WHO guidelines for the clinical management of filovirus disease

World Health Organization

WHO guidelines for the clinical management of filovirus disease

World Health Organization

Suggested citation. WHO guidelines for the clinical management of filovirus disease. Geneva: World Health Organization; 2026. https://doi.org/10.2471/B09774. Licence: CC BY-NC-SA 3.0 IGO.

Cataloguing-in-Publication (CIP) data. CIP data are available at https://iris.who.int/.

Design and layout by L'IV Com Sàrl.

Contents

Acknowledgements

These guidelines were led by the Safe and Scalable Care Unit within the Humanitarian and Disaster Management Department of the WHO Emergencies Programme in Geneva, Switzerland. The technical team was led by Janet Diaz and included Kathryn Alberti, Tania Kelly, Marta Lado and Jamie Rylance (WHO headquarters, Geneva, Switzerland) and John Masina (WHO Regional Office for Africa).

The WHO wishes to thank all those involved in the creation of these guidelines, as listed below.

Methodology Group

- Gordon Guyatt (McMaster University, Hamilton, Canada).
- Manya Prasad (All India Institute of Medical Sciences, New Delhi, India).

Systematic Review Team

- Manya Prasad (All India Institute of Medical Sciences, New Delhi, India).

Guideline Development Group

- Candido Ondo Ondo Avomo (Ministerio de Sanidad y Bienestar Social de Guinea Ecuatorial, Malabo, Equatorial Guinea).
- Abdoul Habib Beavogui (Centre National de Formation et de Recherche en Santé Rurale, Conakry, Guinea).
- Jean Luc Biampata (Institut National pour la Recherche Biomedicale, Kinshasa, Democratic Republic of the Congo).
- Alseny Modet Camara (ALIMA, Paris, France).
- Udeze Obiajulu Chinedu (Alex Ekwueme Federal University Teaching Hospital, Abakaliki, Nigeria).
- Yacouba Cissoko (University of Sciences Techniques and Technology of Bamako, Bamako, Mali).
- Kerry Dierberg (Médecins Sans Frontières, Paris, France).
- Cyril Oshomah Erameh (Institute of Viral Hemorrhagic Fevers and Emergent Pathogens, Irrua, Nigeria).
- William Fischer (University of North Carolina School of Medicine, Chapel Hill, United States of America).
- Tom Fletcher (Liverpool School of Tropical Medicine, Liverpool, United Kingdom of Great Britain and Northern Ireland).
- Louise Fortes (Université Cheikh Anta Diop, Dakar, Senegal).
- Robert Fowler (Sunnybrook Health Sciences Centre, Toronto, Canada).
- Ruggero Guiliano (University of Pisa, ASST Santi Paolo e Carlo, Milan, Italy).
- Beverley J Hunt (Guy's & St Thomas' NHS Foundation Trust, London, United Kingdom).
- Shevin T Jacob (Liverpool School of Tropical Medicine, Liverpool, United Kingdom).
- Frédérique Jacquerioz Bausch (Hôpitaux Universitaires de Genève, Geneva, Switzerland).
- Mohamed Boie Jalloh (National Public Health Agency, 34 Military Hospital, Freetown, Sierra Leone).
- Patricia Kabuni (University Hospital, Kinshasa, Democratic Republic of the Congo).
- David Kaggwa (Fort Portal Hospital, Fort Portal, Uganda).
- Said Kanenda (Bugando Medical Centre, Mwanza, United Republic of Tanzania).
- Michael Kiremeji (Muhimbili University of Health and Allied Science, Dar es Salaam, United Republic of Tanzania).
- Richard Kojan (ALIMA, Paris, France).
- Marie Claire Kolie (Ministry of Health, Conakry, Guinea).
- Sulaiman Lakoh (Directorate of Disease and Control, Ministry of Health, Freetown, Sierra Leone).
- Marie Claire Lamah (Ministry of Health, Conakry, Guinea).
- Hans Joerg Lang (Heidelberg Institute of Global Health, Heidelberg, Germany).
- Marcos Micha (Ministerio de sanidad y bienestar social de guinea ecuatorial, Malabo, Equatorial Guinea).
- Crisanta Mikue (Ministerio de sanidad y bienestar social de guinea ecuatorial, Malabo, Equatorial Guinea).
- Matilda Mattu Moiwo (Republic of Sierra Leone Armed Forces, Freetown, Sierra Leone).

- James Soka Moses (Partnership for Research on Vaccines & Infectious Diseases PREVAIL, Monrovia, Liberia).
- Daniel Mukadi-Bamuleka (National Institute for Biomedical Research, Kinshasa, Democratic Republic of the Congo).
- Imani Prince Musimwa (University of Goma, Goma, Democratic Republic of the Congo).
- Louise Mwiseneza (Kigali University Teaching Hospital, Kigali, Rwanda).
- Dieudonne Nkoghe (Ministry of Health, Franceville, Gabon)
- Marlies Ostermann (Guy's & St Thomas' NHS Foundation Trust, London, United Kingdom).
- Odianosen Otum (Irrua Teaching Hospital, Irrua, Nigeria).
- Apiyo Paska (Gulu Referral Hospital, Kampala, Uganda).
- Noel Kennedy Saitoti (Ministry of Health, Bukoba, United Republic of Tanzania).
- Sorie Samura (National Emergency Medical Systems, Freetown, Sierra Leone).
- Tonny Musoke Sekikongo (Emergency Response, Kampala, Uganda).
- Eric Seruyange (University of Rwanda, Rwanda, Rwanda).
- Rachel Esteves Soeiro (Catholic University of Pernambuco, Recife, Brazil).
- Armand Sprecher (Médecins Sans Frontières, Belgium).
- Okogbenin Sylvanus (Irrua Teaching Hospital, Irrua, Nigeria).
- Celestin Tshimanga (Institut National pour la Recherche Biomedicale, Kinshasa, Democratic Republic of the Congo).
- David Turatsinze (University Teaching Hospital of Kigali, Kigali, Rwanda).
- Theogene Twagirumugabe (University of Rwanda, Kigali, Rwanda).
- Doris Lorette Uwamahoro (Kigali University Teaching Hospital, Kigali, Rwanda).
- Timo Wolff (Frankfurt University Hospital, Frankfurt, Germany).
- Daniel Youkee (University of Cape Town, Cape Town, South Africa).

WHO Steering Group

- Samira Aboubaker (WHO headquarters, Geneva, Switzerland).
- April Baller (WHO headquarters, Geneva, Switzerland).
- Silvia Bertagnolio (WHO headquarters, Geneva, Switzerland).
- Mercedes Bonet Semenas (WHO headquarters, Geneva, Switzerland).
- Shelly Chadha (WHO headquarters, Geneva, Switzerland).
- Samual Chong (WHO Regional Office for the Western Pacific).
- Alarcos Cieza (WHO headquarters, Geneva, Switzerland).
- Janet Diaz (WHO headquarters, Geneva, Switzerland).
- Tarun Dua (WHO headquarters, Geneva, Switzerland).
- Luca Fontana (WHO headquarters, Geneva, Switzerland).
- Fahmy Hanna (WHO headquarters, Geneva, Switzerland).
- Mory Keita (WHO Regional Office for Africa).
- Gary Greg Kuniyoshi (WHO Regional Office for the Eastern Mediterranean).
- Anaïs Legand (WHO headquarters, Geneva, Switzerland).
- John Masina (WHO Regional Office for Africa).
- Julienne Ngoundoung Anoko (WHO Regional Office for Africa).
- Dina Pfeifer (WHO Regional Office for Europe).
- Kamara Rashidatu Fouad (WHO Regional Office for Africa).
- Angel Rodriguez (Pan-American Health Organization).
- Jamie Rylance (WHO headquarters, Geneva, Switzerland).
- Kai von Harbou (WHO headquarters, Geneva, Switzerland).
- Wilson Milton Were (WHO headquarters, Geneva, Switzerland).
- Pushpa Wijesinghe (WHO Regional Office for South-East Asia).

External Review Group

- Carrie Garavan (University of Limerick, Limerick, Ireland).
- Emmanuel Habimana (University of Rwanda, Kigali, Rwanda).
- Mohammed Lamorde (Makerere University, Kampala, Uganda).
- Stacey Mearns (Resolve to Save Lives, London, United Kingdom).

Abbreviations

AMR	antimicrobial resistance
CFR	case fatality rate
CI	confidence interval
CRT	capillary refill time
DIC	disseminated intravascular coagulation
EBOV	Ebola virus
EML	WHO Essential Medicines List
GDG	Guideline Development Group
GRADE	Grading of Recommendations Assessment, Development and Evaluation
ICU	intensive care unit
INR	international normalized ratio
IPC	infection prevention and control
IQR	interquartile range
LMICs	low and middle income countries
MAP	mean arterial pressure
ORS	oral rehydration salts
OSoC	optimized standard of care
PCR	polymerase chain reaction
PICO	population, intervention, comparison, outcomes
PPE	personal protective equipment
RCT	randomized controlled trial
RR	relative risk
SAE	serious adverse event
SSRI	selective serotonin reuptake inhibitor
WHO	World Health Organization

Executive summary

Clinical question: Which interventions can improve patient outcomes from filovirus disease?

Rationale and scope

Filovirus disease includes infections caused by Bundibugyo, Ebola, Marburg, Sudan and Taï Forest viruses. Previous WHO clinical guidance focused on Ebola virus disease, and was based on expert-defined best clinical practice. These guidelines expand the scope to all filoviruses to reduce duplication, harmonize approaches and maximize impact across outbreaks. Recommendations have also been formulated using data from systematic evidence searches, and according to the GRADE (Grading of Recommendations Assessment, Development and Evaluation) framework to maximize transparency and to ensure implementation considerations have been carefully evaluated.

Methods

The guideline was developed in accordance with the *WHO handbook for guideline development*. A multidisciplinary, geographically representative Guideline Development Group (GDG) was convened, with representation across clinical disciplines, regions and genders. All members completed declarations of interest, which were reviewed and managed using standard WHO procedures.

Clinical questions were framed using the PICO (Population, Intervention, Comparison/Comparator, Outcomes) format. Evidence synthesis relied primarily on recent high quality systematic reviews. The GRADE approach was used to assess certainty of evidence and to determine the direction and strength of recommendations. For each recommendation, an evidence-to-decision framework was applied, incorporating: balance of benefits and harms; certainty of evidence; patient values and preferences; feasibility; resource use; equity; acceptability.

Draft recommendations underwent internal and external peer review and final approval by the WHO Guideline Review Committee.

Key recommendations

- Systematic patient monitoring should be established for patients with suspected or confirmed filovirus disease, using structured and documented clinical assessment at regular intervals, with frequency adapted to patient condition (Good practice statement).

- WHO recommends that for patients with suspected or confirmed filovirus disease, systematic laboratory monitoring be performed based on clinical assessment, rather than on routine testing (Strong recommendation for, low certainty of evidence).

- WHO recommends patients with suspected or confirmed filovirus disease with ongoing gastrointestinal fluid losses and some dehydration, be treated with a protocolized oral rehydration regimen (e.g. WHO Plan B) (Strong recommendation for, moderate certainty evidence).

- WHO suggests patients with suspected or confirmed filovirus disease with ongoing gastrointestinal fluid losses and severe dehydration be treated with a protocolized intravenous fluid regimen compared with no protocolized intravenous fluid regimen (Conditional recommendation for, low certainty evidence).

- WHO recommends balanced crystalloids (such as Ringer's lactate) rather than 0.9% sodium chloride for acute intravenous fluid resuscitation in patients with suspected or confirmed filovirus disease (Strong recommendation for, moderate certainty of evidence).

- WHO suggests for patients with suspected or confirmed filovirus disease and clinical signs of shock or circulatory impairment, the serial measurement of lactate as part of the assessment of perfusion to guide further intravenous fluid management (Conditional recommendation for, low certainty of evidence).

- WHO suggests for patients with suspected or confirmed filovirus disease and clinical signs of shock or circulatory impairment, capillary refill time should be used as part of the assessment of perfusion to guide intravenous fluid management (Conditional recommendation for, low certainty of evidence).

- WHO suggests that patients with suspected or confirmed filovirus disease with shock who are being resuscitated with intravenous fluids, vasopressor treatment be initiated early rather than later (Conditional recommendation for, low certainty of evidence).

- WHO recommends that patients with suspected or confirmed filovirus disease requiring a vasopressor be treated with norepinephrine rather than dopamine (Strong recommendation for, moderate certainty evidence).

- WHO suggests that patients with suspected or confirmed filovirus disease requiring a vasopressor be treated with norepinephrine rather than epinephrine (Conditional recommendation for, very low certainty of evidence).

- WHO suggests that for patients with filovirus disease requiring initiation of vasopressors, peripheral intravenous catheters be used rather than central venous catheters (Conditional recommendation for, very low certainty of evidence)

- WHO recommends that for patients with suspected or confirmed filovirus requiring central venous access, ultrasound guided placement be used rather than non-ultrasound guided placement (Strong recommendation for, moderate certainty of evidence).

- WHO suggests for the use of presumptive broad-spectrum antibiotics in patients with confirmed filovirus disease in the presence of suspected sepsis or bacterial co-infection (Conditional recommendation for, low certainty of evidence).

- WHO suggests against the use of tranexamic acid in patients with confirmed filovirus disease and haemorrhage (Conditional recommendation against, very low certainty of evidence).

- WHO suggests for the use of tranexamic acid in patients with confirmed filovirus disease and postpartum haemorrhage (Conditional recommendation for, low certainty evidence).

- WHO recommends that persons who have survived/recovered from filovirus disease be offered structured follow-up after discharge (Strong recommendation for, moderate certainty of evidence).

Practical applications

High-quality supportive care for filovirus disease can reduce mortality. Implementation of clinical interventions is complicated by resource availability, the suboptimal environment in which care is often delivered, the need for stringent infection prevention and control (IPC) procedures and limited staff training. This clinical guideline complements multiple other WHO guidance documents, which together address these challenges. As part of this multidisciplinary approach, applying clinical principles and delivering individualized person-centred care will save lives and improve the outcomes for patients.

Introduction

These guidelines on filovirus disease have been developed in line with the WHO handbook for guideline development *(1)*. Filovirus infections are caused by the family of filamentous, single-stranded RNA *Filoviridae* viruses. Within this family, viruses from two genera are known to cause severe, highly fatal disease in humans; *Orthoebolavirus* (including Ebola, Sudan, Bundibugyo and Taï Forest viruses) and *Orthomarburgvirus* (within which Marburg is the most important) *(2)*. These infections present highly demanding clinical challenges due to their transmissibility, mortality and the resource limitations in the environment in which clinical care is frequently delivered. For further detailed information, see reviews of the pathophysiology and clinical management of Ebola virus disease *(3, 4, 5)*.

Transmission and infection prevention and control

Patients suffering from filovirus disease often produce copious amounts of infectious body fluids at the height of their illness *(3, 6)*. Infection prevention and control (IPC) measures are key to preventing onward transmission, and avoiding health and care worker infection. These are not further detailed in this document, but are well described in WHO guidance *(7, 8, 9, 10, 11)*.

Mortality

A meta-analysis covering cases of Ebola virus disease from 1976 to 2022 included 42 outbreaks and data from 16 countries. The pooled case fatality rate (CFR) was 60.6% (95% CI 51.6–69.4). Ebola virus disease had highest CFR of 66.6% (95% CI 55.9–76.8). In Sudan virus disease the CFR was 48.5% (95% CI 38.6–58.4), in Bundibugyo virus disease 32.8% (95% CI 25.8–40.2) and in Taï Forest virus disease 0% (95% CI 0.0–97.5). Heterogeneity between outbreaks and settings was frequently greater than between viruses *(12)*. This analysis did not include the most recent outbreaks, notably those in the Democratic Republic of the Congo (Ebola virus disease, 2025), Ethiopia (Marburg virus disease, 2025) or Rwanda (Marburg virus disease, 2024).

Environment for providing clinical care

Over the past several decades, multiple outbreaks across diverse settings have provided quantitative and qualitative evidence on how best to deliver safe, effective and compassionate care. Each event has reinforced a central lesson: outcomes improve when skilled clinicians, well designed care structures and cohesive multidisciplinary teams work in concert with affected communities *(13, 14)*. Within a single outbreak, mortality often declines as clinical organization matures, workflows stabilize and teams gain confidence in delivering early, targeted supportive care.

Patients often present with rapidly evolving physiological instability which requires vigilant monitoring, timely interventions and meticulous attention to safe clinical practice. The structure and design of care facilities, ranging from triage flow to infection prevention architecture, directly influence the safety of both patients and staff *(14)*.

Purpose and scope of these guidelines

Even in the most constrained environments, foundational but high-quality supportive care can reduce mortality. More advanced care provision, including some organ support therapy may depend upon availability of resources and staff. This patient-centred guideline is anchored in clinical practice, and aimed at the clinicians who care for those with filovirus disease. It identifies key clinical interventions which may reduce mortality, and presents the evidence and the recommendations of the expert Guideline Development Group (GDG).

As described in the Methods section, priority questions were identified to define the guideline scope. During the guideline meeting, a number of practical issues and knowledge gaps were identified; these are listed in the Uncertainties and future research section.

Accompanying WHO documents

- *Optimized supportive care for Ebola virus disease* ("OSoC manual") *(15)* provides standard operating procedures for clinical management, including the treatment of diseaserelated complications. Although developed for Ebola virus disease, it is a practical resource that can be applied to the care of patients with other filovirus infections. The recommendations in these guidelines, *Guidelines on the clinical management of filovirus disease*, are closely aligned with the OSoC manual. However, they should be considered the authoritative reference where discrepancies exist, particularly regarding the recommendation against the use of tranexamic acid. An updated version of the OSoC manual is currently in development.
- *Therapeutics for Ebola virus disease (16)* describes the specific antiviral therapy for Ebola virus disease (caused by *Ebolavirus Zaire ebolavirus*), which in combination with supportive care reduces mortality.
- *FiloTREAT online training for the clinical management and operational response to filovirus disease (17)* is a useful practical training course which can be used in parallel to these guidelines.
- *Guidelines for the management of pregnant and breastfeeding women in the context of Ebola virus disease (18).*

Other WHO documents

The guideline does not directly address IPC, vaccination or broader aspects of outbreak investigation and control. A plethora of guidance exists on these topics to support filovirus outbreak response, and the broader delivery of care, for example:

Infection prevention and control

- *Summary of WHO infection prevention and control Guideline for Ebola and Marburg disease: a call for evidence-based practice (8)*
  - full document *Infection prevention and control guideline for Ebola and Marburg disease (19).*
- *Infection prevention and control and water, sanitation and hygiene in health facilities during Ebola or Marburg disease outbreaks: rapid assessment tool user guide (7).*
- *Steps to put on personal protective equipment (PPE) for Ebola/Marburg disease: coverall (9).*
- *Steps to remove personal protective equipment (PPE) for Ebola/Marburg disease: coverall (10).*
- *Guidance on regulations for the transport of infectious substances 2021–2022 (11).*
- *How to conduct safe and dignified burial of a patient who has died from suspected or confirmed Ebola or Marburg virus disease: interim guidance (20).*

Diagnostic testing

- *Diagnostic testing for Ebola and Marburg virus diseases: interim guidance (21).*

Facility design

- *Ebola and Marburg treatment centres: facility design and construction standards for preparing for and responding to outbreaks (14).*

Communication with patients and communities

- *Ebola disease – fact sheet (22).*
- *Ebola disease – questions and answers (23).*
- *Risk communication and community engagement readiness and response toolkit: Ebola disease (13).*

Outbreak investigation tools

- *Ebola virus outbreak toolbox (24).*

Vaccination

- Extraordinary Meeting of the Strategic Advisory Group of Experts on Immunization on Ebola Vaccination, May 2024: conclusions and recommendations *(25).*

How to access and use the guideline

How to access the guideline

WHO website in PDF format https://doi.org/10.2471/B09774
From the Magicapp website at https://app.magicapp.org/#/guideline/11037

How to use these guidelines

These guidelines can be used by policy-makers to enable the implementation of recommendations through adequate provision of medical supplies, biomedical equipment and human resources.

At the bedside, clinicians caring for patients can use these guidelines and its evidence tables to discuss with patients and families the benefits and risks of interventions enabling shared decision-making.

It is important that the guideline be adapted for use according to local cultural contexts, espcially considering the uncertainty around patient preferences in the literature and the low certainty of evidence behind some of the recommendations. The recommendations should be implemented with a patient-centred, safety and ethical approach and adhering to quality of care principles: safety, timeliness, effectiveness, efficiency and equity. This is particularly important given that the guideline covers both adults, children (minors), pregnant women and outbreaks which commonly occur in fragile settings.

Methods

These guidelines have been developed in accordance with the *WHO handbook for guideline development (1)*.

Evidence identification and synthesis has undergone the following stages:

1. Prioritization of clinical questions
2. Framing of PICO questions and vetting by the GDG
3. Consensus on priority outcomes and minimal important differences
4. Consideration of the evidence by the GDG
5. Formulation of recommendations
6. Review of draft guidelines (internal and external)
7. Approval by the WHO Guideline Review Committee.

Guideline Development Group (GDG) composition and declarations of interest

GDG members were selected for global geographical representation, gender balance and appropriate technical and clinical expertise, with a minimum requirement that direct experience of a filovirus outbreak was mandatory. Written declarations of interest were obtained from all participants in the process using standard WHO forms and process. Submitted declarations were reviewed by the WHO technical team, and a further online search for potential conflict was performed. There were no identified conflicts which precluded participation.

