re-check serum K level and treat if necessary.
< 2.4 (severe)	10 mmol per hour IV/ for 4 hours. Re-check serum K level. Give additional dose at 2–4 hours, if still needed. Always re-check serum K level between dosing.
	Paediatric dosing
K 2.5–2.9 mmol/l	0.5–1.0 mmol/kg oral dose. Re-check serum K level. Can repeat every 6–12 hours. Can repeat to a total of 2–4 mmol/kg/day in 2–4 divided doses.
K < 2.5 mmol/l	0.5 mmol/kg/hour IV for 2 hours + 2 mmol/kg oral dose. Re-check serum K level. Can repeat every 12 hours.

5.2 Hyperkalaemia

Hyperkalaemia is a dangerous complication that is associated with arrhythmias and/or death and is extremely difficult to manage in EVD outbreaks given that the diarrhoea associated with the disease complicates the use of kayexalate and dialysis is rarely available.

- **Most cases of hyperkalaemia in the EVD patient are due to kidney injury and/or spurious causes like haemolysis of the sample. If a spurious result is suspected repeat the lab.**
- Electrocardiogram (ECG) monitoring if possible: peaked T waves → widened QRS and flattened P waves → loss of P waves, progressive QRS widening and eventual ventricular fibrillation.
- Check for spurious causes, e.g. ethylenediaminetetraacetic acid (EDTA) contamination, haemolysed sample, IV drip sample or leukocytosis.
- Ensure all medications that could potentiate hyperkalaemia are stopped.
- Monitor glucose (every 30 minutes) and potassium (every 60 minutes), if correcting using insulin/dextrose, until stabilized.

Potassium level	
K 5.5–6.4 mmol/l	Repeat test and monitor. Obtain ECG. If K > 5.5 and hyperkalaemia ECG changes, treat as below. Eliminate K through kidneys and GI tract (ensure euvolaemia and establish good urine output). If hypovolaemic: administer fluid bolus. Can consider furosemide only if hypervolaemic.
K > 6.5 mmol/l or ECG changes	
	Adult dosing
	1. Calcium gluconate 10% 10 ml over 10 minutes (may need one to three ampoules to achieve the same effect as calcium chloride); or calcium chloride 10% 5–10 ml IV over 10 minutes, repeat if necessary until ECG changes improve. Calcium chloride may cause local irritation at injection site; use larger vein. 2. Insulin: administer IV 10 units Humulin R insulin with two ampoules 50% glucose. 3. Bicarbonate IV 50 mEq slow push over 2 minutes. 4. Consider use of sodium polystyrene sulfonate 15 or 30 g once and can repeat every 8 hours in patients WITHOUT copious diarrhoea. Caution: does not have immediate effect and DO NOT use in patients with constipation. 5. Dialysis for refractory hyperkalaemia if available.
	Paediatric dosing
	1. 10% calcium gluconate: dose 0.11 mmol/kg (= 0.5 ml/kg) IV slow push over 5 minutes. Maximum 20 ml. 2. IV insulin and dextrose infusion: insulin 0.05 units/kg (maximum 10 units) + 1 ml/kg 50% glucose IV or 5 ml/kg 10% glucose or 2 ml/kg of 25% glucose. 3. Bicarbonate 1 mmol/kg IV slow push over 10–15 minutes. 4. Dialysis for refactory hyperkalaemia if available.

5.3 Hypomagnesemia

- Concomitant magnesium deficiency occurs in approximately 40% of patients with hypokalaemia and should be considered when replacing potassium.
  - » Magnesium should be replaced first in concomitant magnesium and potassium deficiency.
- For refractory hypokalaemia or for hypomagnesemia, give magnesium sulphate 2 g IV over 1 hour in adult patients. In children, give 0.2 mmol/kg (maximum 10 mmol) over 1 hour.

5.4 Hypocalcaemia

General considerations

- Replace calcium if corrected calcium < 1.9 mmol/l (< 7.5 mg/dl).
- Formula to correct calcium for albumin level:

Corrected calcium mg/dl = serum calcium (mg/dl) + (0.8 x (normal albumin (4 mg/dl) – patient's albumin mg/dl).

Acute management in adults

- 1–2 g or 2.25–4.5 mmol calcium gluconate IV in 50 ml of D5 or normal saline (0.9% NS) over 10–20 minutes.
- May repeat after 10 to 60 minutes if needed.

Acute management in children

10% calcium gluconate:

- Dose = 0.11 mmol/kg = 0.5 ml/kg.
- Give slowly over 10–20 minutes. Can dilute dose in D5 or normal saline (0.9% NS).
- May repeat after 10–60 minutes if needed.

5.5 Hyponatraemia

General considerations

- Hyponatraemia is often seen in the EVD patient and may be associated with mental status changes and/or seizures.
- Management should be guided by the volume status, the duration of hyponatraemia and the severity of symptoms.
- In EVD, the acute nature of the disease, makes hypovolaemic hyponatraemia the most likely etiology; individual clinical assessment is warranted.

Acute management

- Avoid administration of free water or hypotonic fluids as this will worsen hyponatraemia. Use isotonic or balanced solutions for IV resuscitation. Use ORS for oral rehydration.
- Determine etiology of hyponatraemia based on volume status: hypovolaemic, euvolaemic, hypervolaemic. For hypovolaemic patient: give fluid resuscitation (as described above). For euvolaemic patient: avoid free water. Treat underlying disease. For hypervolaemic patient, diuretics can be given.
- **Do not correct sodium rapidly as overly rapid correction can cause complications including central pontine myelinolysis. The maximum correction rate is 9 mmol/l in 24 hours.**
- Any clinical change must prompt repeat assessment of sodium level.