Identification of guideline scope and priority questions

The guideline was explicitly conceived as a set of recommendations which could be applied to patients of any age due to an appreciation that clinical staff in many low- and middle-income countries (LMICs) are frequently generalists who encounter adults and children within their usual scope of practice.

Evidence identification and synthesis

PICO definition

Questions were codified using a PICO framework (identifying the population, intervention, comparison and outcomes of interest), and refined by the methodologist, technical team and clinical chairs.

Patient values and preferences

Existing systematic review and qualitative data are clear that, amongst survivors of filovirus disease, there are frequent and significant psychological distress *(26, 27)*. It was inferred that interventions which reduced this would be valued highly, including those which reduced community stigmatization and promoted reintegration after discharge. It was noted that such qualitative work was necessarily selective for those who survived. Similarly, there were no published systematic reviews which specifically discussed patient values in relation to acute filovirus infection. The GDG discussed their experience of being patients, or treating patients with filovirus disease. It was acknowledged that treatment environments had changed considerably since the early West Africa outbreak 2013–2016, with an increasing emphasis over time on supportive care, and an increased availabilty of treatments proven to improve mortality. The panel drafted and agreed an overarching statement believed to capture the preferences of the patient population towards their treatment during most recent filovirus outbreaks.

"Given the high mortality of filovirus disease, some patients may be willing to try an intervention with uncertain benefit; however, many would place high value on avoiding treatments with potential to worsen survival, especially when evidence of benefit is lacking."

This was applied to each PICO, with the relevance considered and recorded.

Priority outcomes

Multiple WHO guidelines were identified which considered acute illness. Amongst these were guidelines for influenza, COVID-19, malaria and arbovirus. The outcomes used in these were extracted into a list, and the GDG members were asked to add any they felt might be missing. A prioritization exercise using an electronic survey of the GDG identified the most important according to the panel's assessment of patient judgements. Critically important outcomes were identified as: mortality; relief of symptoms; major bleeding; prevention of disease spread; quality of life after discharge; kidney injury; stigma and mental health issues; costs to the patient and their family; serious adverse events (SAEs); and length of stay in treatment facilities. Important outcomes were identified as: renal replacement therapy; and invasive mechanical ventilation.

Minimal important differences

In the absence of empirical evidence on patient preferences and to maintain consistency across WHO guidelines wherever possible, values for minimal important differences from the identified guidelines of acute medical care were presented to the panel. These were discussed and subsequently adopted by consensus agreement as the initial estimates.

Identification of existing evidence

For these guidelines, existing recent systematic reviews were used where possible. These were identified using as a systematic search strategy developed by an information specialist. New systematic reviews were conducted in the absence of existing systematic reviews of sufficient quality. Where direct evidence was not available, indirect evidence was considered, including a "chain of evidence" approach, where possible, to make explicit the link from intervention to likely impact.

Where a potentially appropriate systematic review was identified for a single PICO, the following elements were reviewed:

- Population: was the defined population sufficiently similar to an expected population attending hospital for suspected or confirmed filovirus disease?
- Intervention: was the intervention described in the review well aligned with the pre-defined PICO?
- Comparator: were any issues identified with the selection of control populations within the review which might introduce significant indirectness?
- Outcomes: to what degree did reported outcomes align with critical and important outcomes defined by the GDG?
- Recency: where multiple systematic reviews met criteria for inclusion, the most recent was used unless there was a compelling quality reason. For all PICOs, a review of the more recent literature, limited to randomized controlled trials (RCTs) was performed by the informatics team, and the GDG was asked to identify any other sources of more recent evidence. Unless new evidence was identified, the published reviews were used.
- Reporting: reporting of indirectness, imprecision and risk of bias were mandatory criteria for use of the review. If these were not included, and could not be inferred, reviews were excluded.
- Systematic reviews conducted for WHO sepsis guidelines 2025 and WHO guidelines for fluid management in acutely ill children were used for questions pertaining to parenteral fluid use and type and timing of vasopressors.

Synthesis of evidence for these guidelines
For a limited number of PICOs, no recent published and relevant systematic review was available. Such reviews were undertaken and presented to the GDG by MP; they are published online with these guidelines. In these cases, GG acted as primary methodologist. In all cases, independent senior methodology oversight was provided by the MAGIC team."

The following foreground questions required a *de novo* systematic review:

1. In patients with filovirus disease, what effect does systematic laboratory monitoring compared with no laboratory monitoring have on patient-important outcomes?
2. In patients with filovirus disease, what effect does use of routine presumptive antibiotic treatment compared with no routine antibiotic treatment have on patient-important outcomes?
3. In patients with filovirus disease who require administration of a vasopressor, what is the effect of peripheral compared with central venous administration on patient-important outcomes?

Formulation of recommendations

Deliberations on the direction and strength of recommendations were facilitated by the methodologist and clinical chairs according to the GRADE (Grading of Recommendations Assessment, Development and Evaluation) methodology *(1)*, and including review and deliberation of:

- absolute benefits and harms for important and critical outcomes through structured evidence summaries (e.g. GRADE summary of findings tables including effect estimates and confidence intervals (CI) where relevant, and lay summaries). Where outcomes were not available from the available evidence, this was highlighted to the GDG;
- certainty of the evidence;
- values and preferences of patients - in addition to the literature review, the GDG drew on their experience of how patients would balance the benefits, harms and burdens of treatment; and
- resources and other considerations (including feasibility, applicability, equity). When possible, research evidence was used to inform discussion around these key factors. The panel considered a population perspective in which feasibility, acceptability, equity and cost were important considerations. Specific deliberations on values and preferences and associated feasibility and resource-related considerations are presented for each recommendation.

A *priori* voting rules were in place if the GDG failed to reach consensus by discussion (requiring 70% for a strong recommendation, or simple majority for a conditional recommendation), but resolution by discussion was possible for all recommendations.

Formulation of good practice statements

Good practice statements are reserved for situations where compelling linked evidence could be found, but such a search would demand a disproportionate investment of limited time and energy to complete.

Review of draft guidelines

An external review group reviewed the final guideline document to identify, correct and clarify errors, include contextual issues, and check for unanticipated implications for implementation which needed additional consideration.
The final guideline was reviewed and approved by the WHO Guideline Review Committee.

Monitoring

Effective clinical management of patients with suspected or confirmed filovirus disease relies on systematic and structured patient monitoring from the earliest point of contact.

Continuous and frequent reassessment is critical given the often rapid and unpredictable progression of filovirus disease. Monitoring should begin at first clinical contact and continue throughout all phases of care, including during patient transfer, movement within the facility and transitions between clinical zones. Regular reassessment helps clinicians detect early signs of shock, respiratory compromise, neurological changes or other complications. Core measurements typically include vital signs (temperature, respiratory rate, heart rate, blood pressure and oxygen saturation), neurological status, fluid balance, and assessment of gastrointestinal symptoms, hydration and perfusion. Where feasible, additional laboratory parameters, such as point of care tests for glucose, electrolytes, haemoglobin and lactate, can provide valuable information for guiding clinical decisions. To perform these assessments reliably, treatment centres require a set of essential equipment, including thermometers, pulse oximeters, blood pressure devices, clocks and point of care diagnostic tools.

Design

Design principles create an environment in which structured, frequent monitoring can be performed consistently and safely. This includes layouts that support clear communication between team members and safe donning and doffing processes, and optimize visibility, such as clear lines of sight into high dependency areas, and observation windows into the red zone. Adequate lighting and accessible monitoring equipment further facilitate safe and efficient assessment *(14)*.

Clinical monitoring

Good practice statement

Systematic patient monitoring should be established for patients with suspected or confirmed filovirus disease, using structured and documented clinical assessment at regular intervals, with frequency adapted to patient condition.

[Good practice statement]

- This statement applies to all children and adults, including pregnant women.
- Abnormalities which are identified during an assessment and monitoring must be followed by immediate action which is expected to improve the patient's outcome.

Justification

The panel unanimously emphasized the importance of monitoring, and that this be linked directly to clinical interventions, with individualized decision-making to ensure patients' needs are met. The panel postulated very low frequency adverse events related to non-invasive monitoring, and trivial impact where these occurred. By contrast, the panel considered a potential for catastrophic harm when abnormal physiology is not recognized.

The panel were initially presented evidence from randomized controlled trials (RCTs) of continuous telemonitoring, which found very low certainty evidence for outcomes of mortality, major complications and length of stay *(28)*. However, they felt these did not to reflect the real risk:benefit of broader patient monitoring, as this modality was not the expected method of delivering frequent, intermittent monitoring in filovirus outbreaks.

The lack of RCTs was considered to be due to lack of equipoise due to the fundamental principle of monitoring being applied throughout clinical practice. The panel discussed the possibility of creating a linked evidence profile to support a non-discordant strong recommendation. However, this would require disproportionate effort. Experiential evidence was shared about how early detection of abnormalities if acted upon does save lives, and there was universal agreement that patient observations are a fundamental part of delivery of high-quality medical care.

Supporting this were considerations of equity (all patients benefit) and demonstrated acceptability and feasibility as part of everyday practice. Resource needs were discussed including sufficient staff and training. The absolute human resource requirement would be determined by the level of care demanded in the treatment centre.

The panel advocated for improved treatment centre design to facilitate monitoring from the green zone, and communication between the green and red zones.

The panel underlined that the resulting good practice statement had the same strength as a strong recommendation in favour of systematic patient monitoring. The panel underlined the important principle that frequency of monitoring be based on disease severity.

Laboratory monitoring

Strong recommendation for

WHO recommends that for patients with suspected or confirmed filovirus disease, systematic laboratory monitoring be performed based on clinical assessment, rather than on routine testing.

[Strong recommendation, low certainty of evidence]

- This recommendation applies to all children and adults, including pregnant women.
- Laboratory monitoring should be linked to actionable clinical interventions intended to improve patient outcomes. The laboratory result turnaround time should be appropriate to inform clinical decision-making.
- The scope and frequency of laboratory testing should be tailored to the needs of the patient, with selection to use resources wisely and minimize venous punctures.
- The minimal set of available tests should include: point-of-care malaria rapid diagnostic tests, glucose, haemoglobin/haematocrit, complete blood count, pregnancy test, urinary dipstick, tests required for blood transfusion, electrolytes and biochemistry. Additional tests may be required based on level of care.
- Biosafety must be implemented during all phases, including sample collection, transport, laboratory manipulation and sample disposal.

Practical info

Organization

- Laboratory facilities should be as close as possible to patient care areas. This is preferentially delivered using point-of-care devices where they are cheap and available.
- Organize laboratory availability as core laboratories then add on based on level of care.
- Put in place standard operating procedures for use, for training, and for staffing of the laboratory facilities. This will depend on the configuration and choices of assays and analysis platforms.
  - Anticipate the needs in terms of disposables (such as cartridges), reagents and quality assurance.

Frequency of analysis

- Limit sampling to avoid bleeding risk from venepuncture sites.
- Avoid overtesting or "routine monitoring" without consideration of the resource use – this may decrease equity due to unnecessary costs and risk stock-outs which will mean essential care delivery to the highest risk patients is compromised.

Measurement of individual analytes

- Measure and record serum biochemistry and haematology on admission and daily during the resuscitation phase (typically the first 4 days of illness, or longer depending on the clinical condition of the patient) and as clinically indicated.
  - This includes sodium, potassium, bicarbonate, urea/blood urea nitrogen, creatinine, liver transaminases, magnesium, glucose, complete blood count including haemoglobin, white blood cells and platelets, prothromin time/international normalized ratio (INR), creatine kinase, chloride, calcium, 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 (< 3 mmol/dL = 54 mg/dL), patients should be treated immediately and glucose measured every 1–2 hours until stable (i.e. no evidence of hypoglycaemia confirmed by 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.

Polymerase chain reaction (PCR) diagnostics
This section is not focused on PCR diagnostics for filovirus disease, which are considered separately. However, it is noted that:

- WHO has strong recommendations for mba114 and REGN-EB3 for EBOV (Zaire). These are time critical therapeutics, with time delays in therapeutic administration leading to increased mortality. Therefore, for EBOV, where Xpert platform testing is available, the time from admission of suspected case to receipt of PCR result should be within 6 hours.
- Immediate 24-hour access to diagnostic filovirus PCR and CT values are a critical component to drive clinical management including early initiation of antiviral therapies and patient prognostication.
- For confirmed admitted patients with filovirus disease, repeat PCR testing should be offered (for example on day 3) so that CT values can guide prognostication.

Evidence to decision

Benefits and harms	**Substantial net benefits of the recommended alternative** In patients with suspected or confirmed filovirus disease, there was moderate certainty evidence that life threatening biochemical abnormalities occur, including hyperkalaemia and acute kidney injury at a rate of 130 and 220/1000 respectively. The panel inferred that many of these are amenable to clinical interventions which would be expected to improve patient outcomes, and in some severe cases, save lives immediately (such as hyperkalaemia) and reduce harms (adjusting medicine dosing for extent of renal insufficiency or liver abnormalities). Evidence on harms was not shown. The panel expected harm to be very infrequent and clinically insignificant, unless blood sampling and testing was overused or done without proper IPC.
Certainty of the evidence	**Low** The evidence summary for this recommendation was informed by laboratory findings within observational cohorts of Ebola virus disease patients *(29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42)* (systematic review published as online appendix). This provided moderate certainty evidence for hyperkalaemia being associated with mortality, and high certainty for increased mortality risk in for rhabdomyolysis, asparate transferase > 525, elevated creatine and anaemia. The overall certainty including linkage of this evidence to improvement in patient outcome (i.e. mortality) was judged to be low.
Values and preferences	**No substantial variability expected** Patients would be expected to want laboratory monitoring due to the overwhelming benefit/harm balance.

Resources and other considerations	Important issues, or potential issues not investigated **Equity:** Laboratory testing would increase equity for patients admitted to the treatment centre both for suspected and confirmed patients, provided tests were performed on the basis of need, results made available to staff and acted on in a timely fashion. **Feasibility and acceptability:** Testing was noted to be feasible and acceptable only if proximal to the treatment centre, enabling easier sample transfer, improved turnaround time for results and stronger IPC procedures. The panel advocated for improved treatment centre design to enable optimal use of laboratory testing (e.g. point-of-care or near point-of care-testing) inside or very near the treatment centre. **Resources/cost:** We did not do a cost-effectiveness analysis. In general, the cost of clinical laboratory tests is difficult to ascertain, but includes both capital and operational costs, such as medical devices (laboratory equipment) and cartridges/reagents as well as, trained human resources. The panel noted that using testing wisely, based on the clinical needs of patients, would be important. Comments were made around sustainability outside of outbreaks, including storage of laboratory reagents, and laboratory equipment or near point-of-care laboratory tests. The WHO Model List of Essential In Vitro Diagnostics can guide the use of available tests in relation to the assay format, test purpose, specimen type and health care setting *(43)*.

Justification

Evidence was derived from a systematic review commissioned by WHO, published as part of these guidelines *(29)*.

The panel reasoned that laboratory monitoring is a tool which enables earlier recognition of important pathophysiologic abnormality, and provides key data related to disease. Through directly informing clinical action, laboratory results can improve patient outcomes.

The panel gave examples of hypoglycaemia, which is life threatening, and hyperkalaemia, which is both life threatening and impossible to detect without laboratory testing. In both cases, specific treatment can correct the abnormality, thereby reducing the risk of death. Other examples included the detection of kidney or liver impairment for which clinical adjustments in drug dosing are required to avoid iatrogenic harm.

Univariate analysis demonstrated a clear association between abnormality and in-facility mortality: for hyperkalaemia OR 11.11 (95% CI 2.70–45.66), moderate certainty; for rhabdomyolysis aOR 2.18 (95% CI 1.09–4.37); for creatinine aOR 2.3 for each 100 mmol/L increase (95% CI 1.1–4.6), high certainty; and for haemoglobin aOR 0.67 (95% CI 0.47–0.93), high certainty.

Using this linked evidence, overall judged to be low certainty, the panel made a strong recommendation for laboratory monitoring. The panel noted that many life-threatening biochemical abnormalities had no good clinical correlation, but could be treated effectively when identified. A discordant recommendation was therefore justified on the basis of the high potential for catastrophic outcome without the ability to perform laboratory testing.

Experience from the most recent filovirus disease outbreaks demonstrated that laboratory monitoring was not "standard of care", and may in some circumstances be aspirational leading to delayed recognition and adverse patient outcomes. The panel stated that a strong recommendation would be more likely to drive improvements in availability by sending a clear message to policy-makers, public health laboratory administrators and health facility administrators.

The panel listed a core set of laboratory tests that should be made available, and that additional tests be made available based on level of care provided in the treatment centre.

Core tests included: sodium (Na+); potassium (K+); lactate; creatinine; glucose; complete blood count (red blood cells, white blood cells, haemoglobin, haematocrit, platelets); prothrombin time/activated partial thromboplastin time (PT/APTT); malaria rapid diagnostic test (MRDT); HIV as per national protocol; human chorionic gonadotropin (bHCG) for pregnancy test, blood group and matching (for transfusion purposes); urinalysis (urine dipstick).

Comprehensive tests included core tests plus: urea; chloride; bicarbonate; calcium; phosphate; magnesium; creatinine kinase; liver transaminases; fibrinogen; platelets; blood culture; multiplex PCR pathogen testing; c-reative protein (CRP). In addition, in locations with high HIV prevalence, consideration of urinary lipoarabinomannan (LAM) and cryptococcal antigen for patients living with HIV.

PICO

Population: Patients with confirmed filovirus disease.

Intervention: Systematic laboratory monitoring#: glucose, haemoglobin, differential white count, liver transaminases/bilirubin, albumin, urea/nitrogen, creatinine, CK, acid-base balance, other electrolyte (Na, K, Ca, Mg), CRP, PCT, and clotting screen, lactate.

Comparator: No laboratory monitoring.

Outcome	Study results and measurements	Comparator No laboratory monitoring	Intervention Systematic laboratory monitoring	Certainty of evidence (Quality of evidence)
Raised aspartate transaminase	Relative risk (observational (non-randomized))	**728** per 1000	CI 95%	High
Hyponatraemia	Relative risk	**590** per 1000	CI 95%	High
Raised alanine transaminase	Relative risk	**525** per 1000	CI 95%	High
BUN >1x upper limit of normal	Relative risk	**364** per 1000	CI 95%	High
Renal impairment	Relative risk	**220** per 1000	CI 95%	Moderate due to serious imprecision[a]
Anaemia	Relative risk	**270** per 1000	CI 95%	High
Rhabdomyolysis	Relative risk	**225** per 1000	CI 95%	Moderate due to serious imprecision[a]
Hypokalaemia	Relative risk	**190** per 1000	CI 95%	Moderate due to serious imprecision[a]
Hyperkalaemia	Relative risk	**130** per 1000	CI 95%	Moderate due to serious imprecision[a]
Severe hypoglycaemia	Relative risk	**84** per 1000	CI 95%	Moderate due to serious imprecision[a]
Severe thrombocytopaenia	Relative risk	**7** per 1000	CI 95%	Moderate due to serious imprecision[a]

[a] **Imprecision: serious.** Wide confidence intervals.

Fluid therapy in patients with gastrointestinal losses (not shocked)

Strong recommendation for

WHO recommends patients with suspected or confirmed filovirus disease with ongoing gastrointestinal fluid losses and some dehydration[a] be treated with a protocolized oral rehydration regimen (e.g. WHO Plan B).

[Strong recommendation, moderate certainty evidence]

- This recommendation applies to both children and adults, including pregnant women.
- Systematic monitoring of vital signs including fluid input and output is required to identify those patients that may need escalated treatment with intravenous fluid.
- Peripheral venous catheter should be placed in all patients with filovirus disease in case there is need to augment with intravenous fluids.
- This does not apply to patients with sepsis or septic shock, for which intravenous fluid therapy is indicated, nor those with severe acute malnutrition, for which other WHO guidelines should be used.

[a] **In children:** Some dehydration is defined as no signs of severe dehydration, with two or more of the following signs: restlessness; irritability; sunken eyes; thirsty and drinks eagerly; skin pinch goes back slowly. Severe dehydration is defined as two or more of the following signs: lethargy or unconsciousness; sunken eyes; unable to drink or drinks poorly; skin pinch goes back very slowly (≥ 2 seconds).

In adults: Some dehydration is less well defined than for children, but includes symptoms of: feeling thirsty; concentrated urine; infrequent urination; feeling dizzy or lightheaded; tiredness; dry mouth, lips and tongue; sunken eyes.

Practical info

Start fluids early to prevent and mitigate fluid losses and organ damage.

- For initial treatment give oral rehydration salts (ORS) 75 mL/kg in the first 4 hours of treatment.
- Give additional ORS to replace on going losses. Recommended after each loose stool:
  - < 2 years 50–100 mL
  - 2–9 years 100–200 mL
  - ≥ 10 years and adults – as much as wanted.

Further tools may be modified from those for cholera: *Clinical tools for cholera treatment facilities*.

Evidence to decision

Benefits and harms	**Substantial net benefits of the recommended alternative** In patients with some dehydration and suspected or confirmed filovirus disease, protocolized oral rehydration regimens such as WHO Plan B probably reduced mortality (moderate certainty evidence). Data on harms were not directly available from the evidence presented. The panel noted from their clinical experience that in some patient groups the liberal use of fluids could increase the risk of fluid overload (such as pulmonary oedema), and to mitigate these adverse outcomes more intensive monitoring with modifications in high-risk patients of fluid volumes and/or rates of administration would be required.
Certainty of the evidence	**Moderate** The evidence summary on oral rehydration regimen for suspected and confirmed filovirus disease with some dehydration and ongoing fluid loss was informed by one observational study in which systematic administration of intravenous fluids was uncommon and 1230 (70.8%) of 1737 patients with Ebola virus disease died *(44)*. This contrasts with 5 of 27 patients (18.5%) with the disease who were treated with intravenous fluid rehydration in the United States of America and Europe (RR 0.26, 95% CI 0.12–0.58; risk difference –52.4%, 95% CI –62.3 to –29.7) *(45, 46)*. Though this study was observational, the certainty of evidence of the observation study data was upgraded due to large effect size to moderate.
Values and preferences	**No substantial variability expected** See the agreed consensus on patient values and preference in the Methods section which was judged to pertain here.
Resources and other considerations	**No important issues with the recommended alternative** **Equity:** Use of oral rehydration regimens probably increases equity as appropriate use of oral rehydration will enable optimal use of resources for those patients who require more intensive care. **Acceptability:** To health and care workers and patients, oral rehydration therapy is acceptable provided that the patient can swallow safely, does not have significant vomiting and is able to self-administer fluids by mouth. From a health worker perspective, sufficient monitoring is needed to ensure prompt recognition of clinical deterioration and enable rapid corrections to the care plan. **Feasibility:** Oral rehydration is feasible, as has been demonstrated in large-scale cholera outbreaks. It may have advantages in filovirus treatment centres where IPC considerations make frequent manipulation of intravenous fluid very resource intensive. **Resources:** Oral rehydration salts (ORS) solution is widely available and low-cost compared with intravenous rehydration.

Justification

Evidence was drawn from large observational cohorts from cholera, taken before and after the implementation of structured oral fluids (now codified as WHO Plan B). The certainty of evidence was upgraded due to large effect size. The panel discussed the applicability to filovirus disease, and noted that where some dehydration was present, the benefits were likely to be similar. The panel emphasized that most patients with some dehydration would place high value on moderate certainty evidence of mortality impact with an oral rehydration regimen (i.e. WHO Plan B), especially when the harms are insignificant relative to the mortality benefits. The panel recognized that clinically important differences would increase in patients with severe dehydration and/or sepsis and/or shock, or those at high risk of complications from high-volume fluid therapy such as those with pre-existing congestive heart failure, or severe acute malnutrition.

The panel emphasized that this recommendation was only applicable where patients could take oral fluids easily. They noted that for patients with filovirus disease who have the potential for rapid clinical deterioration, intravenous access should be placed even where oral fluids are being given, and close monitoring is required. Similarly, the panel stressed that the presence of sepsis and/or shock necessitates intravenous fluid therapy.

Conditional recommendation for

WHO suggests patients with suspected or confirmed filovirus disease with ongoing gastrointestinal fluid losses and severe dehydration[a] be treated with a protocolized intravenous fluid regimen[b] compared with no protocolized intravenous fluid regimen.

[Conditional recommendation, low certainty evidence]

- This recommendation applies to both adults and children.
- Systematic and frequent monitoring of haemodynamic status, fluid input and output, and signs of fluid overload is required to titrate and individualize fluid therapy.
- Modifications of WHO Plan C are required to enhance monitoring to enable more restrictive fluid regimen in cases where it is difficult to discriminate between severe dehydration and sepsis-induced hypoperfusion (see Practical info section).
- Once dehydration is corrected, administer maintenance fluids based on calculated requirements based on weight and insensible and ongoing losses.
- Patients that develop shock, need careful re-evaluation for etiology of shock to guide appropriate resuscitation.

[a] **In children:** Severe dehydration is defined as two or more of the following signs: lethargy or unconsciousness; sunken eyes; unable to drink or drinks poorly; skin pinch goes back very slowly (≥ 2 seconds).

In adults: Severe dehydration, which requires urgent resuscitation with intravenous fluid, is suggested by any of: systolic blood pressure is less than 100 mmHg; heart rate is more than 90 beats per minute; capillary refill time is more than 2 seconds; peripheries are cold to touch; respiratory rate is more than 20 breaths per minute.

[b] The panel emphasized that the majority of patients with severe dehydration and ongoing gastrointestinal losses would place high value on low certainty evidence of mortality impact with an intravenous rehydration regimen (such as Plan C) and expressed strong concern about the potential serious harms when clinical distinctions between sepsis and severe dehydration are evident in these recommendations. The panel noted that the use of Plan C was widely known by health and care providers treating patients with severe dehydration from other diarrhoeal causes and thus change of practice would require a stronger evidence base. However, adding modifications to the intravenous hydration regimen (modified Plan C, see Practical info) to mitigate harm and optimize effectiveness in populations where risk of harm may be greater such as patients with filovirus disease and sepsis and those with other chronic disease predisposed to volume overload (renal failure, liver failure, cardiac insufficiency, etc.).

This applies to adults, children and pregnant women. However, the panel noted that for children with coexisting severe acute malnutrition, other fluid protocols should be considered *(47)*. For patients with filovirus disease and sepsis, see subsequent recommendations.

Practical info

Plan C is for severe dehydration: if there is clinical suspicion of sepsis or septic shock, use the Fluids in patients with shock section.

Modified Plan C for patients with filovirus disease

- Start intravenous fluid immediately.
- Use large cannulas.
- Reassess at least every 30 minutes, and monitor carefully for pulmonary oedema caused by fluid overload:
  - features of pulmonary oedema include: dyspnoea/discomfort lying down (orthopnoea); worsening tachypnoea; increasing oxygen requirement; worsening hypertension or hypotension;
  - for patients at higher risk of pulmonary oedema (those with pre-existing renal failure, pre-existing liver failure, or pre-existing cardiac insufficiency, or children with severe acute malnutrition), the rates and/or volume of fluid administration should be reduced;
  - if pulmonary oedema is suspected, stop the infusion and perform a full clinical reassessment.
- When signs of severe dehydration have resolved, review the fluid regime and adjust it according to the patient's latest clinical status and the ongoing losses.

Initial fluid plan – review frequently, and adjust according to the patient's response

- Write the start time on the intravenous bag to help track how quickly fluids are being given.
- Give ORS to replace ongoing losses as soon as the patient can drink safely.

Age	First give 30 mL / kg in	...	Then give 70 mL / kg in
Infants (< 12 months)	1 hour		5 hours
All others (12 months +)	30 minutes		2½ hours

A more detailed algorithm is in development.

Evidence to decision

Benefits and harms

Small net benefit, or little difference between alternatives

In patients with severe dehydration and suspected or confirmed filovirus disease, protocolized intravenous rehydration regimens may reduce mortality (low certainty evidence).

Data on harms were not directly available from the evidence presented, but were elicited from the panel and their clinical experiences. There were strong concerns for the risks associated with the use of the WHO Plan C, as the regimen for intravenous fluid therapy includes very high initial fluid doses and that such liberal use of fluids could lead to fluid overload (such as pulmonary oedema). To mitigate these adverse outcomes, more intensive monitoring is required with careful modification and titration of fluid volumes and rates.

Certainty of the evidence

Low

The evidence summary was informed by one observational study in which systematic administration of intravenous fluids was uncommon and 1230 (70.8%) of 1737 patients with Ebola virus disease died, compared with 5 (18.5%) of 27 patients with the disease who were treated with intravenous fluid rehydration in the United States and Europe (RR 0.26, 95% CI 0.12–0.58; risk difference –52.4%, 95% CI –62.3 to –29.7) *(44, 45, 46)*.

The certainty of evidence of the observation study data was initially upgraded due to large effect size. However, the panel noted significant indirectness based on clinically important differences in pathophysiology between cholera and filovirus disease, especially in patients with sepsis and/or shock. The evidence certainty estimate was therefore downgraded to low.

Values and preferences

No substantial variability expected

See the agreed consensus on patient values and preference in the Methods section which was judged to pertain here.

Resources and other considerations	No important issues with the recommended alternative **Equity:** Use of protocolized intravenous fluid regimen with modification may increase equity by harmonizing the clinical approach to all patients. **Feasibility and acceptability:** The panel noted that the use of protocolized intravenous fluid, such as WHO Plan C, would be acceptable and feasible as it is widely used. Modification to WHO Plan C to tailor fluid volumes and rate of administration would be acceptable as these would not change the underlying medical or nursing practice (careful observation remains necessary). **Cost resource:** Intravenous fluids are widely available and low cost. However, the panel noted that investment in monitoring equipment was necessary to titrate intravenous fluids appropriately.

Justification

The panel emphasized that the majority of patients with severe dehydration and ongoing gastrointestinal losses would place high value on low certainty evidence of mortality impact with an intravenous rehydration regimen (such as Plan C) and expressed strong concern about the potential serious harms when clinical distinctions between sepsis and severe dehydration are evident in these recommendations. The panel noted that the use of Plan C was widely known by health and care providers treating patients with severe dehydration from other diarrhoeal causes and thus change of practice would require a stronger evidence base. However, adding modifications to the intravenous hydration regimen (modified Plan C, see Practical info) to mitigate harm and optimize effectiveness in populations where risk of harm may be greater such as patients with filovirus disease and sepsis and those with other chronic disease predisposed to volume overload (renal failure, liver failure, cardiac insufficiency, etc.).

This applies to adults, children and pregnant women. However, the panel noted that for children with coexisting severe acute malnutrition, other fluid protocols should be considered *(47)*. For patients with filovirus disease and sepsis, see subsequent recommendations.

Fluids in patients with shock

Filovirus infections are frequently associated with significant gastrointestinal involvement, with severe vomiting and diarrhoea driving rapid intravascular volume depletion. At the same time, the virus induces a systemic inflammatory response that increases vascular permeability, allowing plasma to leak into the interstitial space. This combination of external fluid loss and internal redistribution can lead to hypovolaemic shock with striking speed, particularly in patients who present late or deteriorate abruptly. Bleeding, which may not be overt, can be a significant contributor to shock. These are discussed in further detail below.

Sepsis syndrome, filovirus disease and fluid use

Sepsis-related capillary leak and vasoplegia contribute to reduced end-organ tissue perfusion and oxygen delivery, which if uncorrected lead to organ dysfunction and death. Intravenous fluid administration for sepsis aims to maintain tissue perfusion through judicious intravascular volume expansion which increases blood pressure, and reduces mortality and morbidity associated with hypoperfusion organ injury.

Choice of crystalloid fluid

Physiologically, the widely used 0.9% w/v sodium chloride (normal saline) has chloride concentrations of 154 mmol/L, which exceed usual human plasma concentrations of around 100 mmol/L *(48)*. Large volumes induce hyperchloraemic metabolic acidosis and can cause renal injury *(49)*. Balanced crystalloids replace some chloride ions with organic buffers such as lactate (such as Ringer's lactate), acetate and/or gluconate. These buffers are metabolized to bicarbonate, predominantly by the liver *(50)*. See Table 1 for the contents of different crystalloids.

Table 1. Composition of crystalloid fluids

	Human plasma	0.9% w/v sodium chloride	Ringer's lactate	Plasma-Lyte 148®, Normosol®
Sodium (mmol/L)	135–145	154	130	140
Chloride (mmol/L)	95–105	154	109	98
Potassium (mmol/L)	3.5–5.0	0	4	5
Calcium (mmol/L)	2.2–2.6	0	2.7	0
Magnesium (mmol/L)	0.8–1.0	0	0	3
Buffer (mmol/L)	Multiple, predominantly bicarbonate (23–27)	None	Lactate (28)	Acetate (27) Glucomate (23)
pH	7.35–7.45	5.5	6.5	7.4
Osmolarity (mOsm/L)	275–295	308	273	294

Haemorrhage

Haemorrhagic disease occurs in a substantial minority of patients with filovirus disease, although this proportion varies between outbreaks and depending on the causative viral species. Haemorrhage, while clinically most obvious from gingival, subconjuctival or vascular access sites, can be larger in volume, for example gastrointestinal bleeding. Initial clinical treatment of intravascular volume loss with organ hypoperfusion is based on intravenous fluid replacement with appropriate vasopressor therapy. These guidelines do not include explicit recommendations for transfusion. Management of haemorrhage should promote the rational and safe use of blood products in line with local guidelines or protocols, if blood and blood components are available. This can be extremely challenging in field settings where clinical and laboratory facilities are both limited in scope, low in resources and where IPC precautions make clinical pathways more complex.

Intravenous fluid therapy

Strong recommendation for

WHO recommends balanced crystalloids (such as Ringer's lactate) rather than 0.9% sodium chloride for acute intravenous fluid resuscitation in patients with suspected or confirmed filovirus disease.

[Strong recommendation, moderate certainty evidence]

- This applies to children and adults including pregnant women, who have sepsis, septic shock and/or dehydration.
- Conditions where 0.9% sodium chloride may be preferred include patients with filovirus disease that have trauma including traumatic brain injury.

Practical info

Volume of fluid to be administered

This recommendation should be applied in the context of others, including those related to vasopressor initiation and monitoring of fluid response.

As for all medications, fluid should be prescribed at a dose (volume) and strength (concentration), route and duration. Titration of the dose should be frequently reviewed, especially during critical phases of resuscitation where the therapeutic window is narrow (that is, under- or over-dosing is easily possible without careful attention and review).

Previously, a fluid volume of 30 mL/kg was used as an initial guide within the first 3 hours of resuscitation, but individualized therapy is key. Clinicians should aim to use fluid volumes which minimize avoidable end-organ hypoperfusion injury and do not provoke clinically significant oedema (notably pulmonary oedema). Frequent monitoring and re-evaluation are necessary which take into consideration pre-existing comorbidity, and tailor each additional fluid intervention. In general terms, smaller and more frequent volumes of fluid (e.g. 250 mL) are appropriate, and this requires high staff:patient ratios.

Uses of fluids apart from intravascular volume expansion

Normal saline is frequently the necessary diluent for medications, or for flushing lines. This is because of potential pH changes, or precipitation of salts associated with balanced crystalloids, which can be harmful. Use only the recommended fluid to reconstitute or dilute medications.

Evidence to decision

Benefits and harms

Substantial net benefits of the recommended alternative

From indirect evidence from patients with sepsis, treatment with balanced crystalloids, compared with 0.9% sodium chloride, was supported by moderate certainty evidence of lower mortality (42 fewer per 1000, 95% CI 42 fewer to 6 more) based on five trials enrolling 6754 patients with sepsis *(51)*. Using indirect evidence from critically ill patients more broadly, balanced solution has no important effect on ventilator-free days (high certainty, three RCTs, 31 622 patients), and we are uncertain about the effect of balanced solution compared with 0.9% sodium chloride on need for renal replacement therapy (very low certainty, five RCTs, 33 554 patients).

Though harms were not reported in the systematic review, the panel noted in a subset of critically ill patients with traumatic brain injury, balanced solutions may increase mortality (OR 1.424, 95% CI 1.100–1.818, probability 0.975 in Bayesian analysis *(52)*).

Certainty of the evidence	**Moderate** Overall certainty was moderate judged from the critical outcome of mortality (42 fewer expected deaths per 1000 in those treated with balanced crystalloid compared with 0.9% sodium chloride, 95% CI 84 fewer to 6 more based on 6754 participants in five RCTs).
Values and preferences	**No substantial variability expected** See the agreed consensus on patient values and preference in the Methods section which was judged to pertain here.
Resources and other considerations	**No important issues with the recommended alternative** **Equity:** No significant differences. **Feasibility and acceptability:** Intravenous fluids are commonly used and there are no meaningful differences in logistics, transport, preparation, administration or monitoring of the two alternatives. **Cost and resources:** The GDG were presented with data compiled from a convenience sample of LMICs sourced from the WHO Medicines unit. For the selected 11 countries, median costs of normal saline and Ringer's lactate per 500 mL were US$ 0.75 and US$ 0.77 respectively.

Justification

The panel felt that the majority of patients would prefer treatment with balanced solution over normal saline, placing high value on the moderate certainty evidence of mortality benefit (using the 600/1000 baseline mortality risk, equating to 42 fewer per 1000, 95% CI 84 fewer to 6 more). In terms of harms, the panel discussed increased prevalence of hyperchloraemic acidosis with 0.9% sodium chloride as a potential mechanism. However, the panel also noted the possible increase in harm if balanced solutions were used in traumatic brain injury. The panel also discussed that monitoring electrolytes in filovirus patients with vomiting and diarrhoea may also impact choice of intravenous fluid. Consensus was achieved, but four panel members stated abstentions which related to specific circumstances in which Ringer's lactate may not be superior to 0.9% sodium chloride. These have been noted in the recommendation remarks, but were expected to be rare in the primary presentation of filovirus disease and thus did not require a conditional recommendation.

Given the lack of sepsis-specific data on renal replacement therapy and ventilator-free days in the meta-analysis, the panel considered data from critically unwell patients more broadly. Additional indirectness in these endpoints was considered and resulted in rating down once, potentially mediated through differences in population (the more general critically unwell study populations included those with traumatic brain injury or advanced liver disease rather than sepsis only).

The panel judged that the recommendation would apply similarly in children, pregnancy and during breastfeeding. The concordance with WHO paediatric fluid guidelines was noted. This recommendation does not apply to patients with filovirus disease and trauma and traumatic brain injury.

The panel noted the cluster randomized trial that was recently published and not included in the systematic review that informed this recommendation *(51)*. This study evaluated the use of balanced solution versus normal saline at hospital level and did not show difference on primary outcome of mortality and was thus deemed too indirect to include in the deliberations.

PICO

Population: Patients with suspected or confirmed sepsis.

Intervention: Balanced crystalloid.

Comparator: 0.9% w/v sodium chloride.

Outcome Timeframe	**Study results and measurements**	**Comparator** 0.9% sodium chloride	**Intervention** Balanced crystalloid	**Certainty of the evidence** (Quality of evidence)	**Summary**
Mortality (high baseline risk) 90 days or end of study	Relative risk 0.93 (CI 95% 0.86–1.01) Based on data from 6754 participants in 5 studies (Randomized controlled)	**600** per 1000	**558** per 1000	**Moderate** due to some imprecision	Balanced crystalloids probably reduce 90-day mortality compared with 0.9% saline.
		Difference: **42 fewer per 1000** (CI 95% 84 fewer–6 more)			
Mortality (low baseline risk) 90 days or end of study	Relative risk 0.93 (CI 95% 0.86–1.01) Based on data from 6754 participants in 5 studies (Randomized controlled)	**300** per 1000	**279** per 1000	**Moderate** due to some imprecision	Balanced crystalloids probably reduce 90-day mortality compared with 0.9% saline.
		Difference: **21 fewer per 1000** (CI 95% 42 fewer–3 more)			
Renal replacement therapy	Relative risk 0.99 (CI 95% 0.78–1.29) Based on data from 33 554 participants in 5 studies (Randomized controlled) Follow up: in hospital or 30 days	**64** per 1000	**63** per 1000	**Very low** due to indirectness, serious imprecision, serious inconsistency, serious indirectness[a]	We are uncertain if balanced crystalloids have an effect on renal replacement therapy compared with 0.9% saline.
		Difference: **1 fewer per 1000** (CI 95% 14 fewer–19 more)			
Ventilator-free days[b] (days)	Based on date from 31 622 participants in 3 studies (Randomized controlled)	Difference: **0.18 more** (CI 95% 0.45 fewer–0.81 more)		**Moderate** due to serious indirectness[c]	Balanced crystalloids probably have no important effect on ventilator-free days compared with 0.9% saline.

[a] **Inconsistency: serious; indirectness: serious; imprecision: serious.**
[b] Measured by: days lower better- critically ill patients
[c] **Indirectness: serious.**

How to monitor intravenous fluid response

Physiological monitoring provides essential information that guides an assessment of haemodynamic status. Core vital signs such as heart rate, blood pressure, respiratory rate and oxygen saturation offer non-specific but clinically useful indications of whether the circulatory system is maintaining sufficient pressure and flow. For example, tachycardia may reflect compensation for reduced stroke volume, while hypotension can indicate impaired cardiac output or systemic vasodilation. Pulse oximetry may inform on the balance between oxygen delivery and demand. Urine output, another key physiological measure, reflects renal perfusion and is a sensitive marker of overall circulatory adequacy. These contribute to the overall clinical picture. More complex phsyiological scoring systems can objectively integrate a number of measures.

A number of measures have been postulated as primary indicators of the sufficiency of fluid resuscitation, which can be used to directly guide clinical decisions on fluid therapy. These vary in complexity and technological sophistication from bedside clinical tests (capillary refill time [CRT]) through non-invasive point-of-care and near patient tests (lactate and passive leg raise) to methods which require central venous and/or arterial access (for example central venous oxygen saturation).

In line with other WHO guideline panels (sepsis guideline), methods requiring central venous catheterization were not considered within scope due to their limited availability, and safety concerns outside of specialist critical care environments. Others, such as microvascular imaging techniques, are less invasive but not broadly established in clinical practice. Those methods which have been considered by the panel in these guidelines are outlined below.

Capillary refill time (CRT)

Capillary refill time is widely measured in children and adults as a routine measure of cardiovascular status, although in isolation its prognostic value is limited in both populations. In adults, a systematic review of CRT as a predictor of death or adverse events in a context at risk or confirmed acute circulatory failure demonstrated an area under the receiver operator curve (AUROC) of 0.66 (95% CI 0.59–0.76) based on 13 studies *(54)*, suggesting poor predictive power in isolation. In children, a similar review examined the measure in the context of dehydration, and calculated a pooled sensitivity of 34.6% (95% CI 23.9–47.1%) and specificity of 92.3% (95% CI 88.6–94.8%) with considerable heterogeneity between the 24 studies *(55)*. Both meta-analyses demonstrated that an abnormal CRT (using a 3-second or more threshold) might have value in identifying high-risk individuals, but that a normal value should not be necessarily reassuring. High-quality measurement is important (see Practical info) and clinicians should be aware that environmental factors affect the reliability including the room temperature (inverse correlation), lighting (difficulty in assessment) and the use of vasopressors (positive correlation) *(56)*.