5.6 Hypernatraemia

General considerations

- Hypernatraemia represents a net water loss or a hypertonic sodium gain. In EVD this is most often due to net water loss (dehydration) from diarrhoea/vomiting.
- Early symptoms include anorexia, muscle weakness, restlessness, nausea and vomiting. More serious signs follow, with altered mental status, lethargy, irritability, stupor and coma.
- Water deficit (in litres) = (current sodium/target sodium – 1) x .6 (body weight in kg); must eliminate the existing water deficit and replace ongoing water losses.
- **The rate of correction should not exceed 9 mmol/l per day.**

6. TREATMENT OF POTENTIAL CO-INFECTIONS

6.1 Co-infection with malaria

General considerations

- Empiric antimalarial therapy should be administered to all febrile patients with suspect and confirmed EVD. Stop treatment once malaria testing is negative or the treatment course is finished.

Severe malaria

Definition of severe malaria – severe malaria usually manifests with one or more of the following: coma (cerebral malaria), metabolic acidosis, severe anaemia, hypoglycaemia, acute renal failure or acute pulmonary oedema.*(9)*

IV artesunate

- **Adults, including pregnant women:** 2.4 mg/kg/dose IV initially, followed by 2.4 mg/kg/dose at 12 hours, 24 hours and 48 hours after the initial dose for a total of four doses over a period of 3 days. Longer treatment duration, e.g. an additional 4 days, may be required in severely ill patients or in patients unable to transition to oral therapy. Transition to oral therapy at least 4 hours after the last dose of artesunate.
- **Infants and children < 20 kg:** 3 mg/kg/dose initially, followed by 3 mg/kg/dose at 12 hours, 24 hours and 48 hours after the initial dose for a total of four doses over a period of 3 days.

Uncomplicated malaria

- Treatment with artesunate-amodiaquine*(10)* or pyronaridine-artesunate.
- A full course of 3 days must be given for all age/weight groups.

Body weight (age)	Dose
≥ 35 kg (≥ 14 years)	50/153 mg tablet: four tablets once daily or 200/540 mg tablet: one tablet once daily
19–35 kg (6–13 years)	100/270 mg tablet: one tablet once daily
9–18 kg (1–5 years)	50/153 mg tablet: one tablet once daily
4.5–9 kg (2–11 months)	25/67.5 mg tablet: one tablet once daily

6.2 Bacterial co-infection

General considerations

Empiric treatment with antibiotics is recommended for patients with EVD. The empiric regimens suggested will cover most community-acquired organisms. It is not unusual for EVD patients to develop new-onset fever that may be associated with leukocytosis in the second or third week of the hospital course, often despite initial improvement in the presenting symptoms and the viral load. In this setting, the development of ETU-acquired secondary infections while on broad spectrum antibiotics, and the development of resistant gram-negative bacteremia or *Clostridium difficile* infection, should be considered. Antibiotic management, including drug choice as well as doses, should be adjusted accordingly. Monitor white blood cell count and/or other inflammatory markers (such as c reactive protein) to assist in determining de-escalation of antibiotics.

Adult patients

Severe disease: IV ceftriaxone 2 g once daily 5 days +/- IV metronidazole 500 mg three times/day (usually 7 days). If suspect bacterial meningitis, then give higher dose, ceftriaxone at 2 g twice daily.
Mild disease: PO cefixime 200 mg twice daily for 5 days.

Neonates

Ampicillin plus gentamycin **or** cloxacillin PLUS gentamycin (if *Staphylococcus aureus* suspected) or cefotaxime PLUS gentamycin. Duration of antibiotics: generally 7–10 days, but may be prolonged if meningitis present.
Note: ceftriaxone is not recommended for use in neonates as there is increased risk of kernicterus, especially in those with elevated bilirubin.

Ampicillin IV
First week of life: 50 mg/kg IV 12 hourly
Weeks 2–4: 50 mg/kg IV 8 hourly
After week 4: 50 mg/kg IV 6 hourly.

Gentamycin IV
First week of life: low birth weight: 3 mg/kg once a day
Normal birth weight: 5 mg/kg/ once a day
Weeks 2–4: 7.5 mg/kg/ once daily.

Cefotaxime IV
Premature infants: 50 mg/kg 12 hourly
First week of life: 50 mg/kg 8 hourly
Weeks 2–4: 50 mg/kg 8 hourly
After week 4: 50 mg/kg 8 hourly.

Cloxacillin IV
First week: 25–50 mg/kg 12 hourly
Weeks 2–4: 25–50 mg/kg 8 hourly
After week 4: 25–50 mg/kg 6 hourly.

Children > 4 weeks and adolescents

Mild disease: cefixime: 4 mg/kg/dose twice daily x 5 days.
Severe disease: IV ceftriaxone (usually 5 days).
- 4 weeks–10 years: 50–100 mg/kg once daily
- 10–17 years: 1–2 g once daily.

+/- IV metronidazole (usually 7 days): 7.5 mg/kg 8 hourly; maximum dose 500 mg.

Alternative antibiotics

Ciprofloxacin if suspect typhoid fever or urinary tract infection:
- Child: oral 15–20 mg/kg/dose twice daily (maximum dose: 750 mg/dose).
- Child: IV 10 mg/kg/dose every 12 hours (maximum dose: 400 mg/dose).
- Adult: oral 500 mg twice daily (7–10 days for typhoid) or IV 400 mg twice daily (5 days).

**** Caution should be taken with the use of fluoroquinolones and macrolides due to potential QT prolongation with these agents.**

7. NUTRITION

On admission, assess the nutritional status of all patients with EVD. This includes body weight, height, and in children, mid-upper arm circumference. Also look for signs of malnutrition, and assess current appetite status.

Oral nutrition should be encouraged, daily, as patients need sufficient energy (kcal) and essential nutrients, in addition to fluid electrolytes. A nutrition specialist should evaluate patients with EVD on a daily basis.

- If food intake is not tolerated as a result of nausea or vomiting, anti-emetic medication can improve intake ability.
- If food intake is limited due to weakness, the patient should be assisted with feeding by a health care provider or survivor assistant.
- If the patient is well enough for oral food intake, offer nutrient dense therapeutic foods. If family members wish to bring food to the patient, familiar foods may provide comfort for the patient if tolerated.
- If the patient is unable to tolerate oral nutrition, the placement of a nasogastric tube by an experienced provider could be considered along with nasogastric feeding. Always ensure proper placement of nasogastric tube before administering feeds, to avoid risk of aspiration.
- If severe malnutrition is present, refer to WHO published guideline. *(11)*

Patients with reduced levels of consciousness are at risk for aspiration and should not be forced to eat. IV supplementation with 10% glucose infusion will be necessary in situations where patients are unable to tolerate oral feeds and have evidence of hypoglycaemia.

For children

Rehydration phase	As above, ORS if able to take orals, or IV fluids.
Maintenance phase (poor or no appetite)	Milk-based fortified diet: • Infants < 6 months: ready to use infant formula has an advantage over powered milk formula as it does not require reconstitution with water. • Infants > 6 months: if animal milk is used then liquid whole fat pasteurized or UHT milk is preferred over powdered milk as it does not require reconstitution with water. Add hygienically prepared and appropriate complementary food.
Transition phase (some appetite; may or may not have eating difficulties)	No eating difficulties, any one or combination: • Ready to use fortified, nutrient rich foods (paste, porridge, biscuits/bar). • One or two porridges of fortified cereal legume blends with added sugar and milk for children. • Common family meal plus micronutrient powders (if no fortified food is given), preferably offer lipid-based nutrient supplements (LNS) in addition as separate meal. Eating difficulties, as above except that: • Common family meal as mashed food or soups. • LNS are not suitable for patients with swallowing difficulties. • Ready to use fortified, nutrient rich biscuit/bars/porridge. • In addition, can also use milk-based, fortified diet.
Boost phase (good appetite)	Any one or combination of the following: • Ready to use fortified, nutrient rich foods (paste, porridge, biscuits/bar). • One or two porridges of fortified cereal legume blends with added sugar and milk for children. • Common family meal plus micronutrient powders (if no fortified food is given), preferably offer LNS in addition as separate meal. • And snacks such as high energy biscuit. Convalescent patients usually want more food. Do not limit their intake and provide ready to use fortified, nutrient rich foods.
Note: LNS refers to any range of fortified, lipid-based spreads, including ready to use therapeutic food to treat severe acute malnutrition, ready to use supplementary food to treat moderate acute malnutrition, and others that are used for fortification.	

8. SYMPTOMATIC CARE

Fever

- Paracetamol
  - » **Adults:** 1 g paracetamol PO/IV every 6–8 hours. Maximum dose 4 g every 24 hours or (2 g if history of chronic liver disease).
  - » **Neonates:** oral dose 10–15 mg/kg 6 hourly, maximum dose 40 mg/kg/day; IV dose 7.5 mg/kg 6 hourly, maximum dose 30 mg/kg/day.
  - » **All other children:** 10–15mg/kg 6 hourly, maximum dose 60 mg/kg/day.

Pain control

Headache, sore throat and generalized muscle and joint pain are common in EVD and should be managed appropriately. Assess pain using a standardized pain scale before and after administration and at every visit.

- Mild pain – paracetamol
  - » **Adults:** 1 g PO/IV every 6–8 hours as needed, maximum dose 4 g every 24 hours or 2 g (if history of chronic liver disease).
  - » **Children:** orally or IV 10–15 mg/kg/dose every 4 to 6 hours as required, maximum usual dose 60 mg/kg/day, but 90 mg/kg/day can be given for short period with medical supervision.

- Severe pain – tramadol
  - » **Adults:** 50–100 mg PO/IV every 4–6 hours as needed, daily maximum 400 mg/day.
  - » **Children > 6 months:** 1–2 mg/kg every 4–6 hours, maximum 400 mg/day.

- Severe pain – morphine (oral dose preferred if patient can tolerate; only use immediate release tables for acute pain)
  - » **Adults:** oral dose is 10 mg every 4 hours as needed, maximum dose is 60 mg/day. IV dose is 1–4 mg SQ/IV every 4 hours as needed – monitor SBP and RR prior to administration of morphine (hold for low SBP or respiratory rate).
  - » **Children:** oral dose is 0.2–0.4 mg/kg/dose every 4 hours. Titrate dose to pain. IV dose is 0.05–0.1 mg/kg/dose every 4–6 hours as required.