Lactate

Arterial lactate concentations are considered normal below 2 mmol/L. Lactic acidosis is frequently defined at levels of 4 mmol/L and above, with higher concentrations being positively associated with mortality *(57)*. Using lactate to improve recognition of sepsis has been suggested in pre-hospital and hospital settings *(58)*. Lactate levels in blood are functions of the rate of production, and removal by excretion (including in urine) and metabolism (predominantly by the liver). The paradigm of “increased lactate results from impaired oxygen delivery to end-organ tissues” is limited by multiple other determinants of lactate concentration, and differential metabolic pathways. Similarly, changes in blood lactate are often inaccurately labelled “lactate clearance”. Additional limitations of its use as a marker of severity of sepsis relate to the complexity of sepsis physiology, including: alterations to hepatic metabolism; the normal physiological shuttling of lactate as a substrate for metabolism; pH changes (alkalosis increases glucose metabolism); drugs (for example, metformin, ethylene glycol); focal or regional tissue ischaemia; malignancy; alcohol use disorder; and, to a lesser degree, the direct administration in lactated intravenous fluid *(59)*.

Conditional recommendation for

WHO suggests for patients with suspected or confirmed filovirus disease and clinical signs of shock or circulatory impairment, the serial measurement of lactate as part of the assessment of perfusion to guide further intravenous fluid management.

[Conditional recommendation, low certainty evidence]

- This recommendation applies to children and adults, including pregnant women.
- Lactate is a marker of poor perfusion and when elevated is associated with poor prognosis.
- The assessment of perfusion also includes other clinical markers such as blood pressure, heart rate, urine output, mental status and capillary refill time.
- Reduction of lactate over time can be used to infer the effectiveness of fluid replacement. However, normalization of lactate should not be the target.
- There are situations where elevated lactate levels are not associated with poor perfusion and these include: advanced liver disease when lactate metabolism is impaired, excessive muscles activity, focal or regional areas of tissue ischaemia, and some drugs (for example metformin). Persistent raised lactate should prompt a search for other coexistent pathologies.
- Lactate can be measured in arterial, venous or capillary blood. The choice of sample type should follow local practice and be used consistently, especially when comparing lactate levels over time. Arterial puncture is the reference standard for accuracy, but it is not encouraged due to bleeding risk in filovirus disease.

Practical info

- Minimize the use of tourniquet and direct pressure when collecting lactate sample to minimize artefactual high levels.
- Interpretation should use all clinical information available, including blood pressure, urine output, conscious level and skin changes.
- Consider other causes of hyperlactaemia for example seizure, drugs (notably metformin, ethylene glycol), malignancy, and alcohol use disorder *(59)*.
- Trends in lactate are important, and should be interpreted in the context of the patient's clinical condition and medical interventions. Take note particularly of the initiation of vasopressors (increasing adrenergic drive and increased lactate levels) and recent fluid therapy. If the trend is not improving, or unexpectedly increasing, consider potential underlying factors, including focal tissue ischaemia (for example bowel obstruction).

There was no strict protocolization of how information on lactate should be used across the studies. Cut points of 2 mmol/L and 4 mmol/L have been frequently used to describe the upper limit of normal and the threshold of lactate acidosis respectively. Lactate can be used for identifying patients at high risk of adverse outcome.

The choice of arterial, venous or capillary measurement may be driven by available resources. These are not necessarily directly comparable, and therefore for serial measures in a single patient, the same test type should be used.

Evidence to decision

Benefits and harms	**Substantial net benefits of the recommended alternative** In patients with filovirus disease and clinical signs of shock or circulatory impairment, the use of lactate as part of the assessment of perfusion to guide further intravenous fluid therapy may decrease mortality (low certainty evidence) and may decrease intensive care unit (ICU) length of stay (low certainty evidence). Harms related directly to the intervention were not captured in the summary of findings tables, but would usually be limited to discomfort and potential bruising or bleeding relating to blood sampling, however for capillary and venous measurements these would be minimal.
Certainty of the evidence	**Low** The evidence summaries for the mortality outcome was informed by two studies enrolling 430 patients with sepsis, with certainty rated as low due to very serious imprecision. The baseline rate was 600/1000 and with lactic acid guided resuscitation it is estimated as 126 fewer deaths (95% CI 228 fewer to 6 more). The ICU length of stay outcome was informed by one study enrolling 82 participants with sepsis demonstrating an effect estimate of reduction in ICU length of stay by 1.5 days (95% CI 3 fewer to 0.1 fewer) certainty was rated as low due to serious risk of bias and serious imprecision.
Values and preferences	**No substantial variability expected** See the agreed consensus on patient values and preference in the Methods section which was judged to pertain here.
Resources and other considerations	**Important issues, or potential issues not investigated** **Equity:** No anticipated issues. **Feasibility and acceptability:** The panel noted that lactate measurement was not usually available in filovirus disease treatment centres, but its use has increased in ICU settings at some referral hospitals in the region. The panel agreed that lactate measurement should be part of the minimal clinical laboratory package (see lactate recommendation) and that it would become acceptable as long as clinicians are trained on its use and interpretation and the results can be made available quickly to inform patient care decisions. **Resources and cost:** The addition of lactate to the assessment of perfusion to guide fluid therapy would incur capital and operational costs which would depend on the implementation platform. At lower testing volumes, point-of-care devices have lower overall costs and minimal maintenance and may allow wider use in outbreak situations without a laboratory. However, laboratory-based machines might offer high-volume testing at lower per-test costs, and lactate measures as part of a panel of tests for no additional cost. These considerations make the implementation decision highly context specific.

Justification

The panel chose a conditional recommendation, judging that the majority of patients, would choose to have lactate added to assessment of perfusion as it may reduce mortality. However, this evidence was not compelling enough to warrant universal use where resource limitations were significant. The panel also noted that lactate is not used alone but rather as part of an assessment of perfusion, where serial measurements of lactate are used to guide fluid management and that normalization of lactate should not be a target. In the included RCTs, there were variable standards of care, and

many used mean arterial pressure (MAP), central venous pressure monitoring and other tools to monitor perfusion. The panel noted that there was uncertainty how this would apply in situations with more limited monitoring as "standard of care". A strong emphasis was placed on instituting the best possible monitoring given local resources, using all the measures available, including basics such as blood pressure, heart rate, urine output and mental status and CRT (see next recommendation). The panel also raised concern about use of lactate in filovirus disease patients with liver dysfunction and should be considered as an area for further research.

In addition, lactate could be used for identifying patients at high risk of adverse outcome. The panel judged that the recommendation should apply to adults and children and pregnant women given similar associations with outcome, and the use of lactate as part of frequently used sepsis definitions and screening tools.

RCTs used mostly arterial measurements as these are considered most accurate, although other modalities were allowed. In field implementation, venous or capillary measures might be more frequently used. The panel considered that while this might introduce some indirectness, this was unlikely to be an important consideration especially where the lactate was used to consider dynamic changes in individual patients.

PICO

Population: Patients with suspected or confirmed sepsis that will receive intravenous fluid infusion (inpatient setting).

Intervention: Lactic acid guided resuscitation.

Comparator: Standard of care.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard of care	**Intervention** Lactic acid guided resuscitation	**Certainty of the evidence** (Quality of evidence)	**Summary**
Mortality (high baseline risk)	Relative risk 0.79 (CI 95% 0.62–1.01) Based on data from 430 participants in 2 studies (Randomized controlled)	**600** per 1000	**474** per 1000	**Low** due to very serious imprecision[a]	Lactic acid guided resuscitation may decrease mortality.
		Difference: **126 fewer per 1000** (CI 95% 228 fewer–6 more)			
Mortality (low baseline risk)	Relative risk 0.79 (CI 95% 0.62–1.01) Based on data from 430 participants in 2 studies (Randomized controlled)	**300** per 1000	**237** per 1000	**Low** due to very serious imprecision[a]	Lactic acid guided resuscitation may decrease mortality.
		Difference: **63 fewer per 1000** (CI 95% 114 fewer–3 more)			
ICU length of stay (days)	Lower better Based on data from 82 participants in 1 study (Randomized controlled)	**6** days (mean)	**4.5** days (mean)	**Low** due to serious risk of bias, serious imprecision[b]	Lactic acid guided resuscitation may decrease ICU length of stay.
		Difference: **MD 1.5 lower** (CI 95% 3 lower–0.01 lower)			

[a] **Imprecision: very serious.** 95% CI including no benefits, 180 events overall.
[b] **Risk of bias: serious**. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Imprecision: serious.** 82 patients overall.

Conditional recommendation for

WHO suggests for patients with suspected or confirmed filovirus disease and clinical signs of shock or circulatory impairment, capillary refill time should be used as part of the assessment of perfusion to guide intravenous fluid management.

[Conditional recommendation, low certainty evidence]

- This recommendation applies to children and adults, including pregnant women.
- The assessment of perfusion also includes other markers such as blood pressure, heart rate, urine output, mental status and lactate.
- Use of capillary refill time can also be integrated into assessments using complementary technologies such as ultrasound, depending on availability, training and level of care.
- Use of standardized protocols for capillary refill time assessment will reduce variability in measurements and increase reliability and accuracy.

Practical info

CRT is an accessible marker of end-organ perfusion. It measures the time for blood to return to the skin capillaries after they have been emptied by applying pressure. It is quick, visual and non-invasive test, although education of health care workers is paramount to ensure correct measurement and interpretation. It is used for recognition of hypoperfusion and for monitoring of fluid administration.

What factors affect CRT?

CRT can be affected by multiple factors, including room temperature, skin temperature, age, sex, room lighting, procedural technique, presence of underlying vascular disease, and the site of testing. Variability can be minimized through training, education and standardized protocols to mitigate the impact of ambient factors *(56, 60)*.

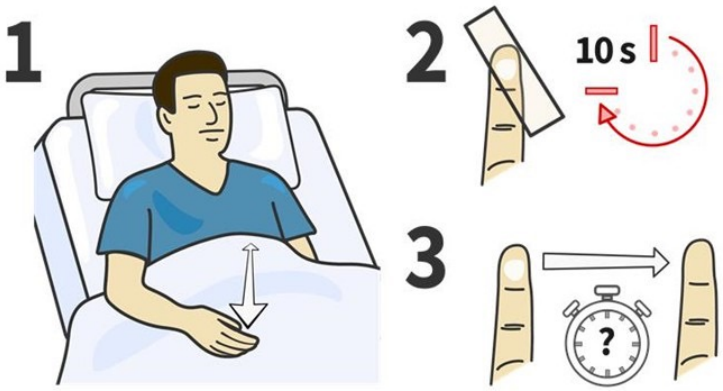
CRT standardization protocol

Standardized procedures can enhance reliability and reduce interobserver variability (Fig. 1). To reflect the procedure in the research studies, in infants, children and adults:

- Check the environment:
  - Ensure a warm room.
  - Choose a site free from skin abnormalities.
  - Place the patient's hand at the level of the thorax/heart.
- Apply firm pressure to the ventral surface of the distal phalanx of the index finger for 10 seconds.
- Remove the pressure.
- Measure the time for the return of pre-existing skin colour.
- Use a chronometer.
- A CRT longer than 3 seconds should be considered abnormal *(60)*.

A microscope slide was used to apply pressure in the RCTs as this enables visualization of skin blanching and ensures even pressure. The GDG panel recognized that usual clinical practice does not require a glass slide.

Fig. 1. Suggested way to measure standardized capillary refill time



1. Place the patient's hand at the level of their heart (mid chest).
2. Apply firm pressure to the ventral surface of the distal phalanx of one finger for 10 seconds. This can be done using your thumb or, if available, a glass microscope slide, so that blanching of the skin underneath can be confirmed.
3. Release the pressure and measure the time taken for the skin colour to return to the same as before.

Evidence to decision

Benefits and harms	**Small net benefit, or little difference between alternatives** Evidence was drawn from the ANDROMEDA-2 study *(61)*. The use of CRT to guide fluid therapy may have little or no impact on mortality (1 fewer per 1000 than standard of care, 95% CI 51 fewer to 56 more, low certainty), may increase vital support-free days (1.1 more, mean 16.5 days vs 15.4 days in standard of care, low certainty) and may have little or no impact on hospital length of stay (0.85 fewer days, mean 15.3 vs 16.2 in standard of care, low certainty). Harms were judged by these same endpoints, with no direct harms expected from the measurement of capillary refill itself.
Certainty of the evidence	**Low** Overall certainty was low, due to a very serious imprecision in mortality estimate from a single trial of 1467 participants.
Values and preferences	**No substantial variability expected** See the agreed consensus on patient values and preference in the Methods section which was judged to pertain here.
Resources and other considerations	**Important issues, or potential issues not investigated** **Equity:** Universal application of capillary refill assessment would be expected to increase equity, and improve the individualization of intravenous fluid therapy. **Feasibility and acceptability:** Bedside assessment can easily and quickly incorporate CRT, and established practice in many areas of paediatric and adult practice has demonstrated acceptability. **Resources and cost:** CRT is a simple bedside test which has no recurrent cost, although training is required. This is particularly to ensure standardized measurement which improves reliability, including optimizing conditions for measurement within treatment centres, for example, lighting for visibility and clocks for timing.

Justification

The panel considered the ANDROMEDA-SHOCK2 study as the primary source of evidence *(61)*. The addition of data from a second RCT of 30 patients was felt to be uninformative *(62)*. The evidence from patients with septic shock was judged sufficiently direct to filovirus disease not to reduce level of certainty. The panel considered the data for separate endpoints (mortality, vital support-free days and hospital length of stay) although these were secondary endpoints within the trial. The panel noted that the primary (hierarchical) endpoint from the trial gave low certainty evidence of superiority of capillary refill-driven intravenous fluid treatment (win ratio 48.9% vs 42.1%), and that this was mostly driven by a difference in vital support-free days. In resource-limited settings, the panel judged that reduction in ventilation particularly, captured within the vital support-free days, would represent an important benefit.

Harms were not directed captured, although would be expected to be represented in the outcomes above, and the measurement itself has no important associated harms.

Given the simple and low-cost nature of the test, and universal ability to perform, the panel felt that a conditional recommendation for CRT was appropriate.

The panel noted that when implemented in clinical practice, CRT is not used alone, and rather should be used within a protocolized resuscitation which includes assessment of perfusion through blood pressure, heart rate, urine output and lactate, where available. It was suggested that the strength of pulse oximetry trace might also be incorporated by clinicians into a overall impression of circulatory sufficiency. Members noted that CRT is more established in the assessment of children but its use in adults was less common so standardization of measurement would be important (see Practical info).

The panel judged that the recommendation should apply to all ages in view of RCT evidence from adults which was felt to be relevant to children, and its incorporation as standard of care within paediatric clinical practice.

PICO

Population: Patients with suspected or confirmed sepsis that will receive intravenous fluid infusion (inpatient setting).

Intervention: Capillary refill time guided resuscitation.

Comparator: Standard of care.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard of care	**Intervention** Capillary refill time guided resuscitation	**Certainty of the evidence** (Quality of evidence)	**Summary**
Mortality	Relative risk 0.99 (CI 95% 0.81–1.21) Based on data from 1467 participants in 1 study (Randomized controlled) Follow up: 28 days	**266** per 1000	**265** per 1000 Difference: **1 fewer per 1000** (CI 95% 51 fewer–56 more)	**Low** due to extremely serious imprecision, serious indirectness, serious risk of bias[a]	Capillary refill time directed therapy may have little or no effect on mortality compared with standard of care.
Hierachical composite (mortality, duration of vital support, length of hospital stay)	Measured by: win ratio High better Based on data from 1501 participants in 1 study (Randomized controlled)	**42.1**	**48.9**	**Low** due to serious indirectness, serious imprecision[b]	Capillary refill directed therapy may reduce composite outcomes which include mortality, organ support and hospital stay compared with standard of care.
Vital support free days	High better Based on data from 1467 participants in 1 study (Randomized controlled)	**15.4** (mean)	**16.5** (mean) Difference: **MD 1.1 higher**	**Low** due to serious risk of bias, serious imprecision[c]	Capillary refill time possibly improves the time spend on vital organ support therapy compared with standard of care.
Hospital length of stay	Lower better Based on data from 30 participants in 1 study (Randomized controlled)	**16.2** days (mean)	**15.3** days (mean) Difference: **MD 0.85 lower** (CI 95% 1.8 fewer–0.1 more)	**Low** due to serious risk of bias, serious imprecision[d]	Capillary refill time possibly has little to no effect on hospital length of stay compared with standard of care.

[a] **Risk of bias: serious.** Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Indirectness: serious. Imprecision: serious.** 5% CI including important benefits and harms. 16 events and 30 patients overall.
[b] **Indirectness: serious. Imprecision: serious.**
[c] **Risk of bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Imprecision: serious.**
[d] **Risk of bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias.

Use of vasopressors in shock

Rationale for the use of vasopressors

Adequate perfusion of end organs requires sufficient arterial pressure. The mean arterial pressure (MAP) is a frequently used index of this "driving pressure" and approximates to (2 x diastolic + systolic)/3. It is influenced by cardiac output and systemic vascular resistance.

While both of these may be reduced in sepsis, a fall in systemic vascular resistance related to vasoplegia is a rationale for using vasopressors to maintain an adequate MAP, i.e. that which prevents end-organ hypoperfusion *(63, 64)*.

Extensive investigation from physiological and animal studies have demonstrated the relationship between lower MAP and increased organ damage. There is variation by organ system of the optimal MAP – the brain, heart and kidneys, for example, are highly sensitive to hypoperfusion *(65)*.

Target for vasopressor titration

The target MAP during vasopressor therapy has not been discussed in these guidelines. Retrospective cohorts demonstrated a correlation between MAP thresholds and survival *(66, 67, 68)*, leading to a suggested lower threshold of acceptable MAP of 60–65 mmHg.

Physiological studies have suggested autoregulation compromise in cerebral vascular beds below 60 mmHg *(69)*. Higher MAP (70–80 mmHg) compared with lower values are associated in prospective sepsis cohorts with lower rates of acute kidney injury *(70, 71)*.

However, sufficient perfusion must be balanced against harmful vasoconstriction, and potential for other vasopressor-associated adverse events such as cardiac arrhythmias. Higher doses of norepinephrine have been associated with mortality independent of MAP *(72)*, although this may reflect the dose as a marker of cardiovascular severity. Clinicians should individualize therapy based on their knowledge of their patient's specfiic circumstances.

Choice of vasopressor

In these guidelines the role as first-line agents of norepinephine, epinephrine and dopamine were considered by the panel. The pharmacology and clinical action of these agents has been recently reviewed *(64)*, and is summarized briefly below.

Norepinephrine

Norepinephrine is a strong α- and β1-adrenergic agonist with minimal β2 activity. Through receptor binding, it increases smooth-muscle cytosolic calcium and produces arterial and venous vasoconstriction through α-adrenergic stimulation. This raises diastolic arterial pressure and improves coronary perfusion. Norepinephrine raises mean systemic filling pressure and therefore venous return. To a lesser extent than the vasopressive effect, β1 activation induces a modest positive inotropic effect. Tachycardia, and therefore myocardial oxygen demand, is limited as the baroreflex response to vasoconstriction increases parasympathetic tone.

Epinephrine

Epinephrine is a potent β1- and β2-adrenergic agonist with α-adrenergic induced vasoconstriction. Its β1-driven inotropic and chronotropic effects are stronger than those of norepinephrine. Activation of β2 receptors in skeletal muscle can cause lactic acidosis by stimulating Na^+/K^+-ATPase activity and accelerating aerobic glycolysis, increasing pyruvate and lactate production; this represents a physiological metabolic effect rather than necessarily being a marker of shock severity.

Dopamine

Dopamine, the immediate precursor of norepinephrine and epinephrine, has effects which are dose-dependent. At low doses (< 5 µg/kg/ min), it causes vasodilation of cerebral, coronary, renal and mesenteric vessels via D1 receptor activation without altering arterial pressure. At intermediate doses (5–10 µg/kg/min), it produces β1-mediated chronotropic and inotropic effects. At high doses (10–20 µg/ kg/min), it acts as an α-adrenergic vasopressor similar to norepinephrine. Its clinical effects can vary widely due to a complex relation between infusion rates and plasma concentrations.

Timing of vasopressor

Septic shock with distributive shock is widely treated first with intravenous fluid to expand the circulating volume, followed by vasopressor infusion if blood pressure or circulatory indices are not attained. Retrospective studies noted an association of fluid volumes administered and adverse outcomes *(73, 74)*. Systematic review has not demonstrated mortality differences in lower versus higher fluid volume administration *(75)*. However, changing clinical practice resulting in part from early studies of goal-directed therapy, make observational studies difficult to interpret. The timing of initation of vasopressors is debated because early initiation of vasopressors may reduce the total fluid administered but, if this results in increased vasopressor dose, or time administered, this may expose patients to potentially increased drug-related adverse events including arrhythmias and vasconstriction-related ischaemia.

Conditional recommendation for

WHO suggests that for patients with suspected or confirmed filovirus disease with shock who are being resuscitated with intravenous fluids, vasopressor treatment be initiated early rather than later.

[Conditional recommendation, low certainty evidence]

- This recommendation applies to children and adults, including pregnant women.
- Vasopressors should be used within a resuscitation strategy that includes: appropriate intravenous fluid therapy, frequent monitoring, including for arrhythmia, and individualized titration of the dose to desired effect (targeting arterial blood pressure).
- The recommendation does not apply to shock caused predominantly by severe dehydration with ongoing gastrointestinal losses, where fluid replacement should be the primary treatment for circulatory insufficiency.