**** Nonsteroidal anti-inflammatory drugs (NSAIDs) should be AVOIDED given their effects on platelet function and risk of gastritis.**

Nausea/vomiting

- Ondansetron: ondansetron is associated with QT prolongation, thus it is important to note other medications that may also prolong the QT interval and to monitor regularly with ECGs if available.
  - » **Adults:** 8 mg PO every 12 hours or 4 mg IV every 8 hours as needed.
  - » **Children:** orally or IV 0.15 mg/kg every 12 hours, maximum dose 8 mg.

- Promethazine
  - » **Only for adults:** use 12.5–25 mg PO every 4–6 hours as needed (can provide QT interval).

Dyspepsia

» **Adult:** omeprazole 40 mg PO/IV every 24 hours.
» **Child:** omeprazole (first-line): 5–10 kg: 5 mg once daily; 10–20 kg: 10 mg once daily; ≥ 20 kg: 20 mg once daily.

Diarrhoea

Diarrhoea should be managed conservatively. The use of anti-motility agents is not generally recommended given the potential for ileus.

Anxiety

Anxiety is a commonly reported symptom in ETUs.

- First-line therapy is to talk with a mental health counsellor.
- For moderate to severe anxiety, diazepam can be considered, but an evaluation of the patient's mental status should precede its use. Benzodiazepines should not be given to patients with altered mentation.
  » **Adults:** diazepam 5–10 mg PO every 8 hours as needed and as long as mentation is unaffected.
  » **Children:** diazepam 0.05–0.1 mg/kg PO every 6 hours as needed. Continual supervision by a health aid is indicated to keep the child calm. Sedatives should only be used if necessary to perform procedures and give interventions.

Agitation

If patient is agitated and becomes a danger to self, health care providers or other patients, consider pharmacotherapy.

- **Adults:** diazepam 2–10 mg PO/IV every 6–8 hours as needed as long as patient can protect airway.
- **Adults:** haloperidol 0.5–5 mg every 4–6 hours, as needed.
- **Children: > 6 years**: haloperidol IM 1–3 mg every 4–8 hours, as needed.
- **Children: 3–6 years:** haloperidol PO 0.01–0.03 mg/kg once daily.
- Haloperidol is associated with QT prolongation, thus it is important to note other medications that may also prolong the QT interval and to monitor regularly with ECGs if available.

9. PREVENTION OF COMPLICATIONS

Feeding

Encourage early enteral nutrition.

Early mobility

- Assess patient daily for early mobility.
- Once patient is improving, then encourage early mobility and ambulation to prevent pressure ulcers and thrombotic events. Provide assistance for patient to sit up, dangle on side of bed, then to stand and walk.
- If unable to mobilize, turn patient in bed every 2–4 hours to prevent pressure ulcers.

Stress ulcer prophylaxis

Use of a proton pump inhibitor or H2 receptor blocker in critically ill patients at high risk of bleeding.

- **Adults:**
  - » Omeprazole: 40 mg PO every 24 hours.
  - » Ranitidine: 150 mg PO twice daily or 50 mg IV three times daily.

- **Children:**
  - » Omeprazole:
    - **Neonates:** 0.7 mg/kg dose once daily.
    - **Children and adolescents: 5–10 kg:** 5 mg once daily; **10–20 kg:** 10 mg once daily; ≥ **20 kg:** 20 mg once daily.
  - » Ranitidine: IV and oral doses are not equivalent:
    - **Child:** IV 1 mg/kg 6–8 hourly all ages, maximum dose 50 mg.
    - **Child:** oral 2–4 mg/kg 12 hourly all ages, maximum daily dose 300 mg/day.

10. MANAGEMENT OF COMPLICATIONS

The complications of EVD include:

- seizure
- altered mental state and encephalopathy
- haemorrhage
  - » haematemesis
  - » haematochezia
  - » vaginal bleeding
  - » gingival bleeding
  - » bleeding at the site of IV
  - » intracerebral haemorrhage
- acute renal failure/kidney injury
- metabolic acidosis
- hypoxic respiratory failure
- sepsis and septic shock.

10.1 Seizure

Seizures can occur in EVD for a number of different reasons, including hypoglycaemia, sepsis, Ebola viral meningoencephalitis, intracranial haemorrhage and underlying seizure disorder, among others. Exercise caution when treating a patient with active seizure as performing injections and/or placing an IV can pose risks to the provider and the patient if the patient is actively moving. Always treat the underlying cause and provide supportive care:

- Position patient in the recovery position.
- Provide supplementary oxygen.
- Establish IV/IO access if safe to do so or treat with pharmacotherapies delivered rectally or intramuscular (IM) first and then re-establish IV/IO access.
- Check for hypoglycaemia and treat with bolus therapy.
- **Child:** treat fever.