Practical info

Earlier use of vasopressors is used in combination with more restrictive fluid strategies for resuscitation. These can include *(76)*:

- Lower thresholds for intravenous fluid resuscitation before vasopressor support is considered, for example routine assessment after 1000 mL to 2000 mL has been delivered.
- Adopting strict "rescue criteria" which limits fluid administration after the first 500 mL to specific triggers, for example severe hypotension (systolic blood pressure < 70 mmHg), tachycardia > 130/min, signs of severe hypoperfusion (such as mottled skin or new alteration of consciousness).
- Use of bolus intravenous fluid (250–500 mL) in place of "maintenance therapy" after initial resuscitation, triggered by specific indications such as: plasma lactate ≥ 4.0 mmol/L; MAP < 50 mmHg despite vasopressors; skin mottling; oliguria (urine output < 0.1 mL/kg/hour).
  Note: this bolus use should be used in addition to fluid to correct ongoing losses, or to correct dehydration where the oral route is not possible.
- Reduction of intravenous fluid in administered medication through use of the oral route, or choice of low-volume alternatives. Use the lowest dose necessary to achieve perfusion target. Check markers of perfusion every 30 minutes.
- In pregnant women and in children, these approaches may not be appropriate: the principles of individualized care based on high-frequency monitoring should be adopted, and specialist advice sought.
- All protocols aim to avoid end-organ hypoperfusion, and required active monitoring and management to do this. In RCTs, vasopressors were initiated after initial intravenous fluid therapy. Protocols varied but early treatment typically initiated norepinephrine after between 1000 mL and 30 mL/kg of initial intravenous fluid had been given. Late administration allowed more liberal fluid use, and typically used repeated boluses to reach a target MAP. In the largest trial, time from randomization to first vasopressor was 1.8 hours in the early group, and 3.2 hours in the liberal fluid group *(76)*.

Evidence to decision

Benefits and harms	**Small net benefit, or little difference between alternatives** In patients being resuscitated with intravenous fluid, we are uncertain if earlier initiation of vasopressor has any effect on mortality when compared with later initiation (very low certainty). Early vasopressor initiation probably reduces pulmonary oedema compared with later initiation (moderate certainty). Early initiation probably has no important impact on ventilator-free days (moderate certainty).
Certainty of the evidence	**Low** This four RCTs containing 2073 patients provided evidence with significant imprecision for mortality based on septic shock (144 fewer per 1000 deaths in those treated earlier, 95% CI 270 fewer to 30 more, when using a 600/1000 baseline risk). Fewer pulmonary oedema events occur in early versus late administration (27 fewer episodes per 1000, 95% CI 37 fewer to 7 fewer) with moderate certainty after downgrading due to imprecision. Ventilator-free days were probably no different (0.29 more, 95% CI 0.42 fewer to 1 fewer days, moderate certainty). There was no evidence of increased harm in early treatment. ICU length of stay was possibly no different between interventions (mean difference 0.71 days higher with earlier vasoactive therapy, CI 95% 0.2 lower to 1.63 higher), given low certainty evidence. Evidence for reduction of pulmonary oedema (a severe adverse event) in early treatment suggested the overall certainty was low.
Values and preferences	**Substantial variability is expected or uncertain** See the agreed consensus on patient values and preference in the Methods section which was judged to pertain here.
Resources and other considerations	**Important issues, or potential issues not investigated** **Equity:** Increasing access to vasopressors may increase inequity if resources for other clinical activity are less available as a result. However, the panel felt that delivering higher level of care to filovirus disease patients would improve broader equity. **Feasibility and acceptability:** In settings where the administration of vasopressors is already feasible, the difference between early and late treatment would have negligible feasibility or acceptability concerns (for example in many critical care units in the African Region). An appropiate facility design that facilitates frequent/continuous monitoring is needed. **Cost and resources:** The cost associated with vasopressor therapy will be significant where this is not current practice, and will affect training needs, equipment and time-based staff costs. There would be an anticipated increase in costs with earlier treatment as more patients may be started on vasopressor treatment. It is uncertain how this would be offset by reduced costs associated with the reduction in pulmonary oedema. See also recommendations on vasopressors and mode of administration.

Justification

While the very low certainty evidence of a mortality benefit of early administration was noted, the panel's decision was primarily driven by moderate certainty evidence of a reduction in pulmonary oedema. Particularly in LMICs where access to invasive mechanical ventilation (as a "rescue therapy" for this complication) is particularly limited, the panel felt the avoidance of pulmonary oedema was particularly valuable. They noted, however, that this potential benefit was not reflected in the ventilator-free days outcome; the definition of pulmonary oedema within the studies was unclear. The panel emphasized that vasopressors should be given as part of the resuscitation package, after fluid therapy has been initiated, and at the lowest necessary dose to achieve the required target.

Systematic review of four studies underpinned the recommendation *(77)*, which all employed norepinephrine as vasopressor of first choice. The panel felt that there was no reason to rate down for indirectness even if in practice other agents might be used. Odds ratios from the review were converted to risk ratios in order to estimate absolute effects. The evidence from sepsis trials was felt to be sufficiently direct to not rate down the certainty of evidence.

The panel considered that later administration might lead to fewer people requiring vasopressor therapy (because of sufficient response to fluids in the intervening period). In this case, resource use would be expected to be higher where an early intervention strategy were adopted. From the largest available study (CLOVERS, *n*=1563 *(76)*), use during the first 24 hours was 59% in the earlier (more fluid restrictive) group compared with 37% in the later (liberal fluid) group. However, the mean number of days free from vasopressor use at 28 days was 22.0 and 21.6 respectively (difference 0.4, 95% CI -0.5–1.3) suggesting that earlier use was not significantly associated with increased use. It was not possible to quantify the likely effect in real-world practice.

Subgroups of interest to the panel were age (65 or more); chronic heart failure; and end-stage renal disease. These were addressed in the CLOVERS study *(76)*, which provided no evidence of subgroup interaction. The panel therefore did not consider subgroups separately when forming a recommendation.

Data from two pilot RCTs in children suggest feasibility of early norepinephrine or epinephrine therapy in emergency departments and wards in high-income settings, and did inform definitively on outcomes *(78, 79)*. An open-label RCT in 63 children provided supportive evidence that early vasopressor therapy (with a fluid restrictive strategy) might be beneficial compared with later initiation and liberal fluid use *(80)*. This trial was underpowered to generate definitive results but reported lower mortality in early vs late initiation (RR 3.1, 95% CI 1–10), and less mechanical ventilation (RR 4, 95% CI 1.3–12).

While there were no direct data on the use in pregnancy, the panel judged that the clear mortality benefit in favour of norepinephrine would likely also apply to pregnant women. This is consistent with principles of obstetric practice in critical illness; optimizing maternal circulation is the most effective strategy to preserve fetal perfusion, and delays in vasopressor initiation may worsen outcomes for both mother and fetus *(81)*.

PICO

Population: Patients with sepsis needing vaspressors.

Intervention: Early vasoactive therapy.

Comparator: Later vasoactive therapy.

Summary: Data were from a systematic review of early vs late administration of norepinephrine for septic shock *(77)*. Odds ratios were converted to relative risks, and applied to baseline risks of 600/1000 and 300/1000 as described in the methods section.

Outcome Timeframe	**Study results and measurements**	**Comparator** Later vasoactive therapy	**Intervention** Early vasoactive therapy	**Certainty of the evidence** (Quality of evidence)	**Summary**
Mortality End of study (mostly 90 days)	Relative risk 0.76 (CI 95% 0.55–1.05) based on data from 2073 participants in 4 studies (Randomized controlled) Follow up: end of study (90 day mortaility in 2 RCTS involving 1663 patients; 28 day or in-hosptial mortality in remaining 2 RCTs with 411 patients	**600** per 1000	**456** per 1000 Difference: **144 fewer per 1000** (CI 95% 270 fewer–30 more)	**Very low** due to extremely serious imprecision[a]	We are uncertain if earlier vasoactive therapy has any effect on mortality compared with later vasoactive therapy.
Mortality End of study (mostly 90 days)	Relative risk 0.76 (CI 95% 0.55–1.05) based on data from 2073 participants in 4 studies (Randomized controlled) Follow up: end of study (90 day mortaility in 2 RCTS involving 1663 patients; 28 day or in-hosptial mortality in remaining 2 RCTs with 411 patients	**300** per 1000	**228** per 1000 Difference: **72 fewer per 1000** (CI 95% 135 fewer–15 more)	**Very low** due to extremely serious imprecision[a]	We are uncertain if earlier vasoactive therapy has any effect on mortality compared with later vasoactive therapy.
Pulmonary oedema	Relative risk 0.43 (CI 95% 0.22–0.86) based on data from 1972 participants in 3 studies (Randomized controlled) Follow up: end of study	**48** per 1000	**21** per 1000 Difference: **27 fewer per 1000** (CI 95% 37 fewer–7 fewer)	**Moderate** due to serious risk of bias (subjective outcome assessment)[b]	Earlier vasoactive therapy reduces pulmonary oedema compared with later vasoactive therapy.
Arrhythmia	Relative risk 0.6 (CI 95% 0.29–1.25) based on data from 1873 participants in 2 studies (Randomized controlled) Follow up: in hospital	**33** per 1000	**20** per 1000 Difference: **13 fewer per 1000** (CI 95% 36 fewer–24 more)	**Low** due to serious inconsistency and extremely serious imprecision[c]	We are uncertain whether earlier vasoactive therapy increases or decreases arrhythmia compared with later vasoactive therapy.
Renal replacement therapy-free days (higher better)	Based on data from 1884 participants in 3 studies (Randomized controlled)	Difference: **0 fewer** (CI 95% 1.2 fewer–1.2 more)		**Low** due to very serious imprecision[d]	Earlier vasoactive therapy may have no important effect on duration of renal replacement therapy compared with later vasoactive therapy.

Outcome Timeframe	**Study results and measurements**	**Comparator** Later vasoactive therapy	**Intervention** Early vasoactive therapy	**Certainty of the evidence** (Quality of evidence)	**Summary**
Ventilator-free days (higher better)	Based on data from 1953 participants in 3 studies. (Randomized controlled)	Difference: **0.29 more** (CI 95% 0.42 fewer–1 fewer)		**Moderate** due to serious imprecision[e]	Earlier vasoactive therapy probably has no important effect on ventilator-free days compared with later vasoactive therapy.
ICU length of stay[f] (days, fewer better)	Based on data from 409 participants in 2 studies (Randomized controlled)	Difference: **0.71 more** (CI 95% 0.2 fewer–1.63 more)		**Low** due to very serious imprecision[g]	Earlier vasoactive therapy may have no important effect on ICU length of stay compared with later vasoactive therapy.
Use of vasopressors (in the first 24 hours)	Based on data from 1563 participants in 1 study[h]	**372** per 1000	**590** per 1000	**Low** due to serious inconsistency, serious imprecision; based on Permipikul et al. and CLOVERS study[i]	

[a] **Imprecision: extremely serious.**
[b] **Risk of bias: serious.**
[c] **Inconsistency: serious. Imprecision: extremely serious.**
[d] **Indirectness: serious. Imprecision: very serious.**
[e] **Imprecision: serious.**
[f] Measured by: days – lower better.
[g] **Imprecision: very serious.**
[h] **Supporting references:** *(76)*.
[i] **Inconsistency: serious. Imprecision: serious.**

Strong recommendation for

WHO recommends that patients with suspected or confirmed filovirus disease requiring a vasopressor be treated with norepinephrine rather than dopamine.

[Strong recommendation, moderate certainty evidence]

- This recommendation applies to children and adults, including pregnant women.
- Vasopressors should be used within a resuscitation strategy that includes: appropriate intravenous fluid therapy; frequent monitoring, including for cardiac arrhythmia.
- Individualize titration of the dose to desired effect (targeting arterial pressure as an indicator of perfusion).
- To minimize adverse effects, use the lowest dose possible for desired effect and discontinue vasopressors when no longer indicated.

Practical info

General considerations

- Establish large bore veinous access (16–18 gauge catheter) or intraosseous line or central venous catheter.
- Appropriate dilution in selected carrier and precise delivery mechanism, such as infusion pumps.
- Establish close haemodynamic monitoring, and adequate staffing to provide close monitoring.
- Close monitoring of the intravenous site is mandatory to identify any signs of extravasation:
  - If signs of extravasation, administer 5–10 mL of phentolamine diluted in 10 mL of 0.9% sodium chloride subcutaneously at the venous access site.
- Use the lowest dose necessary to achieve perfusion target. Check markers of perfusion every 30 minutes.

To make up norepinephrine and epinephrine solutions:

- Adults: add 4 mL of 1:1000 norepinephrine/epinephrine to 46 mL of 5% w/v dextrose solution to make 50 mL of 80 µg/mL concentration.
- Children: use a more dilute solutions. Add 1 mL of 1:1000 norepinephrine/epinephrine to 49 mL of 5% w/v dextrose solution to make 50 mL of 20 µg/mL concentration.
- Peripheral administration: use a more dilute solution (equivalent to that used centrally for children). Add 1 mL of 1:1000 norepinephrine to 49 mL of 5% w/v dextrose solution to make 50 mL of 20 µg/mL concentration.

	Norepinephrine	Epinephrine
Central vein	Initial: **0.05 µg/kg/min** Increase by 0.1 µg/kg/min increments Maximum dose 0.5–0.75 µg/kg/min	Initial: **0.05 µg/kg/min** Increase by 0.1 µg/kg/min increments Maximum dose 0.5–0.75 µg/kg/min
Peripheral vein	Same dosing regimen, use dilute solution (20 µg/mL)	Same dosing regimen, use dilute solution (20 µg/mL)

Evidence to decision

Benefits and harms	**Substantial net benefits of the recommended alternative** From evidence from patients with septic shock, treatment with norepinephrine probably reduced mortality (moderate certainty) and probably reduced the risk of arrhythmia (moderate certainty evidence) when compared with dopamine.
Certainty of the evidence	**Moderate** In the 1768 patients from 11 RCTs of septic shock, mortality in patients given norepinephrine was lower than those receiving dopamine (56 fewer per 1000, 95% CI 97 fewer to 10 fewer, moderate certainty) *(82)*. For each illustrative baseline risk, the mortality benefit exceeded the minimal important difference of 3 per 1000. Risks of arrhythmias were reported in four RCTs including 1390 participants, giving moderate certainty evidence of lower rates with norepinephrine compared with dopamine (difference 196 per 1000, 95% CI 226 fewer to 158 fewer). Similarly, reductions in severe adverse events were noted based on three trials (356 patients, difference 57 per 1000, 95% CI 74 fewer to 14 fewer), with low certainty due to imprecision.
Values and preferences	**No substantial variability expected** See the agreed consensus on patient values and preference in the Methods section which was judged to pertain here.
Resources and other considerations	**Important issues, or potential issues not investigated** **Equity:** No significant effect anticipated. **Feasibility:** Access to central venous line placement, monitoring equipment and staff training may affect the ability to give vasopressors safely. Availability of norepinephrine varies and is dependent on national and local medicines policies and supply. Dopamine, but not norepinephrine, is included in the WHO Model List of Essential Medicines (EML) which may affect relative availability. An application to add norepinephrine has been programmed for the next EML review. If available, use of norepineprhine is feasible, as it can be delivered initially via peripheral venous catheter (see vasopressor route recommendation). However, for longer term use, norepinephrine would require central venous catheter placed under ultrasound guidance which may be challenging in many filovirus treatment centres. For children, appropriate equipment such as paediatric perfusion sets and appropriate sized equipment to assess perfusion are required. **Acceptability:** No anticipated difference between the alternatives and patients would likely prefer to be treated with a beneficial drug with least harm. **Resource use and cost:** There were no available data on cost differentials between norepinephrine and dopamine, although the panel noted that the placement of central catheters for administration was a major determinant of overall complexity and cost, and would be the same for either agent. Peripheral administration of each is feasible (see vasopressor route recommendation). There are specific training needs for staff who constitute, administer and monitor vasopressor administration which are common to either intervention. Materials, including checklists and infusion calculation charts should be available to increase clinical safety.

Justification

The panel's strong recommendation for norepinephrine was driven by evidence of mortality reduction as a critically important outcome, and supported by lower rates of observed arrhythmias and serious adverse events. The evidence from sepsis trials was felt to be sufficiently direct to not rate down the certainty of evidence. The panel weighed the arrhythmia outcome in their decision as although it was not previously prioritized, it was judged an important and proximal marker of safety/harm.

No direct RCT comparisons were available for paediatric populations. The panel judged that this recommendation was appropriate to children and adults, considering the current clinical use of norepinephrine or epinephrine as first choice vasopressor in recent trials of early therapy *(83, 84)*.

While there were no direct data on the use in pregnancy, the panel judged that the clear mortality benefit in favour of norepinephrine would likely also apply to pregnant women. This is consistent with principles of obstetric practice in critical illness; optimizing maternal circulation is the most effective strategy to preserve fetal perfusion, and delays in vasopressor initiation may worsen outcomes for both mother and fetus *(81)*.

PICO

Population: Patients with filovirus needing vaspressors.

Intervention: Norepinephrine.

Comparator: Dopamine.

Summary: Most studies were open label, with attendant serious risk of bias. Data from systematic review and meta-analysis of Avni et al. *(85)*.

Outcome Timeframe	**Study results and measurements**	**Comparator** Dopamine	**Intervention** Norepinephrine	**Certainty of the evidence** (Quality of evidence)	**Summary**
Mortality 28–30 days (baseline risk from trials)	Relative risk 0.89 (CI 95% 0.81–0.98) Based on data from 1768 participants in 11 studies (Randomized controlled) Follow up: 28–30 days	**508** per 1000	**452** per 1000 Difference: **56 fewer per 1000** (CI 95% 97 fewer–10 fewer)	**Moderate** due to risk of bias[a]	Norepinephrine probably reduces mortality compared with dopmaine.
Mortality 28–30 days (higher baseline risk)	Relative risk 0.89 (CI 95% 0.81–0.98) Based on data from 1768 participants in 11 studies (Randomized controlled) Follow up: 28–30 days	**600** per 1000	**534** per 1000 Difference: **66 fewer per 1000** (CI 95% 114 fewer–12 fewer)	**Moderate** due to risk of bias[a]	Norepinephrine probably reduces mortality compared with dopmaine.
Mortality 28–30 days (lower baseline risk)	Relative risk 0.89 (CI 95% 0.81–0.98) Based on data from 1768 participants in 11 studies (Randomized controlled) Follow up: 28–30 days	**300** per 1000	**267** per 1000 Difference: **33 fewer per 1000** (CI 95% 57 fewer–6 fewer)	**Moderate** due to risk of bias[a]	Norepinephrine probably reduces mortality compared with dopmaine.
Severe adverse events	Relative risk 0.34 (CI 95% 0.14–0.84) Based on data from 356 participants in 3 studies (Randomized controlled)	**86** per 1000	**29** per 1000 Difference: **57 fewer per 1000** (CI 95% 74 fewer–14 fewer)	**Low** due to serious risk of bias and serious imprecision[b]	Norepinephrine may reduce risk of severe adverse events compared with dopamine.

Outcome Timeframe	**Study results and measurements**	**Comparator** Dopamine	**Intervention** Norepinephrine	**Certainty of the evidence** (Quality of evidence)	**Summary**
Arrhythmia	Relative risk 0.48 (CI 95% 0.4–0.58) Based on data from 1390 participants in 4 studies (Randomized controlled)	**377** per 1000	**181** per 1000 Difference: **196 fewer per 1000** (CI 95% 226 fewer–158 fewer)	**Moderate** due to serious risk of bias[c]	Norepinephrine probably reduces arrhythmias compared with dopamine.

[a] **Risk of bias: serious.** Inadequate sequence generation/generation of comparable groups, resulting in potential for selection bias. Incomplete data and/or large loss to follow up. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**

[b] **Risk of bias: serious.** Inadequate sequence generation/generation of comparable groups, resulting in potential for selection bias. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. Incomplete data and/or large loss to follow up. **Selective outcome reporting. Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Wide confidence intervals. **Publication bias: no serious.**

[c] **Risk of bias: serious.** Use of unvalidated and/or subjective outcome measures. Inadequate sequence generation/generation of comparable groups, resulting in potential for selection bias. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. Incomplete data and/or large loss to follow up. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**

Conditional recommendation for

WHO suggests that patients with suspected or confirmed filovirus disease requiring a vasopressor be treated with norepinephrine rather than epinephrine.

[Conditional recommendation, very low certainty evidence]

- This recommendation applies to children and adults, including pregnant women.
- The choice of norepinephrine or epinephrine may depend on availability and local practices.
- For some patients, for example, those with cardiac systolic dysfunction, epinephrine may may be preferable to norepinephrine alone.
- Vasopressors should be used within a resuscitation strategy that includes appropriate fluid therapy, frequent monitoring, including early identification of arrythmia.
- Individualize titration of the dose to desired effect (improved perfusion).
- To minimize adverse effects, use the lowest dose possible for desired effect and discontinue vasopressors when no longer indicated.

Practical info

Given the higher lactate levels in patients treated with epinephrine compared with norepinephine, the use choice of agent should be considered when using lactate monitoring (see lactate recommendation) *(59)*.

Evidence to decision

Benefits and harms	**Small net benefit, or little difference between alternatives** Using evidence from septic shock, it is uncertain whether the choice of norepinephrine or epinephrine alters mortality or rates of arrhyhmias (very low certainty). However, the panel determined that in patients with filovirus disease requiring vasopressors, norepinephrine was preferred despite the uncertainty due to its predominance in clinical practice and clinicians' widespread understanding of its use and adverse event profile.
Certainty of the evidence	**Very low** Evidence for norepinephrine versus epinephrine was derived from a systematic review from 2025 which incorporated four RCTs (comprising 560 patients with sepsis) *(82)*. Absolute effects were considered using the baseline mortality risk from the trials, as they already reflecting individuals at high-risk of poor outcome. There was very low certainty for mortality due to extremely serious imprecision and risk of bias (560 patients in four RCTs) with absolute mortality difference 5 per 1000 fewer with norepinephrine than epinephrine (95% CI 78 fewer to 82 more). Similarly, evidence for harms (arrhythmias) was also of very low certainty due to extremely serious imprecision and serious risk of bias.
Values and preferences	**Substantial variability is expected or uncertain** See the agreed consensus on patient values and preference in the Methods section which was judged to pertain here.

Resources and other considerations	**No important issues with the recommended alternative** **Equity:** No significant differences anticipated. **Feasibility:** Epinephrine is included on the EML, but norepinephrine is not. This is reflected in many similar national lists and is an important limitation to its use. Epinephrine is widely available due to its broad use for other indications such as anaphylaxis, making its feasibility superior to epinephrine in some countries. The panel noted that norepinephrine will be evaluated by the EML and if listed its availability will improve. There is no anticipated challenges with acceptability. **Resource use and cost:** A limited convenience sample of available costs for wholesale or retail price from WHO procurement (whichever is cheaper) from 23 LMICs suggested that norepinephrine was approximately 1.6 times more expensive than epinephrine per milligram (US$ 12.93 vs US$ 7.89), although minimum and maximum costs ranged from US$ 0.20 to US$ 42.55 and from US$ 0.12 to US$ 52.99, respectively. The panel noted the significant fixed costs associated with vasopressor therapy related to personnel, ability to safely place central venous access and monitoring equipment.

Justification

The panel judged that a conditional recommendation for norepinephrine over epinephrine would ensure more consistent use of the vasopressor with the most evidence on efficacy, while leaving room for clinicians to use epinephrine in settings where norapinephrine is not available or where cardiac insufficiency may warrant epinephrine preferentially. The panel weighed the arrhythmia outcome in their decision and, though it was not previously prioritized, it was judged an important and proximal marker of safety/harm. Estimates of absolute risk for mortality were used from the original meta-analysis, and were not corrected for different baseline risks given the very wide confidence intervals.

Theoretical considerations of harm were considered with use of epinephrine and its higher β-1 antagonism leading to enhanced arrhythmogenicity and splanchnic vasoconstriction. The panel also noted its previous strong recommendation for use of norepinephrine over dopamine based on moderate certainty evidence for mortality and this would increase its availability and use in general. The panel noted that trials which included norepinephrine as a comparator also included patients who received concurrent inotropic agents.

However, there was no subgroup interaction effect for norepinephrine alone compared with norepinephrine with another inotropic (e.g. dopexamine), p = 0.56. These data were consistent with a network meta-analysis *(86)* which estimated the odds ratio for mortality of norepinephrine (+/- dobutamine) versus epinephrine of 0.87 (95% CI 0.67–1.12).

The GDG judged that this recommendation should apply to adults and children. This was supported by data from an RCT of 67 children which suggested no difference in mortality between norepinephrine [+dobutamine] and epinephrine treatment (RR 0.59; 95% CI 0.28–1.25), but which was underpowered to confidently inform on benefits or harms *(83)*.

While there were no direct data on the use in pregnancy, the panel judged there was no reason to believe that decisions on epinephrine versus dopamine in pregnant women with a life-threatening infection would have a different harm:benefit balance than the wider population, which is supported by current clinical practice *(81)*.

PICO

Population: Patients with sepsis needing vaspressors.

Intervention: Norepinephrine.

Comparator: Epinephrine.

Outcome Timeframe	**Study results and measurements**	**Comparator** Epinephrine	**Intervention** Norepinephrine	**Certainty of the evidence** (Quality of evidence)	**Summary**
Mortality, 90 days	Relative risk 0.99 (CI 95% 0.83–1.18) Based on data from 560 participants in 4 studies (Randomized controlled) Follow up: 90 days in 3 RCTs, unclear in 1 small RCT	**458** per 1000	**453** per 1000 Difference: **5 fewer per 1000** (CI 95% 78 fewer–82 more)	**Very low** due to serious risk of bias and extremely serious imprecision[a]	We are uncertain if norepinephrine alone or combined with inotropic agents (dobutamine or dopexamine) increases or decreases mortality compared with epinephrine.
Arrhythmias, 90 days	Relative risk 0.92 (CI 95% 0.59–1.45) Based on data from 360 participants in 2 studies (Randomized controlled) Follow up: 90 days	**176** per 1000	**162** per 1000 Difference: **14 fewer per 1000** (CI 95% 72 fewer–79 more)	**Very low** due to extremely serious imprecision, serious risk of bias[a]	We are uncertain whether norepinephrine alone or combined with inotropic agents (dobutamine or dopexamine) increases or decreases arrhythmias compared with epinephrine.

[a] **Risk of bias: serious. Inconsistency: no serious. Indirectness: no serious. Imprecision: extremely serious. Publication bias: no serious.**

Conditional recommendation for

WHO suggests that for patients with suspected or confirmed filovirus disease requiring initiation of vasopressors, peripheral intravenous catheters be used rather than central venous catheters.

[Conditional recommendation, very low certainty evidence]

- This recommendation applies to children and adults, including pregnant women.
- Peripheral intravenous administration avoids the delay associated with central venous catheterization and enables more timely treatment which may improve outcomes.
- Use the largest bore peripheral intravenous catheter possible to minimize the risk of extravasation.
- Systematic and frequent monitoring of intravenous site is required.
- Transition to the use of central venous administration should be anticipated.

Practical info

Managing a vasopressor such as norepinephrine through a peripheral line requires strict adherence to safety protocols to prevent tissue necrosis.

1. Pre-administration requirements

- Use a large-bore intravenous cannula. The preferred site is a large vein in the forearm – be careful of antecubital lines which can occlude if the elbow is flexed.
- Check patency: confirm brisk blood return and flush the line with 10 mL of 0.9% sodium chloride to ensure no resistance or swelling.
- Use a standard 4 mg in 250 mL concentration. Higher concentrations increase the risk of severe injury if extravasation occurs.

2. Initiation and titration

- Use a dedicated infusion pump.
- Pump settings and concentration should be verified by two clinical staff.
- Record blood pressure and heart rate immediately prior to starting.

3. Monitoring

- To detect extravasation early, monitoring must be frequent and documented. Check the administration site every 30 minutes, including visual inspection and palpation of the site for coolness, blanching or oedema.
- Monitor physiological parameters according to standard operating procedures.
- **Warning signs:** if the patient complains of pain, burning, or if the skin appears pale/cold at the site, stop the infusion immediately.

4. Management of extravasation

- Leak into the subcutaneous tissue can causes intense local vasoconstriction, leading to ischaemia and necrosis.
- Immediately:
  - Stop the infusion: do not remove the intravenous catheter immediately.
  - Aspirate: attempt to aspirate as much residual drug as possible through the existing cannula.
  - Notify: alert the clinical team.

- Administer phentolamine
  - Phentolamine is an alpha-adrenergic antagonist that reverses the vasoconstriction.
  - Dose: 0.1–0.2 mg/kg, maximum 10 mg.
  - Dilute in 0.9% sodium chloride to 10 mL volume.
  - Inject the solution into the extravasated area using the existing cannula, and infiltrating into the soft tissue using a fine-gauge needle (25G or 27G).
  - Remove the cannula.
- Consider how to administer the vasopressor through another site, and beware hypotension related to the phentolamine and the pause in vasoactive medication.
- Document the leak and the action you took in the patient notes.

Evidence to decision

Benefits and harms

Small net benefit, or little difference between alternatives

From analysis of a single RCT, in patients requiring initiation of vasopressors it is very uncertain whether peripheral versus central venous administration affects mortality or major complications.

Additional data were sought from on absolute rates from observational studies, and are shown in Table 2 (data from ref *(87)*).

Table 2. Rates of adverse events in peripheral and central venous catheters used for vasopressor administration

	Studies	Central venous route	Peripheral venous route
Extravasation	4613 participants from 19 studies *(88)*		14.3 per 1000 (95% CI 7.2–23.2) [93 events]
Thrombosis	4613 participants from 19 studies *(88)*		14.7 per 1000 (95% CI 3.2–31.8) [117 events]
Catheter-related infections	3363 participants from 9 studies		7.2 per 1000 (95% CI 1.4–16) [61 events]
Catheter-related infections	2040 participants from 11 studies *(89)*	30 per 1000 (95% CI 13–47)	
Any complication	2406 participants from 4 trials *(90)*	39 per 1000 (95% CI 23–70)	
Arterial puncture	4388 participants from 22 trials *(90)*	26 per 1000 (95% CI 17–41)	

Certainty of the evidence

Very low

From a single randomized trial of 263 participants, there was very low certainty of evidence for mortality or complications *(92)*. Observational evidence (Table 2) was of low certainty, but could not be used to directly compare the alternatives as the populations were likely to be considerably different *(93, 94, 95, 96, 97)* (systematic review published as online appendix).

Values and preferences	Substantial variability is expected or uncertain Given the likelihood of earlier treatment which could be life-saving, most patients would be expected to prefer peripheral initiation of vasopressors, although may prefer central administration only due to the risks of extravasation, which include the need for surgical intervention including amputation if not recognized and managed immediately. See the agreed consensus on patient values and preference in the Methods section which was judged to pertain here.
Resources and other considerations	Important issues, or potential issues not investigated **Equity:** Initiation through peripheral catheters would be expected to increase equity through reducing barriers for patients to receive vasopressors promptly. **Feasible and acceptable:** Nearly all patients with filovirus disease would have a peripheral cannula placed, and find this acceptable. An additional line would need to be placed for vasopressor administration, but staff would be expected to find this acceptable. **Cost and resources:** The additional costs of peripheral cannulation are minimal, and part of routine clinical practice for patients with filovirus disease. Resources for careful observation and titration of the vasopressor would be similar irrespective of the choice of route, but standard operating procedures must be in place to recognize with minimal delay extravasation, and to enact medical countermeasures in case that it occurs.

Justification

Evidence was derived from a systematic review commissioned by the WHO, published as part of these guidelines *(88)*.

The panel made a conditional recommendation on the basis of their field experience of the time taken to initiate treatment being shorter for peripheral administration, and in conjunction with evidence that earlier vasopressor treatment was likely to improve important outcomes (see early vasopressor recommendation).

The panel judged that initiation of vasopressors via peripheral rather than central venous catheters would be easier, faster and lead to more rapid initiation of life-saving medicine (see norepinephrine recommendation). Concerns were raised about the risk of extravasation with peripheral administration, which requires extremely careful monitoring and immediate clinical action to prevent serious harm. Meta- analysis of observational cohorts suggest this occurs at rates of 14 per 1000 (95% CI 7.2–23.2) based on 93 events in 4613 participants from 19 studies *(88)*. The panel emphasized that peripheral administration would be a bridge to necessary placement of a central venous catheter.

PICO

Population: Patients with confirmed filovirus disease and shock requiring administration of a vasopressor.

Intervention: Administration of vasopressors via peripheral venous or intraosseous route.

Comparator: Administration of vasopressors via central venous route.

Outcome Timeframe	**Study results and measurements**	**Comparator** Administration of vasopressors via central venous route	**Intervention** Administration of vasopressors via peripheral venous or intraos	**Certainty of the evidence** (Quality of evidence)	**Summary**
Overall mortality (low baseline risk)	Hazard ratio 1.3 (CI 95% 0.84–2.01) Based on data from 263 participants in 1 study (Randomized controlled)	**300** per 1000	**371** per 1000 Difference: **71 more per 1000** (CI 95% 41 fewer–212 more)	**Very low** due to extremely serious imprecision[a]	We are very uncertain whether administration of vasopressors via PIVC reduces mortality as compared with administration via central venous catheter.
Overall mortality (high baseline risk)	Hazard ratio 1.3 (CI 95% 0.84–2.01) Based on data from 263 participants in 1 study (Randomized controlled)	**600** per 1000	**696** per 1000 Difference: **96 more per 1000** (CI 95% 63 fewer–241 more)	**Very low** due to extremely serious imprecision[a]	We are very uncertain whether administration of vasopressors via peripheral intravenous catheter reduces mortality as compared with administration via central venous catheter.
Overall mortality	Relative risk 0.95 (CI 95% 0.6–1.51) Based on data from 2504 participants in 5 studies (Observational (non-randomized))	**300** per 1000	**285** per 1000 Difference: **15 fewer per 1000** (CI 95% 120 fewer–153 more)	**Very low** due to extremely serious imprecision[a]	We are very uncertain whether administration of vasopressors via peripheral intravenous catheter reduces mortality as compared with administration via central venous catheter.
Overall mortality	Relative risk 0.95 (CI 95% 0.6–1.51) Based on data from 2504 participants in 5 studies (Observational (non-randomized))	**600** per 1000	**570** per 1000 Difference: **30 fewer per 1000** (CI 95% 240 fewer–306 more)	**Very low** due to extremely serious imprecision[a]	We are very uncertain whether administration of vasopressors via peripheral intravenous catheter reduces mortality as compared with administration via central venous catheter.
Major complications	Relative risk 1.28 (CI 95% 0.92–1.78) Based on data from 263 participants in 1 study (Randomized controlled)	**311** per 1000	**398** per 1000 Difference: **87 more per 1000** (CI 95% 25 fewer–243 more)	**Very low** due to extremely serious imprecision[a]	We are very uncertain whether administration of vasopressors via peripheral intravenous catheter reduces mortality as compared with administration via central venous catheter.

[a] **Imprecision: extremely serious.** Wide confidence intervals.

Strong recommendation for

WHO recommends that for patients with suspected or confirmed filovirus disease requiring central venous access, ultrasound guided placement be used rather than non-ultrasound guided placement.

[Strong recommendation, moderate certainty evidence]

- This recommendation applies to children and adults, including pregnant women.
- Ultrasound guided central venous catheter placement requires trained health workers, essential equipment and supplies.
- Ensure appropriate IPC measures are in place to reduce risk of infection when using ultrasound.
- Systematically monitor the catheter site.
- Remove the catheter when no longer needed.

Evidence to decision

Benefits and harms	**Substantial net benefits of the recommended alternative** In patients requiring insertion of a central venous cannula, the use of ultrasound to guide placement probably reduces arterial puncture risk compared with landmark method (moderate certainty), probably reduces other complications such as pneumothorax (moderate certainty), possibly improves success (low certainty), and probably reduces risk of infection (moderate).
Certainty of the evidence	**Moderate** Meta-analysis of RCTs gave moderate certainty evidence for outcomes of complications (including emphysema and pneumothorax; 20 fewer per 1000 for ultrasound guided compared with landmark guided, 95% CI 25 fewer to 7 fewer based on 3942 participants in 11 RCTs), and catheter-related infection (15 fewer per 1000, 95% CI 23 fewer to 6 fewer). Trials were limited by lack of allocation concealment, and for some outcomes ascertainment bias. Low certainty evidence for arterial puncture was due to serious risk of bias, but suggested superiority of ultrasound approach (68 fewer per 1000, 95% CI 77 fewer to 53 fewer).
Values and preferences	**No substantial variability expected** Due to improved safety profile, nearly all patients would be expected to choose ultrasound guided rather than the landmark guided approach. See the agreed consensus on patient values and preference in the Methods section which was judged to pertain here.

Resources and other considerations	Important issues, or potential issues not investigated **Equity:** The panel noted that mandatory use of ultrasound may reduce the number of patients able to access the treatment due to heterogeneity of skilled operators and equipment. However, the recommendation for peripheral administration of vasopressors might offset this. **Feasibility and acceptability:** Both approaches to insertion of central venous catheters rely on experienced, trained staff and fastidious attention to IPC procedures. The availability of skilled staff will limit both interventions. Feasibility of sterile field and controlled environment for IPC at the insertion site can be challenging in filovirus treatment centres, and is made more complex by the need for additional manipulation of an ultrasound probe and machine. Safety and confidence of the operator is higher with ultrasound-guided approaches, which improves acceptability to staff and patients alike, especially given the prime "do no harm" consideration of medical practice. **Resource and cost:** The difference between approaches is most obvious in the capital cost of ultrasound equipment which must be dedicated to the red zone. Central venous catheters have an associated cost to both approaches, although the degree to which more successful attempts (due to ultrasound) offset costs due to decreased wastage is unknown. Additional cost (and staff limitations) to establish and maintain ultrasound competence is ill-defined but likely to be significant.

Justification

The panel felt that the safety of patients could be impacted by their other recommendations for vasopressor use. Particularly that, while initial peripheral administration was preferred, the use of central venous catheterization would be more common if all the recommendations were enacted. The panel therefore considered the evidence for the mode of placement of central venous catheter, which might mitigate risks of placement of catheters.

Data were drawn from a systematic review of ultrasound vs landmark approaches for jugular vein cannulation which included multiple reasons for insertion *(90)*. The evidence was considered to directly pertain to filovirus disease patients as the procedures' risks and benefits were expected to be similar. The panel noted that bleeding in the context of filovirus-related haemorrhagic syndrome might be expected to worsen outcomes related to arterial puncture. Although outcomes had not been prioritized, the GDG had pre-agreed that SAE was a critical outcome. In the context of venous cannulation, SAE included arterial puncture, pneumothorax and severe subcutaneous emphysema.

The panel unanimously agreed that a recommendation for ultrasound-guided placement be made. A minority, citing feasibility concerns, felt that this should be a conditional recommendation despite moderate certainty evidence of benefit. However, after deliberation, a vote was taken in which 80% of the panel opted for a strong recommendation. The justification for this was the high risk of catastrophic outcomes if bleeding or pneumothorax occurred in the context of patients with increased bleeding risk, and within a complex environment constrained by resources and the need for procedures performed with full PPE. The panel felt that ultrasound and associated materials for IPC were essential, and noted that skilled workforce and safety protocols were also mandatory.

PICO

Population: Patients requiring placement of a central venous catheter.

Intervention: Insertion of central venous catheter using ultrasound guidance.

Comparator: Insertion of central venous catheter using anatomical landmarks.

Outcome Timeframe	**Study results and measurements**	**Comparator** Landmark guided	**Intervention** Ultrasound guided	**Certainty of the evidence** (Quality of evidence)	**Summary**
Any complication	Relative risk 0.29 (CI 95% 0.17–0.52) Based on data from 2406 participants in 14 studies[a] (Observational (non-randomized))	**135** per 1000	**39** per 1000	**Very low** due to very serious risk of bias, serious inconsistency[b]	We are uncertain if ultrasound guided jugular vein line placement reduces complications compared with landmark method.
		Difference: **96 fewer per 1000** (CI 95% 112 fewer–65 fewer)			
Arterial puncture	Relative risk 0.28 (CI 95% 0.18–0.44) Based on data from 4388 participants in 22 studies[a]	**94** per 1000	**26** per 1000	**Low** due to very serious risk of bias[c]	Ultrasound guided jugular vein line placement possibly reduces arterial puncture compared with landmark method.
		Difference: **68 fewer per 1000** (CI 95% 77 fewer–53 fewer)			
Other complication (emphysema, pneumothorax)	Relative risk 0.34 (CI 95% 0.15–0.76) Based on data from 3942 participants in 11 studies	**30** per 1000	**10** per 1000	**Moderate** due to serious risk of bias[d]	Ultrasound guided jugular vein line placement probably reduces other complications compared with landmark method.
		Difference: **20 fewer per 1000** (CI 95% 25 fewer–7 fewer)			
Success rate	Relative risk 1.12 (CI 95% 1.08–1.17) Based on data from 4349 participants in 23 studies[e]	**876** per 1000	**981** per 1000	**Low** due to very serious risk of bias[c]	Ultrasound guided jugular vein line placement possibly improves success compared with landmark method.
		Difference: **105 more per 1000** (CI 95% 70 more–149 more)			
Catheter-related infection	Relative risk 0.68 (CI 95% 0.53–0.88) Based on data from 5052 participants in 11 studies[a]	**48** per 1000	**33** per 1000	**Moderate** due to serious risk of bias[d]	Ultrasound guided jugular vein line placement probably reduces catheter related infections compared with landmark method.
		Difference: **15 fewer per 1000** (CI 95% 23 fewer–6 fewer)			

[a] **Supporting references:** *(89, 90)*.
[b] **Risk of bias: very serious. Inconsistency: serious.**
[c] **Risk of bias: very serious.**
[d] **Risk of bias: serious.**
[e] **Supporting references:** *(89, 90)*.

Treatment of co-infection

Conditional recommendation for

WHO suggests for the use of presumptive broad-spectrum antibiotics in patients with confirmed filovirus disease in the presence of suspected sepsis or bacterial co-infection.

[Conditional recommendation, low certainty evidence]

- This recommendation applies to children and adults, including pregnant women.
- Presumptive antibiotics means use when there is clinical suspicion of sepsis and/or bacterial co-infection.
- Administration of intravenous antibiotics should occur without delay, where there is a suspicion of sepsis, or shock.
- When possible, antibiotic choice should be based on local antimicrobial resistance (AMR) patterns.
- This does not apply to patients with low likelihood of bacterial co-infection. These patients should not be routinely given antibiotics, but rather monitored and re-assessed for the presence of bacterial infection and sepsis to guide antibiotic treatment.
- Use available laboratory tools, including bacteriology and biomarkers, to guide microbiological diagnosis and antimicrobial therapy with appropriate de-escalation when possible.