Age	Diazepam rectal gel*	Diazepam IV	Phenobarbital IV		Phenytoin IV	
			Loading dose	Maintenance dose	Loading dose	Maintenance dose
Neonates	2 mg	0.3 mg/kg/dose, maximum 10 mg/dose	20 mg/kg at maximum rate 1 mg/kg/min	2.5–5 mg/kg 1–2 times a day	20 mg/kg	2.5–5 mg/kg twice a day
< 1 year	5 mg					
2–11 years	5–10 mg					
12–17 years	10–20 mg		20 mg/kg, maximum dose 1 g. Maximum rate 1 mg/kg/min	300 mg twice daily	20 mg/kg	100 mg 3–4 times a day
17+ years	10–20 mg	0.15 mg/kg over 3–5 minutes, every 5–10 minutes. Maximum dose 10 mg/dose. NOT to exceed 30 mg	10 mg/kg. Maximum dose 1 g IV. Maximum rate 100 mg/min diluted 1:10 with water for injection		20 mg/kg, maximum dose 2 g IV	100 mg every 8 hours

Note: * Do not use if patient has diarrhoea.

10.2 Altered mental status and encephalopathy

There are a number of potential aetiologies of altered mentation and encephalopathy that should be considered in patients with EVD including:

- hypoglycaemia (see treatment of hypoglycaemia, Section 4. Hypoglycaemia)
- acidosis (see treatment of metabolic acidosis, Section 10.5 Metabolic acidosis)
- hyponatraemia (see treatment of hyponatraemia, Section 5.5 Hyponatraemia)
- iatrogenesis from pharmacotherapy:
  » treatment – avoid centrally acting medications
- ureamia (see treatment of acute renal failure, Section 10.4)
- hepatic encephalopathy
- viral encephalitis:
  » treat underlying disease

Delirium:

- treat underlying disease
- avoid secondary infections (urinary catheters etc.)
- avoid centrally acting medications
- non-pharmacologic interventions (family visits, remove IV lines if not needed)
- as needed, antipsychotics (i.e. haloperidol).

It is important to exercise caution around patients with altered mental status as they can change position and/or be aggressive and pose a risk to health care providers and/or other patients.

For patients who are at risk of harming themselves or others, consider the use of diazepam or haldol to mitigate these risks.

10.3 Haemorrhage

General considerations

- Stabilize the patient, ensure two large bore IV cannulae. Measure Hb, platelets and coagulation cascade.

- Consider transfusion if active bleeding and haemodynamic instability or Hb < 7 g/dl.
- If available, transfuse with red blood cells to target Hb > 7g/dl, fresh plasma to target international normalized ratio < 1.5, and platelets to target > 50.
- Keep patient warm with a blanket. Blood products can be warmed in a warm water bath. Fresh whole blood can be used to manage massive haemorrhage only when component therapy is not available.

High dose proton pump inhibitor for GI bleed:
- **Adult:** pantoprazole 80 mg IV over 60 minutes then 8 mg/hour for 72 hours as continuous infusion or 40 mg omeprazole twice daily IV.
- **Child:** high dose proton pump inhibitor: 0.5 to 3 mg/kg IV daily, in one or two divided doses (maximum 80 mg daily).

Consider tranexamic acid:
- **Adult:** 1 g IV tranexamic acid (in 100 ml 0.9% saline) over 10 minutes followed by 1 g over 8 hours.
- **Child:** 15 mg/kg IV load (maximum 1 g) then 10–15 mg/kg (maximum 1 g) 8 hourly.

Consider vitamin K:
- **Neonates:** 1 mg IV;
- **Children:** 1–2 mg IV;
- **Adults:** 5–10 mg IV.*(12)*

Monitor hypocalcaemia and treat as needed (see Section 5. Electrolyte management).

Note: There is no direct evidence for the use of TXA or vitamin K for treatment of EVD but extrapolation from other bleeding conditions may support their use.

10.4 Acute kidney injury

Renal failure or dysfunction is common in EVD patients. Data from the West African outbreak suggest the etiology is likely a mix of pre-renal causes (hypovolaemia from GI losses) and intrinsic renal disease (acute tubular necrosis related to severe hypovolaemia, hypotension, direct Ebola virus infection or myoglobin pigment damage). In the absence of renal replacement therapy, typically not available in most settings, the prevention of acute kidney injury or the complications of acute kidney injury are crucial to improving outcomes. The prevention of renal injury related to hypovolaemia is perhaps the most important reason to ensure EVD patients are monitored closely for volume depletion and treated accordingly.

General considerations

Recognize acute kidney injury: increased serum creatinine > 0.3 mg/dl (or > 26.5 mmol/l within 48 hours) or reduced urine output (< 0.5 ml/kg for 6 hours in adults or < 1 ml/kg for 6 hours in children).
- Monitor urine output. Consider placement of a foley catheter to rule out urinary retention.
- Evaluate for reversible causes of acute kidney injury and treat accordingly.
- Ensure good volume status: maintain renal perfusion with adequate crystalloid fluid resuscitation and vasopressors. Provision of adequate renal perfusion is essential to avoid further renal injury (see Section 3. Fluid resuscitation).
- Correct electrolyte disorders.
- Prevent further injury: avoid nephrotoxic drugs, such as NSAIDs, aminoglycosides, angiotensin-converting enzyme (ACE) inhibitors.
- Appropriately dose drugs.
- Do not use diuretics to stimulate urine production in a dehydrated patient.
- If resources are available (experienced staff, equipment and supplies), the use of renal replacement therapy can be considered.

10.5 Metabolic acidosis

As acute renal failure, sepsis, shock and large volume diarrhoea are all known complications of EVD, patients are at risk of developing metabolic acidosis. Perform a blood gas analysis (if available) to measure pH to confirm acidosis.

General considerations

- Early recognition and treatment of reversible causes of acute renal failure will help prevent metabolic acidosis.