Evidence to decision

Benefits and harms	**Substantial net benefits of the recommended alternative** In patients with confirmed filovirus disease, antibiotic treatment may reduce mortality when compared with no antibiotic (low certainty). Antibiotic use in hospital may be associated with severe adverse events (low certainty) and may increase AMR (low certainty).
Certainty of the evidence	**Low** Evidence was drawn from one non-randomized trial with 424 patients with Ebola virus disease *(100)*. This provided low certainty of evidence for mortality endpoint (no up- or downgrading) through propensity-matched conditional logistic regression within an observation cohort (systematic review published as online appendix). The blood culture positivity rate was informed by observational data from a single study reported at a medical conference *(101)*. The certainty was very low due to very serious risk of bias and very serious imprecision. Evidence summary for severe adverse events related to antibiotic administration to hospital inpatients was informed by 19 studies (9049 patients) which provided low certainty evidence due to risk of bias and imprecision *(102)*. Within this analysis, rates of AMR were drawn from nine studies (2330 participants).

Values and preferences	**No substantial variability expected** See the agreed consensus on patient values and preference in the Methods section which was judged to pertain here. It was uncertain the degree to which individual patients would value AMR in their decision-making, but considerations of immediate mortality or adverse outcome were expected to be more important.
Resources and other considerations	**No important issues with the recommended alternative** **Equity:** No anticipated issues. **Feasibility:** Intravenous access will be established in most patients with filovirus disease. The use of intravenous antibiotics would therefore be feasible, as would oral antibiotics if the patient is able to swallow and has no vomiting. The choice of antibiotics should be consistent with WHO AWaRe guidance *(97)* to maximize acceptability to health care workers and ensure availability is not a limiting issue. **Resource use and cost:** The cost of antibiotics based on AWaRe list (specifically third-generation cephalosporins) would be minimal. The panel felt strongly that laboratory testing (such as culture and biomarkers) which are not systematically available should be made available to support decision-making and antimicrobial selection (see [link]).

Justification

Evidence was derived from a systematic review commissioned by the WHO, published as part of these guidelines *(98)*.

The panel determined that in patients with confirmed filovirus disease that presumptive antibiotics (the administration without objective clinical evidence of bacterial infection) may reduce mortality. They reasoned that the major clinical manifestation of severe filovirus disease is a sepsis-like syndrome, and bacterial co-infection cannot be excluded. There is also a postulated increased translocation of bacteria from the gastrointestinal tract, as is seen in other critical illness. Given the pre-existing high mortality rate, in a population with severe disease, the large expected benefit from antibiotics where undiagnosed bacterial infection takes place, the panel felt that the individual patient benefit was likely to outweigh potential public harms associated with AMR, and the individual concerns of adverse events.

The panel qualified that AMR was a global threat, but the number of patients to whom this recommendation would be applied would be very small, and their contribution as a driver of AMR would be negligible. However, good practice would determine that the most appropriate agent should be used for the shortest time possible.

For non-severe cases of filovirus disease, and where patients have no evidence of bacterial co-infection, the panel questioned the benefit and noted that the possible harms related to severe adverse events and AMR remained. This recommendation should not be applied under these circumstances. The panel noted that there was no formal tool which established a pre-test likelihood of bacterial infection, and that the physician should decide on the basis of an individualized risk assessment.

The panel judged that the same justification would apply to children and adults, including pregnant women.

The recommendation applies at the point of admission to the isolation unit for suspected cases and/or filovirus treatment centre. The possibility of subsequent hospital acquired infection, with later onset and alternative bacterial etiologies, necessitates an individualized approach. The panel noted that determining etiology through bacterial culture and antibiogram would be best practice outside of outbreaks, but rarely available to filovirus treatment centres.

PICO

Population: Patients with confirmed filovirus disease.

Intervention: Routine administration of antibiotic therapy.

Comparator: No routine administration of antibiotic therapy (therapy at clinician discretion).

Outcome Timeframe	**Study results and measurements**	**Comparator** No routine administration of antibiotic therapy (therapy at clinic)	**Intervention** Routine administration of antibiotic therapy	**Certainty of the evidence** (Quality of evidence)	**Summary**
Mortality (low baseline risk)	Odds ratio 0.48 (CI 95% 0.32–0.71) Based on data from 424 participants in 1 study (Observational (non-randomized))	**300** per 1000	**171** per 1000 Difference: **129 fewer per 1000** (CI 95% 179 fewer–67 fewer)	**Low**	Antimicrobials may reduce mortality as compared with no antimicrobials.
Mortality (high baseline risk)	Odds ratio 0.48 (CI 95% 0.32–0.71) Based on data from 424 participants in 1 study (Observational (non-randomized))	**600** per 1000	**419** per 1000 Difference: **181 fewer per 1000** (CI 95% 276 fewer–84 fewer)	**Low**	Antimicrobials may reduce mortality as compared with no antimicrobials.
Blood culture positivity	Relative risk Based on data from 32 participants in 1 study (Observational (non-randomized))		**94** per 1000 CI 95%	**Very low** due to serious risk of bias, very serious imprecision[a]	We are very uncertain about the rate of blood culture positivity.
Adverse events in inpatient antibiotic use	Odds ratio 1.04 (CI 95% 1.02–1.07) Based on data from 20 345 participants in 65 studies (Randomized controlled)		**199** per 1000 CI 95%	**Moderate** due to serious risk of bias[b]	Antibiotics used in hospital are probably associated with adverse events.
Serious adverse events in inpatient antibiotic use	Odds ratio 1.09 (CI 95% 1–1.19) Based on data from 9049 participants in 19 studies (Randomized controlled)		**138** per 1000 CI 95%	**Low** due to serious risk of bias, serious imprecision[c]	Antibiotics used in hospital may be associated with severe adverse events.
Antimicrobial resistance in inpatient antibiotic use	Odds ratio 1.03 (CI 95% 0.98–1.07) Based on data from 2330 participants in 9 studies (Randomized controlled)		**106** per 1000 CI 95%	**Low** due to serious risk of bias, serious imprecision[c]	Antibiotics used in hospital may be associated with antimicrobial resistance.

[a] **Risk of bias: serious.** Risk of bias could not be assess as this was a conference abstract. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Wide confidence intervals. **Publication bias: no serious.**

[b] **Risk of bias: serious.** Incomplete data and/or large loss to follow up. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Inconsistency: no serious.**

[c] **Risk of bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. Incomplete data and/or large loss to follow up. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Wide confidence intervals. **Publication bias: no serious.**

Management of haemorrhagic disease

WHO guidance is also available on the safe use of blood products and the administration of patient blood management systems *(102, 103, 104)*.

Tranexamic acid

Tranexamic acid is an antifibrinolytic, competitively inhibiting the activation of plasminogen to plasmin. This prevents plasminogen from attaching to fibrin, and therefore limits clot breakdown. Multiple RCTs have demonstrated effective reduction in blood loss and improvement in patient important outcomes, particularly in elective surgeries, emergency trauma and postpartum haemorrhage *(105, 106, 107)*. In cases of severe traumatic haemorrhage, administering tranexamic acid within the first 3 hours reduces the risk of death due to bleeding, but may become disadvantageous if given after 3 hours *(108, 109)*.

The pathogenesis of bleeding in filovirus is still unclear, but disseminated intravascular coagulation (DIC) is implicated *(110)*. The use of tranexamic acid in DIC is likely to stabilize disseminated clots preventing their breakdown. This limits recovery from DIC and is contraindicated in many haematological guidelines *(111, 112)* with the exception of rare cases where extreme fibrin breakdown is the cause of chronic DIC associated with aortic aneurysms or some cancers.

Management of postpartum haemorrhage

WHO guidelines for prevention and treatment of postpartum haemorrhage state: “Early use of intravenous tranexamic acid (within 3 hours of birth) in addition to standard care is recommended for women with postpartum haemorrhage following vaginal birth or caesarean section.” *(113)*. Additionally, this should be given in the context of “A standardized and timely approach to the management of postpartum haemorrhage, comprising an objective assessment of blood loss and use of a treatment bundle supported by an implementation strategy, is recommended for all women having a vaginal birth. The care bundle for first-line treatment of postpartum haemorrhage should include rapid institution of uterine massage, administration of an oxytocic agent and tranexamic acid, intravenous fluids, examination of the genital tract and escalation of care.”

Conditional recommendation against

WHO suggests against the use of tranexamic acid in patients with confirmed filovirus disease and haemorrhage.

[Conditional recommendation, very low certainty of evidence]

- This recommendation applies to adults and children with filovirus disease that have bleeding from intravenous sites, gastrointestinal tract and oral mucosa.
- This does not apply to patients with filovirus that are bleeding due to a condition for which tranexamic acid has a proven benefit, such as postpartum haemorrhage, surgical bleeding or trauma.

Evidence to decision

Benefits and harms	**Important harms** In patients with filovirus disease and haemorrhage, there is no direct evidence for the use of tranexamic acid. Using indirect evidence from gastrointestinal bleeding, we are uncertain if tranexamic acid reduces mortality or controls bleeding (very low certainty). The same indirect evidence suggests treatment with tranexamic acid possibly increases risk of thromboembolism (low certainty). Indirect evidence from administration for trauma gives moderate certainty evidence that tranexamic acid increases mortality if given after 3 hours.
Certainty of the evidence	**Moderate** There was no direct evidence for the use of tranexamic acid in filovirus disease. Presented evidence for benefits (from 13 432 patients in seven studies of gastrointestinal bleeding) was extremely indirect and imprecise and therefore rated down three times to very low certainty. For harms, which were judged to be less indirect, including thromboembolic events, the evidence was low certainty *(114)*. In the largest study of trauma, patients more than 3 hours post trauma (where DIC was likely to be a common factor) were at higher risk of mortality (translating to 264 more deaths per 1000, 95% CI 72 more to 108 more, based on 600/1000 baseline mortality, moderate certainty) *(109, 115)*.
Values and preferences	**No substantial variability expected** Given the potential for harm, and in the absence of data suggesting benefit, nearly all patients would be expected to decline tranexamic acid. See the agreed consensus on patient values and preference in the Methods section which was judged to pertain here.
Resources and other considerations	**Important issues, or potential issues not investigated** **Equity:** Calls to scale up global availability of tranexamic acid in conditions for which evidence is strong *(116, 117)* could be undermined by its unproven use in filovirus disease, and therefore increase inequity. The panel agreed that investment in improving access to clinical laboratory testing of platelets and coagulation factors, and developing access to blood transfusion services would instead improve equity by allowing access to life-saving treatment to filovirus patients. **Feasibility and acceptability:** Anecdotally, tranexamic acid has been used in recent filovirus outbreaks as a "last ditch" effort where tools are limited, and blood transfusion has been unavailable. The panel estimated that, presented with evidence of potential harm, health workers and patients would find non-administration of tranexamic acid acceptable. **Resources and cost:** No anticipated issues.

Justification

There is a clear need for more biological studies to understand the pathophysiological mechanisms of bleeding in filovirus disease. The panel agreed that the current mechanistic understanding from sepsis, where DIC is an important contributor to altered haemostasis, raises strong concerns about potential harm associated with tranexamic acid. The closest parallel source of evidence was judged to be from delayed treatment of patients after trauma, because DIC is likely to be a common pathophysiological process. Here, tranexamic acid is associated with increased mortality.

Additional concern was raised by the low certainty evidence of increased thrombosis in patients with gastrointestinal haemorrhage. These suggestions of harm, in the absence of direct evidence of benefit led the panel to make a conditional recommendation against tranexamic acid.

This recommendation applies to children and adults, and pregnant women who do not have postpartum haemorrhage; the panel decided to make a separate recommendation for the use in postpartum haemorrhage.

PICO

Population: Patients with confirmed filovirus disease and symptoms or signs of haemorrhage.

Intervention: Tranexamic acid.

Comparator: No tranexamic acid.

Outcome Timeframe	**Study results and measurements**	**Comparator** No tranexamic acid	**Intervention** Tranexamic acid	**Certainty of the evidence** (Quality of evidence)	**Summary**
Mortality (high baseline risk)	Relative risk 0.77 (CI 95% 0.56–1.07) Based on data from 13 432 participants in 7 studies (Randomized controlled)	**600** per 1000	**462** per 1000 Difference: **138 fewer per 1000** (CI 95% 264 fewer–42 more)	**Very low** due to serious indirectness, very serious imprecision[a]	We are very uncertain whether tranexamic acid reduces mortality as compared with no tranexamic acid.
Mortality (low baseline risk)	Relative risk 0.77 (CI 95% 0.56–1.07) Based on data from 13 432 participants in 7 studies (Randomized controlled)	**300** per 1000	**231** per 1000 Difference: **69 fewer per 1000** (CI 95% 132 fewer–21 more)	**Very low** due to serious indirectness, very serious imprecision[a]	We are very uncertain whether tranexamic acid reduces mortality as compared with no tranexamic acid.
Rebleeding	Relative risk 0.64 (CI 95% 0.45–0.91) Based on data from 13 449 participants in 7 studies (Randomized controlled)	**91** per 1000	**58** per 1000 Difference: **33 fewer per 1000** (CI 95% 50 fewer–8 fewer)	**Very low** due to serious imprecision, very serious indirectness[b]	Tranexamic acid may reduce rebleeding as compared to no tranexamic acid, as inferred from use in gastrointestinal bleeding.
Failure to control bleeding	Relative risk 0.55 (CI 95% 0.32–0.93) Based on data from 13 376 participants in 6 studies (Randomized controlled)	**116** per 1000	**64** per 1000 Difference: **52 fewer per 1000** (CI 95% 79 fewer–8 more)	**Very low** due to serious indirectness, serious imprecision, serious inconsistency[c]	We are very uncertain about the effect of tranexamic acid on failure to control bleeding.
Thromboembolic events	Relative risk 1.52 (CI 95% 0.51–4.51) Based on data from 13 473 participants in 7 studies (Randomized controlled)	**30** per 1000	**46** per 1000 Difference: **16 more per 1000** (CI 95% 15 fewer–105 more)	**Low** to serious indirectness, serious imprecision[d]	Tranexamic acid may increase the risk of thromboembolic events as compared to no tranexamic acid, as inferred from use in gastrointestinal bleeding.

Outcome Timeframe	**Study results and measurements**	**Comparator** No tranexamic acid	**Intervention** Tranexamic acid	**Certainty of the evidence** (Quality of evidence)	**Summary**
Mortality (subgroup: physiologic fibrinolysis in trauma)	Relative risk 5.52 (CI 95% 2.59–11.76) Based on data from 114 participants in 1 study (Observational (non-randomized))	**110** per 1000	**607** per 1000 Difference: **497 more per 1000** (CI 95% 175 more–1184 more)	**Very low** to serious indirectness[e]	We are very uncertain whether TXA reduces mortality as compared to no TXA in patients with physiologic fibrinolysis phenotype
Mortality due to bleeding (subgroup: >3 h in trauma)	Relative risk 1.44 (CI 95% 1.12–1.18) Based on data from 6634 participants in 1 study (Randomized controlled)	**600** per 1000	**864** per 1000 Difference: **264 more per 1000** (CI 95% 72 more–108 more)	**Moderate** due to serious indirectness[f]	TXA given in suspected thrombotic DIC may increase mortality due to bleeding
Mortality due to bleeding (subgroup: >3 h in trauma)	Relative risk 1.44 (CI 95% 1.12–1.18) Based on data from 6634 participants in 1 study (Randomized controlled)	**300** per 1000	**432** per 1000 Difference: **132 more per 1000** (CI 95% 36 more–54 more)	**Moderate** due to serious indirectness[f]	TXA given in suspected thrombotic DIC may increase mortality due to bleeding

[a] **Inconsistency: no serious. Indirectness: serious.** Differences between the population of interest and those studied. **Imprecision: very serious.** Wide confidence intervals. **Publication bias: no serious.**

[b] **Inconsistency: no serious. Indirectness: very serious.** Differences between the population of interest and those studied. Imprecision: serious. Wide confidence intervals. Publication bias: no serious.

[c] **Inconsistency: serious.** The confidence interval of some of the studies does not overlap with those of most included studies/the point estimate of some of the included studies. The magnitude of statistical heterogeneity was high, with I^2:... %.. **Indirectness: serious.** Differences between the population of interest and those studied. **Imprecision: serious.** Wide confidence intervals. **Publication bias: no serious.**

[d] **Inconsistency: no serious. Indirectness: serious.** Differences between the population of interest and those studied. **Imprecision: extremely serious.** Wide confidence intervals. **Publication bias: no serious.**

[e] **Inconsistency: no serious. Indirectness: serious. Imprecision: no serious. Publication bias: no serious.**

[f] **Inconsistency: no serious. Indirectness: serious.** Differences between the population of interest and those studied. **Imprecision: no serious. Publication bias: no serious.**

Conditional recommendation for

WHO suggests for the use of tranexamic acid in patients with confirmed filovirus disease and postpartum haemorrhage.

[Conditional recommendation, low certainty evidence]

- Employ standard care protocols for postpartum haemorrhage, including a uterotonic (oxytocin is preferred where available).
- Tranexamic acid should be given intravenously within 3 hours of birth.

Evidence to decision

Benefits and harms	**Small net benefit, or little difference between alternatives** There is direct evidence of benefit from tranexamic acid in postpartum haemorrhage, underpinning a strong WHO recommendation in general guidelines for pregnancy *(113)*. Mechanistic reasons for concern, including the potential to worsen DIC related to filovirus were noted (see tranexamic acid in broader population). The risk of harm related to DIC in filovirus disease was not quantifiable from available data.
Certainty of the evidence	**Low** From evidence used in WHO guidelines, the number of women needed to treat to prevent one maternal death from bleeding is 258 (95% CI 133–4052) *(118)*.
Values and preferences	**Substantial variability is expected or uncertain** See the agreed consensus on patient values and preference in the Methods section which was judged to pertain here.
Resources and other considerations	**Important issues, or potential issues not investigated** **Equity:** Global advocacy for the use of tranexamic acid, in line with the WHO postpartum haemorrhage roadmap, suggests that its use in the treatment of postpartum haemorrhage would increase equity *(116)*. **Feasibility and acceptability:** Tranexamic acid is feasible and acceptable, based on trials and practical use in low-income countries *(119)*. **Resources and cost:** No anticipated issues.

Justification

Given the proven benefit in postpartum haemorrhage, the panel judged that implementation of tranexamic acid treatment in this specific subpopulation would be likely to be beneficial. While the potential for theoretical risk of harm related to DIC remained, this was not quantifiable and the availability of broader evidence for benefit in postpartum haemorrhage was robust. The panel judged that treatment should therefore be instituted in line with WHO recommendations *(113)*. For those with filovirus disease, the panel felt there was indirectness of evidence from the general population, which resulted in reduced certainty (rated down to low), and a subsequent conditional recommendation.

Post-discharge follow-up

Strong recommendation for

WHO recommends that persons who have survived/recovered from filovirus disease be offered structured follow-up after discharge.

[Strong recommendation, moderate certainty evidence]

- This recommendation applies to children and adults.
- Structured follow-up includes access to free and comprehensive care to assess and treat complications such as mental health symptoms, ocular disease and persistence of virus in sanctuary sites; as well as ensure safe delivery for pregnant women who have recovered.

Practical info

Different elements of survivor support should be tied to interventions resulting from abnormal findings. The following were specifically noted:

1. Follow up to reduce onward transmission:
   - viral screening of semen, breastmilk, vaginal fluids and appropriate counselling and care based on results to prevent sexual transmission;
   - maternity care follow-up for enhanced IPC around birth given potential for persistent filovirus in amniotic fluid.

2. Medical follow up for complications:
   - medical specialist support and escalation of therapy according to findings;
   - neurological follow-up for neurological symptoms such as hearing impairment;
   - nutritional assessment and support;
   - mental health and psychosocial support for mental health symptoms;
   - ophthalmology care for ocular issues;

The selection of interventions will depend on local capability and capacity, and the potential for specialist referral.

3. Concrete socioeconomic support for survivors, their families, and families of non-survivors, and support of the epidemic-affected vulnerable population.

Evidence to decision

Benefits and harms

Small net benefit, or little difference between alternatives

Benefits were inferred from the prevalence of symptoms amongst filovirus survivors, linked with evidence of the efficacy of treatment in depression as a key target, as follows:

- Among filovirus survivors, depression occurs at 150 per 1000 (95% CI 110–210) *(126)*.
- Relative risk (RR) of "clinical response to treatment" 1.28 (95% CI 1.15–1.43) for selective serotonin reuptake inhibitors (SSRIs) compared with placebo. Number needed to treat for benefit = 7 *(121, 122)*.

Table 3. Expected number of patients benefiting from treatment of depression as a result of structured screening

No structured follow-up		Structured follow-up
People detected with depression	**People successfully treated for depression**	**Additional successful treatments[a]**
0 per 1000	0 per 1000	21 per 1000[b]
20 per 1000	3 per 1000	18 per 1000[b]
36 per 1000[c]	**5 per 1000**	**16 per 1000[b]**
40 per 1000	6 per 1000	15 per 1000[b]
80 per 1000	11 per 1000	10 per 1000
150 per 1000	21 per 1000	0 per 1000

[a] If all patients are followed up, and all those screened positive for depression are commenced on an SSRI antidepressant.
[b] Above the 15/1000 threshold for minimal important difference for "avoiding stigma and mental health issues".
[c] Best estimate of likely diagnostic rates of depression applying a 76% non-treatment rate from LMICs more broadly *(120)*.