Management

- Measure the anion gap (AG): Na – (Cl + HCO_3), which helps differentiate both the etiology of the metabolic acidosis and guide therapy:
  - » normal AG is 2.5 x albumin +/- 2 (= 8–12)
  - » an AG is present if the calculated AG is > the normal AG.

Anion gap metabolic acidosis	Normal gap metabolic acidosis
Renal failure (uremia)	Diarrhoea
Ketoacidosis (diabetic or alcohol-induced, starvation)	Dilutional acidosis (hyperchloraemic acidosis)
Ingestion of toxic substances (ethylene glycol, isoniazid, methanol, paraldehyde, salicylates)	Renal loss of HCO_3/renal tubular dysfunction
Lactic acidosis (sepsis)	

- Treatment of metabolic acidosis WITH an AG is directed toward the underlying condition.
- Treatment of metabolic acidosis associated with acute kidney injury includes a bicarbonate containing solution with low chloride concentration.
  - » Add 150 mEq of $NaHCO_3$ to 1 litre D5W to make an isotonic fluid and start at 50–100 cc/hour adult dose with close monitoring of the sodium and HCO_3 levels.
- Treatment for hyperchloraemic metabolic acidosis (normal AG metabolic acidosis with elevated chloride) includes changing to Ringer's lactate for fluid resuscitation.
  - » To avoid hyperchloraemic metabolic acidosis, resuscitation fluid should be changed to Ringer's lactate after the first 3 litres if NS is used initially.

10.6 Hypoxic respiratory failure

Acute respiratory distress may occur for multiple reasons. If hypoxaemia is not present, then rapid breathing can be associated with acute/severe pain, shock state and/or metabolic acidosis. When hypoxaemia is present, then a pulmonary condition should be considered, such as volume overload/pulmonary oedema from congestive heart failure or renal failure, secondary bacterial pneumonia, haemothorax or bronchospasm from anaphylaxis.*(9)*

Oxygen therapy

- Face mask with reservoir bag at 15 l/min can be used for adults and children in an emergency situation.
- Titrate to lowest flow rate necessary to reach target SpO_2 > 94%.
- Nasal cannula is preferred in children as it may be easier to tolerate.

Age	< 1 month	1–12 months	Pre-school age	School age
Oxygen flow rate	0.5–1.0 l/min	1–2 l/min	1–4 l/min	1–6 l/min

- Requirements of 6–9 l oxygen – use a simple face mask.
- Requirements of >10 l oxygen – use a face mask with reservoir bag.
- If severe hypoxaemia persists, then consider continuous positive airway pressure or high flow oxygen systems.

11. PSYCHOSOCIAL AND PALLIATIVE CARE

Psychosocial care

Each patient should be assessed upon admission and daily for both physical, social and psychological well-being.

Physical well-being	Social well-being	Psychological well-being	Spiritual well-being
Pain Fatigue Dyspnea Nausea/vomiting	Extreme poverty Social stigma Social isolation	Depression Anxiety Mood Survivor's guilt	Loss of sense of meaning of life Loss of faith

Source: Adapted from WHO (2018).*(13)*

Treatment of physical complications involves symptom management as described in this guideline. Psychological support by psychologists, social workers and/or other medical care workers can assist with the prevention and relief of psychological suffering. All patients, patients' families and survivors should have access to psychological counselling. Complications of social well-being can be mediated through both counselling for social stigma and isolation and/or the provision of in-kind support, including food, blankets, clothes, soap, toothbrushes, toothpaste where available.*(13)* Spiritual health can be supported through local spiritual counsellors.

Palliative care

Palliative care is the prevention and relief of suffering of adult and paediatric patients and their families facing life-threatening illness.*(13)* This approach incorporates the prevention and relief of suffering by means of early identification, the serial assessment and treatment of pain and other symptoms, and discontinuation of therapies or interventions which may be painful. Palliative care is applicable through all stages of illness, including early on in the course of illness, in combination with therapies intended to prolong life and even after a patient's death, with support for bereaved family members or discharge with psychological and clinical support.

Pain, dyspnea, nausea, vomiting, body aches, respiratory distress, bleeding and encephalopathy are all symptoms that can contribute to the suffering of patients with EVD. Assessment and relief of these symptoms not only relieve suffering but also can also protect against contamination of enclosed shared spaces. Psychological suffering is also commonly seen among both patients with active Ebola virus infection and survivors.

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APPENDIX 1. KEY CRITERIA USED TO ASSESS NUTRITION AND VITAL SIGNS IN CHILDREN

Age	< 1 month	1 month – year	1–5 years	5–12 years	> 12 years
Normal RR/min	30–40	30–40	20–30	20–25	12–20
RR/min in severe distress	> 60 or < 20	> 50 or < 10	> 40	> 40	> 40
Normal HR/min	120–180	120–180	100–140	90–140	90–140
Normal systolic BP (mm Hg)	60	80	90 + (2 × age)		120
Lower limit systolic BP (mm Hg)	50	70	70 + (2 × age)		90
Normal urine output	1–2 ml/kg/hour		1 ml/kg/hour		0.5–1 ml/kg/ hour

KEY TIPS FOR ASSESSING A SICK CHILD

Blood pressure measurement in children:

- Cuff should cover two thirds to three quarters of the upper arm, calf or thigh.
- Cuffs that are too small give falsely high readings.
- Cuffs that are too large give falsely low readings.
- Child should be at rest and not distressed as this will falsely elevate the reading.

To perform capillary refill assessment:

- Press the nail bed of finger or thumb (peripheral capillary refll) or over the sternum (central capillary refll) for 3 seconds.
- Release and count in seconds the time taken for the return of colour (perfusion).

Weight estimates in children:

It is always best to weigh children rather than estimate their weight.
In an emergency, weight can be estimated in visibly well-nourished children:

- term infants: 2.5–4.5 kg
- estimate at 6 months of age: 5–7 kg
- estimate after 1 year of age: (age in years + 4) x 2 kg.

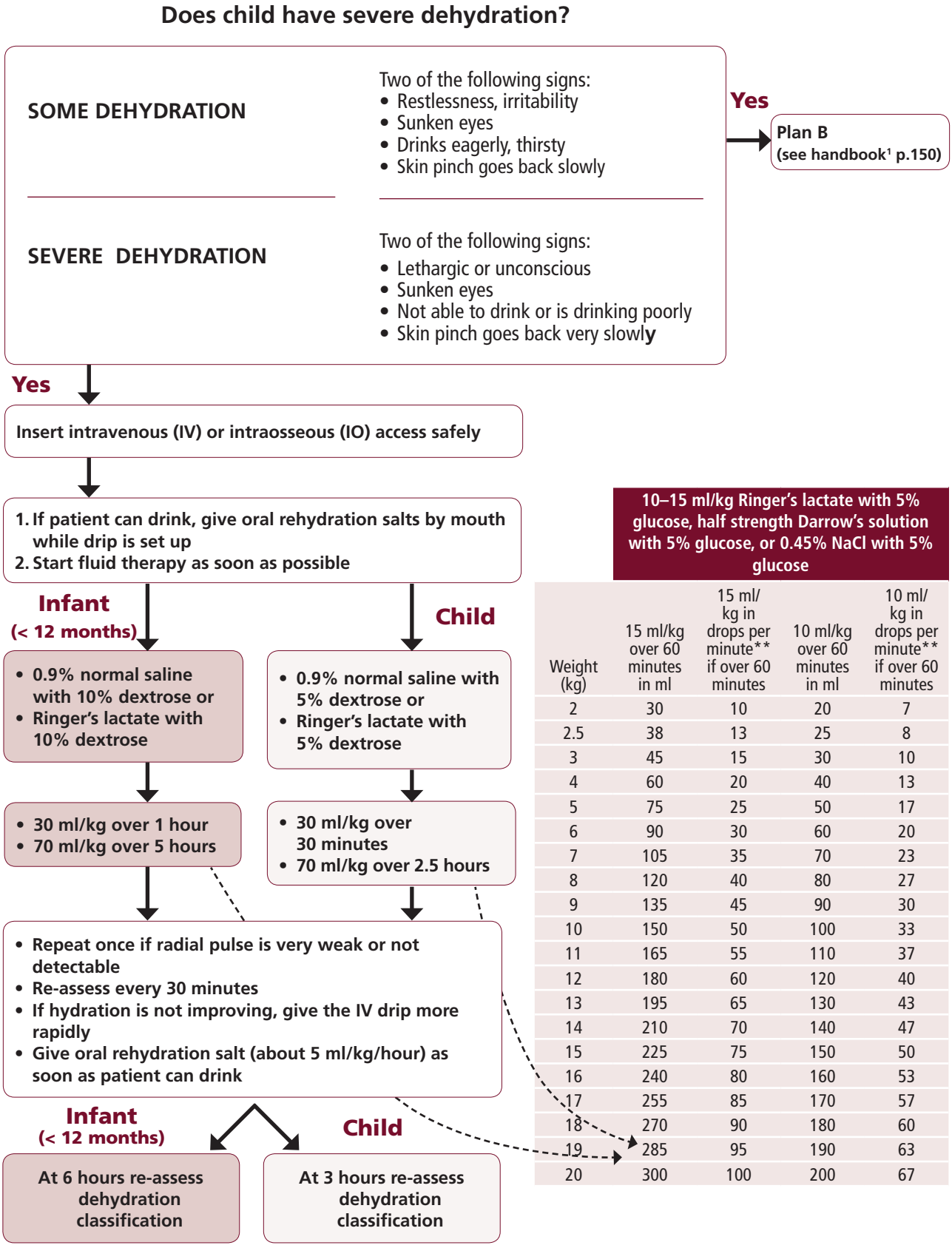
Criteria to define severe malnutrition

- Clinical signs of severe malnutrition: visible ribs and no fat on the buttocks, thighs, arms or shoulders.
- Mid-upper arm circumference < 11.5 cm.
- Bilateral pedal oedema.
- Severe wasting: < 70% weight-for-length or -3 SD (see charts in the Pocket book of hospital care for children, WHO, 2013).*(14)*

Signs of respiratory distress:

- Fast respiratory rate (normal ranges in table above).
- Nasal flaring, grunting.
- Intercostal recession and tracheal tug.
- In-drawing of the lower chest wall (very severe).
- Central cyanosis of the lips and tongue (very severe).
- Inability to breastfeed, drink (very severe).
- Lethargy (very severe).

APPENDIX 2. MANAGEMENT OF CHILDREN WITH DEHYDRATION AND GASTROINTESTINAL LOSSES – PLAN C



10–15 ml/kg Ringer's lactate with 5% glucose, half strength Darrow's solution with 5% glucose, or 0.45% NaCl with 5% glucose

Weight (kg)	15 ml/kg over 60 minutes in ml	15 ml/kg in drops per minute** if over 60 minutes	10 ml/kg over 60 minutes in ml	10 ml/kg in drops per minute** if over 60 minutes
2	30	10	20	7
2.5	38	13	25	8
3	45	15	30	10
4	60	20	40	13
5	75	25	50	17
6	90	30	60	20
7	105	35	70	23
8	120	40	80	27
9	135	45	90	30
10	150	50	100	33
11	165	55	110	37
12	180	60	120	40
13	195	65	130	43
14	210	70	140	47
15	225	75	150	50
16	240	80	160	53
17	255	85	170	57
18	270	90	180	60
19	285	95	190	63
20	300	100	200	67

** Assumes "adult" IV giving sets where 20 drops = 1 ml. Calculate separately if using paediatric burette where 60 drops = 1 ml.

[1] Clinical management of patients with viral haemorrhagic fever (2016). Geneva: WHO (http://apps.who.int/iris/bitstream/handle/10665/205570/9789241549608_eng.pdf?sequence=1).

APPENDIX 3. MANAGEMENT OF SHOCK SYNDROME IN EBOLA VIRUS DISEASE

Health care worker has to wear full set of PPE: scrubs, boots, long-sleeved gown, mask, eye protection (face shield or goggles), head cover, apron, double gloves

Shock features in children (all three features)
1. Delayed capillary refill > 3 seconds **AND**
2. Weak, fast pulse **AND**
3. Cold extremities

OR hypotension (**LATE** finding)

Age	< 1 month	1–12 months	1–12 years	> 12 years
SBP mm Hg	< 50	< 70	70 + (2 x age)	< 90

SpO_2 < 94%

Yes — Monitor for fluid overload

No

Shock features in adults
- SBP < 100 mm Hg, HR > 90/min
- Signs of hypoperfusion:
  - » Delayed capillary refill > 3 sec
  - » Cold extremities
  - » RR > 22/min
  - » Decreased urine output (< 0.5 ml/kg/hr)
  - » Altered mental status
  - » Elevated lactate

- Give oxygen therapy immediately to maintain SpO_2 > 94%
  - » Face mask with reservoir bag at 10–15 l/min
  - » Use nasal cannula in children
- **DO NOT** share nasal prongs
  - » Oxygen delivery devices are for **single** use

Fluid resuscitation
Use crystalloid: Ringer's lactate or normal saline

Caution in children
Rapid fluid therapy may be harmful if there is severe dehydration, anaemia (Hct < 0.15 or Hb < 50 g/l) or malnutrition*

Insert intravenous (IV) or intraosseous (IO) line safely

Give initial fluid bolus

Paediatric patient: 10–20 ml/kg over 30–60 minutes

Adult patient: 1 litre over 15–30 minutes

Re-assess vital signs **every 30 minutes for fluid responsiveness, markers of perfusion and fluid losses**

Fluid responsiveness: *When fluid therapy improves blood pressure or markers of perfusion (i.e. test blood pressure after fluid bolus or passive leg raise)*

Markers of good perfusion:
- SBP > 90–100 mm Hg for adult, or age-appropriate for child
- Strong pulse
- Normal RR
- Normal mental status (AVPU)
- Urine output > 0.5 mL/kg/hr for adult; > 1 mL/kg/hr for child
- Brisk capillary refill

Fluid overload:
- Dyspnea, drop in SpO_2, increase in RR
- Elevated JVP > 12 cm (> ~7 cm above sternal angle)
- Peripheral oedema
- Hepatomegaly in child

Are targets of perfusion met?

Yes — Stop fluid challenges.
Switch to maintenance fluids (IV or oral per patient)
Check vitals every 1 hour
Follow general Ebola treatment centre (ETC) management guidelines

No

Is there volume overload?

Yes — Stop fluid challenges

No — Repeat fluid challenge and re-assess targets of perfusion.* Keep up with fluid losses

Paediatric patient: 10 ml/kg over 60 min

Adult patient: 500 mL over 30 min

General ETC management:
1. Give empiric antimicrobials (within 1st hour). Consider other sources of infection (e.g. malaria).
2. Check serum glucose, replete as needed
3. Monitor and replete K+ and Mg+
4. Treat severe acidemia (pH < 7.2) with bicarbonate
5. Transfuse blood products for severe bleeding or coagulopathy
6. Recognize and prevent acute kidney injury
7. Monitor fluid balance
8. Provide symptom relief (i.e. paracetamol)
9. Begin early nutrition (if tolerating oral)
10. Counsel patient and family

Refractory shock

If markers of perfusion are stable/ improving, reduce inotrope and vasopressor dose

Initiate vasopressor infusion:
- Adrenaline/noradrenaline: start 0.1 mcg/kg/min, titrate up by 0.1 mcg/kg/min every 10–15 minutes. Maximum: 1.0 mcg/kg/min

* If despite fluid challenge x 2, targets of perfusion are not met.

RR	respiratory rate
SBP	systolic blood pressure
SpO_2	oxygen saturation
Hct	haematocrit
Hb	haemoglobin
HR	heart rate
AVPU	alert voice pain unresponsive
JVP	jugular venous pressure

Sources for Appendix 3:

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