Certainty of the evidence

Moderate

Linked evidence from RCTs of SSRI in depression is of high certainty (RR 1.28, 95% CI 1.15–1.43) *(121)*. Rates of depressive symptoms after 150 per 1000 (95% CI 110–210) are consistent across multiple studies. Overall, the panel judged the linked evidence to be of moderate certainty, acknowledging that estimates of detection are uncertain.

Values and preferences

No substantial variability expected

It is expected that most patients would wish to receive structured follow-up care provided that screening and treatment could provide benefits they judged important, and that care could be provided close to their homes.

Resources and other considerations

Important issues, or potential issues not investigated

Equity: Not providing services is likely to reduce equity as people would be unable to access care (or incur higher costs) as a result of their illness. Particularly vulnerable populations include: children; pregnant women (infectious transmission at birth); mothers with young infants; older adults, patients with specific needs/disability. Stigma and fear among health care providers may compromise the quality of care they receive if structured follow-up is not in place, whereas a structured follow-up may address this and improve equity.

Feasibility and acceptability: After an outbreak, specialist care may be available directly or indirectly and should be integrated into local health services. Where used in recent filovirus disease outbreaks, this was highly valued by communities *(26)*. However, the required resources have been significant, and supplied by bilateral donation agreements. Follow-up duration is likely to be an important determinant of feasibility, and unnecessary clinic visits should be avoided.

Costs: There are consequential costs to survivors and their families in their recovery from disease due to loss of productivity, ill-health, quality of life and health-related costs, which are not precisely described or quantified, but widely recognized. Costs borne by the health care system are likely to be considerable, especially for specialist care and treatments when needed. However, structured follow-up would enable earlier diagnosis of symptoms that need treatment, therefore reducing the longer term cost to survivors and families.

Justification

The panel originally considered evidence which included the prevalence of symptoms and medical abnormalities after filovirus infection. However, without evidence of interventions which would be expected to have a benefit, the evidence was considered of low certainty. Further work was therefore undertaken to identify multiple areas of linked evidence with the potential for significant improvement in patient-important outcomes. The panel agreed that the complexity of care required, together with high rates of post-infection chronic symptoms would be unlikely to be adequately treated in existing health systems without specific guidance. The interventions would be most efficiently delivered as a package of assessment and treatment at post-filovirus follow-up clinics, which could integrated into primary health services and potentially lead to local strengthening of capacity.

The following were identified in terms of evidence linking the incidence of disease with positive outcomes from its treatment:

1. Screening for depression, with subsequent initiation of SSRIs, which have been shown to improve patient-important mental health outcomes *(123)*. Depression was considered a critical outcome as "avoiding stigma and mental health issues" had a median score 8/9 on a prioritization exercise. The panel estimated that a maximum of 25% of those 150 per 1000 survivors with depression would receive treatment (i.e. would have depressive symptoms recognized and treated if typical usual care approaches were taken, i.e. reactive, patient-driven care-seeking). This is consistent with WHO reported figures for the proportion of people with severe mental disorders who receive no treatment for their disorder in LMICs of 76–85% *(120)*. Using the conservative estimate (76%), the number of expected additional cases of treated depression if structured follow-up were employed would be 16/1000, and would exceed the minimal important difference of 15/1000.
2. Reduction of onward transmission related to sexual activity through structured counselling on safe sex practices and regular semen tests until virus RNA clearance has been verified. Viral persistence has been documented in Sudan virus disease *(124)*, and in Ebola virus disease *(125)* where the median time to negative PCR was 204 days and where risk-reduction in sexual practices has the potential to reduce transmission *(126)*. The absence of such a programme could have catastrophic consequences in the re-emergence of infection and potential for a new outbreak.

3. Identification of visual loss known to occur at high rates as a result of uveitis following filovirus infection. Specialist treatment would be required, but the absence of a screening programme would necessarily mean patients did not receive any appropriate treatment [data not shown].

The risks of establishing this structured care environment were felt to be minimal, provided that significant costs (direct or indirect) were not incurred by patients or their families, and that stigma was reduced.

PICO

Population: Patients discharged from filovirus treatment centres.

Intervention: Structured post-discharge medical follow-up.

Comparator: Usual care.

Outcome Timeframe	**Study results and measurements**	**Comparator** Usual care	**Intervention** Structured post-discharge medical follow-up	**Certainty of the evidence** (Quality of evidence)	**Summary**
Patients with improved mental health as inferred from successful treatment of depression	(Randomized controlled) Follow up: Model based on effective screening for depression and initiation of SSRI antidepressant	**5**	**21** Difference: **16 more**	**Moderate** due to serious imprecision[a]	Structured follow-up probably improves mental health compared with no structured follow-up.

[a] **Imprecision: serious.** Uncertainty around rate of detection where structured follow-up does not take place.

Use of PPE by survivors working in treatment centres

Health and care workers who have recovered from filovirus disease and who work in a filovirus treatment centre should use PPE as outlined in *Infection prevention and control guideline for Ebola and Marburg disease (19)*.

Anecdotally, people who have recovered from filovirus have been employed in the capacity of caregivers during ongoing outbreaks. This has potential advantages in increasing the availability of carers, particularly for children admitted to a filovirus treatment centre without a guardian or parent. This need for continuous surveillance of young children has led to longer stays in the red zone. Some panel members acknowledged that this has in some cases led to the practice of such carers using "light" PPE compared with other non-survivor carers.

The panel discussed this discrepancy, and raised a number of levels of concern:

1. While immune responses, including antibodies, are raised following infection, this gives incomplete protection. It is certain that immunity wanes with time, but the exact dynamics are unclear, as is the degree of protection afforded by natural infection. The consequences of reinfection would be severe for the person.
2. The use of non-standard PPE could increase inequity and stigma amongst health and care workers.
3. The disruption of usual systems and standardized IPC messaging within treatment centres could be detrimental to outbreak control.
4. Survivors wearing less than full (optimal) PPE who re-enter and then leave a filovirus treatment centre may be a vehicle for virus transmission to their community.

The panel strongly requested more advocacy for innovations in PPE and treatment centre design to allow for improved comfort of all health workers, including survivors, and potential to enable longer stays in the red zone and improved visibility of patients needing constant care, such as young children.

Uncertainties and future research

Throughout discussion of the recommendations, the GDG were faced with a lack of direct evidence from filovirus disease outbreaks/cases. A number of strategically important questions were raised as priorities for future research, as below.

Pathophysiology and mechanistic studies

- Haematological derangements: conduct pathophysiological studies of clotting and bleeding mechanisms in human subjects.
- Immunological correlates: demonstrate and define the correlates of protection against reinfection to understand long-term immunity.

Clinical epidemiology and outcome determinants

- Stratified mortality analysis: determine mortality rates within treatment centres, stratified by disease severity, patient presentation timing and delay to care.
- Comparative virology: perform cross-virus comparisons (e.g. Ebola virus vs Sudan virus vs Marburg virus) of clinical outcomes while controlling for confounding variables.
- Risk factor identification: conduct systematic reviews of non-laboratory risk factors to improve triage and community-level screening.

Optimized supportive care and haemodynamic management

- Cardiovascular support: evaluate the relative safety and efficacy of epinephrine vs norepinephrine as primary vasopressors, and track patient outcomes following inotrope use for shock.
- Renal replacement therapy: how to identify patients who may benefit from dialysis/haemofiltration, and how this can be delivered safely in the context of limited resource and complex IPC requirements.
- Rational antimicrobial use:
  - describe bacterial co-infections in both severe and non-severe disease.
  - identify low-risk patient populations to evaluate the necessity and benefit of empirical antibiotic therapy.
- Haemorrhage management: develop high-quality clinical trials for bleeding therapeutics once mechanistic understanding and safety is established.

Operational design and implementation

- Dignified, patient-centred care: improve facility design to allow for the humane care of young children who are admitted without a caregiver inside the “red zone”.
- Risk-based PPE: investigate the potential for “lighter” PPE protocols using a risk-based approach to improve clinician dexterity and patient connection.

References[1]

1. WHO handbook for guideline development. Geneva: World Health Organization; 2014 (https://iris.who.int/handle/10665/75146). Licence: CC BY-NC-SA 3.0 IGO.
2. Kuhn JH, Adachi T, Adhikari NKJ, Arribas JR, Bah IE, Bausch DG et al. New filovirus disease classification and nomenclature. Nat Rev Microbiol. 2019;17:261–3 (https://doi.org/10.1038/s41579-019-0187-4).
3. Feldmann H, Sprecher A, Geisbert TW. Ebola. N Engl J Med. 2020;382:1832–42 (https://doi.org/10.1056/NEJMra1901594).
4. Marshall Lyon G, Mehta AK, Ribner BS. Clinical management of patients with Ebola virus disease in high-resource settings. Curr Top Microbiol Immunol. 2017;411:115–37 (https://doi.org/10.1007/82_2017_19).
5. Sprecher A, Van Herp M, Rollin PE. Clinical management of Ebola virus disease patients in low-resource settings. Curr Top Microbiol Immunol. 2017;411:93–113 (https://doi.org/10.1007/82_2017_18).
6. Frankfurter RG, Willet V, Richardson ET, Rutherford GW, Baller A, Kelly JD. Infection prevention and control studies for care of patients with suspected or confirmed filovirus disease in healthcare settings, with focus on Ebola and Marburg: an integrative review. BMJ Public Health. 2024;2:e000556 (https://doi.org/10.1136/bmjph-2023-000556).
7. Infection prevention and control and water, sanitation and hygiene in health facilities during Ebola or Marburg disease outbreaks: rapid assessment tool user guide. Geneva: World Health Organization; 2025 (https://iris.who.int/handle/10665/380798). Licence: CC BY-NC-SA 3.0 IGO.
8. Willet V, Dixit D, Fisher D, Bausch DG, Ogunsola F, Khabsa J et al. Summary of WHO infection prevention and control guideline for Ebola and Marburg disease: a call for evidence based practice. BMJ. 2024:2811 (https://doi.org/10.1136/bmj.p2811).
9. Steps to put on personal protective equipment (PPE) for Ebola/Marburg disease: coverall. Geneva: World Health Organization; 2024 (https://www.who.int/multi-media/details/steps-to-put-on-ppe-for-ebola-marburg-disease-coverall). Licence: CC BY-NC-SA 3.0 IGO.
10. Steps to remove personal protective equipment (PPE) for Ebola/Marburg disease: coverall. Geneva: World Health Organization; 2024 (https://doi.org/https://www.who.int/multi-media/details/steps-to-remove-ppe-for-ebola-marburg-disease-coverall). Licence: CC BY-NC-SA 3.0 IGO.
11. Guidance on regulations for the transport of infectious substances 2021-2022. Geneva: World Health Organization; 2021 (https://iris.who.int/handle/10665/339825). Licence: CC BY-NC-SA 3.0 IGO.
12. Izudi J, Bajunirwe F. Case fatality rate for Ebola disease, 1976-2022: a meta-analysis of global data. J Infect Public Health. 2024;17:25–34 (https://doi.org/10.1016/j.jiph.2023.10.020).
13. Risk communication and community engagement readiness and response toolkit: Ebola disease. Geneva: World Health Organization; 2025 (https://iris.who.int/handle/10665/381929). Licence: CC BY-NC-SA 3.0 IGO.
14. Ebola and Marburg treatment centres: facility design and construction standards for preparing for and responding to outbreaks. Geneva: World Health Organization; 2024 (https://iris.who.int/handle/10665/378261). Licence: CC BY-NC-SA 3.0 IGO.
15. Optimized supportive care for Ebola virus disease: clinical management standard operating procedures. Geneva: World Health Organization; 2019 (https://iris.who.int/handle/10665/325000). Licence: CC BY-NC-SA 3.0 IGO.

[1] All references were accessed 9 June 2026.

16. Therapeutics for Ebola virus disease. Geneva: World Health Organization; 2022 (https://iris.who.int/handle/10665/361697). Licence: CC BY-NC-SA 3.0 IGO.

17. FiloTREAT online training for the clinical management and operational response to filovirus disease [website]. Geneva: World Health Organization (https://whoacademy.org/coursewares/course-v1:WHOAcademy-Hosted+H0107EN+2025_Q1?from=discovery&source=edX).

18. Guidelines for the management of pregnant and breastfeeding women in the context of Ebola virus disease. Geneva: World Health Organization; 2020 (https://iris.who.int/handle/10665/330851). Licence: CC BY-NC-SA 3.0 IGO.

19. Infection prevention and control guideline for Ebola and Marburg disease. Geneva: World Health Organization; 2026 (https://iris.who.int/handle/10665/385879). Licence: CC BY-NC-SA 3.0 IGO.

20. How to conduct safe and dignified burial of a patient who has died from suspected or confirmed Ebola or Marburg virus disease: interim guidance. Geneva: World Health Organization; 2017 (https://iris.who.int/server/api/core/bitstreams/a93fddb2-243a-40ec-a0a0-27967bfb99ee/content). Licence: CC BY-NC-SA 3.0 IGO.

21. Diagnostic testing for Ebola and Marburg virus diseases: interim guidance. Geneva: World Health Organization; 2024 (https://iris.who.int/handle/10665/380073). Licence: CC BY-NC-SA 3.0 IGO.

22. WHO fact sheet: Ebola disease [website]. Geneva: World Health Organization; 2026 (https://www.who.int/news-room/fact-sheets/detail/ebola-disease).

23. WHO questions and answers: Ebola disease [website]. Geneva: World Health Organization (https://www.who.int/news-room/questions-and-answers/item/ebola-disease).

24. Ebola virus outbreak toolbox [website]. Geneva: World Health Organization (https://www.who.int/emergencies/outbreak-toolkit/disease-outbreak-toolboxes/ebola-and-marburg-virus-outbreak-toolbox).

25. Extraordinary meeting of the Strategic Advisory Group of Experts on Immunization on Ebola vaccination, May 2024: conclusions and recommendations. Geneva: World Health Organization; 2024 (https://iris.who.int/handle/10665/378109). Licence: CC BY-NC-SA 3.0 IGO.

26. Rutakumwa R, Ninsiima S, Settuba E, Kyohangirwe L, Mpango RS, Tusiime C et al. A qualitative study of Ebola survivors' psychological experiences of evacuation, treatment and community reintegration: lessons in holistic person-centred care from the 2022 outbreak in Uganda. PLoS Ment Health. 2025;2:e0000316 (https://doi.org/10.1371/journal.pmen.0000316).

27. James PB, Wardle J, Steel A, Adams J. Post-Ebola psychosocial experiences and coping mechanisms among Ebola survivors: a systematic review. Trop Med Int Health. 2019;24:671–91 (https://doi.org/10.1111/tmi.13226).

28. Bowles T, Trentino KM, Lloyd A, Trentino L, Jones G, Murray K et al. Outcomes in patients receiving continuous monitoring of vital signs on general wards: a systematic review and meta-analysis of randomised controlled trials. Digit Health. 2024;10:20552076241288826 (https://doi.org/10.1177/20552076241288826).

29. Evidence report - laboratory monitoring. Geneva: World Health Organization; 2026 (https://files.magicapp.org/guideline/529d5810-e79e-4b7a-b0e8-5fd936d440cd/files/Evidence_report_laboratory_monitoring_-_FINAL_r975881.docx).

30. Schieffelin JS, Shaffer JG, Goba A, Gbakie M, Gire SK, Colubri A et al. Clinical illness and outcomes in patients with Ebola in Sierra Leone. N Engl J Med. 2014;371:2092–100 (https://doi.org/10.1056/NEJMoa1411680).

31. Hunt L, Gupta-Wright A, Simms V, Tamba F, Knott V, Tamba K 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;15:1292–9 (https://doi.org/10.1016/S1473-3099(15)00144-9).

32. Vernet M-A, Reynard S, Fizet A, Schaeffer J, Pannetier D, Guedj J et al. Clinical, virological, and biological parameters associated with outcomes of Ebola virus infection in Macenta, Guinea. JCI Insight. 2017;2:e88864 (https://doi.org/10.1172/jci.insight.88864).

33. Dickson SJ, Clay KA, Adam M, Ardley C, Bailey MS, Burns DS et al. Enhanced case management can be delivered for patients with EVD in Africa: experience from a UK military Ebola treatment centre in Sierra Leone. J Infect. 2018;76:383–92 (https://doi.org/10.1016/j.jinf.2017.12.006).

34. Cournac JM, Karkowski L, Bordes J, Aletti M, Duron S, Janvier F et al. Rhabdomyolysis in Ebola virus disease. Results of an observational study in a treatment center in Guinea. Clin Infect Dis. 2016;62:19–23 (https://doi.org/10.1093/cid/civ779).

35. Rollin PE, Bausch DG, Sanchez A. Blood chemistry measurements and D-Dimer levels associated with fatal and nonfatal outcomes in humans infected with Sudan Ebola virus. J Infect Dis. 2007;196 Suppl 2:S364-371 (https://doi.org/10.1086/520613).

36. Kjaldgaard L, Claude KM, Mukadi-Bamuleka D, Kitenge-Omasumbu R, Dixit D, Edidi-Atani F et al. Virus kinetics and biochemical derangements among children with Ebolavirus disease. EClinicalMedicine. 2022;53:101638 (https://doi.org/10.1016/j.eclinm.2022.101638).

37. Kasereka MC, Mukadi-Bamuleka D, Kitenge-Omasumbu R, Edidi-Atani F, Kuamfumu MM, Mulangu S et al. Rhabdomyolysis, acute kidney injury, and mortality in Ebola virus disease: retrospective analysis of cases from the Eastern Democratic Republic of the Congo, 2019. J Infect Dis. 2024;230:e465–73 (https://doi.org/10.1093/infdis/jiae224).

38. Yeabah TO, Kaba I, Ramaswamy G, Dahal P, Delamou A, Vonhm BT et al. Factors associated with death in patients admitted with Ebola virus disease to Ebola treatment units in Guinea, Sierra Leone, and Liberia - December 2013 to March 2016. F1000Res. 2024;13:672 (https://doi.org/10.12688/f1000research.149612.2).

39. van Griensven J, Bah EI, Haba N, Delamou A, Camara BS, Olivier KJ-J et al. Electrolyte and metabolic disturbances in Ebola patients during a clinical trial, Guinea, 2015. Emerg Infect Dis. 2016;22:2120–7 (https://doi.org/10.3201/eid2212.161136).

40. Fitzpatrick G, Vogt F, Moi Gbabai OB, Decroo T, Keane M, De Clerck H et al. The contribution of Ebola viral load at admission and other patient characteristics to mortality in a Médecins Sans Frontières Ebola case management centre, Kailahun, Sierra Leone, June-October 2014. J Infect Dis. 2015;212:1752–8 (https://doi.org/10.1093/infdis/jiv304).

41. Crowe SJ, Maenner MJ, Kuah S, Erickson BR, Coffee M, Knust B et al. Prognostic indicators for Ebola patient survival. Emerg Infect Dis. 2016;22:217–23 (https://doi.org/10.3201/eid2202.151250).

42. Nsanzimana S, Remera E, Nkeshimana M, Westergaard RP, Firew T, Semakula M et al. Marburg virus disease in Rwanda, 2024 - public health and clinical responses. N Engl J Med. 2025;393:983–93 (https://doi.org/10.1056/NEJMoa2415816).

43. The selection and use of essential in vitro diagnostics: report of the fourth meeting of the WHO Strategic Advisory Group of Experts on in Vitro Diagnostics, 2022 (including the fourth WHO Model List of Essential In Vitro Diagnostics). Geneva: World Health Organization; 2023 (https://iris.who.int/handle/10665/373322). Licence: CC BY-NC-SA 3.0 IGO.

44. WHO Ebola Response Team, Aylward B, Barboza P, Bawo L, Bertherat E, Bilivogui P et al. Ebola virus disease in West Africa – the first 9 months of the epidemic and forward projections. N Engl J Med. 2014;371:1481–95 (https://doi.org/10.1056/NEJMoa1411100).

45. Uyeki TM, Mehta AK, Davey RT, Liddell AM, Wolf T, Vetter P et al. Clinical management of Ebola virus disease in the United States and Europe. N Engl J Med. 2016;374:636–46 (https://doi.org/10.1056/NEJMoa1504874).

46. Health worker Ebola infections in Guinea, Liberia and Sierra Leone: a preliminary report 21 May 2015. Geneva: World Health Organization; 2015 (https://iris.who.int/handle/10665/171823). Licence: CC BY-NC-SA 3.0 IGO.

47. Guideline: updates on the management of severe acute malnutrition in infants and children. Geneva: World Health Organization; 2013 (https://iris.who.int/handle/10665/95584). Licence: CC BY-NC-SA 3.0 IGO.

48. Williams EL, Hildebrand KL, McCormick SA, Bedel MJ. The effect of intravenous lactated Ringer's solution versus 0.9% sodium chloride solution on serum osmolality in human volunteers. Anesth Analg. 1999;88:999–1003 (https://doi.org/10.1097/00000539-199905000-00006).

49. Hydroxyethyl-starch solutions (HES) no longer to be used in patients with sepsis or burn injuries or in critically ill patients [news release]. European Medicines Agency; 2013 (https://www.ema.europa.eu/en/news/hydroxyethyl-starch-solutions-hes-should-no-longer-be-used-patients-sepsis-or-burn-injuries-or-critically-ill-patients-cmdh-endorses-prac-recommendations).

50. Lewis SR, Pritchard MW, Evans DJ, Butler AR, Alderson P, Smith AF et al. Colloids versus crystalloids for fluid resuscitation in critically ill people. Cochrane Database Syst Rev. 2018;8:CD000567 (https://doi.org/10.1002/14651858.CD000567.pub7).

51. Hammond NE, Zampieri FG, Di Tanna GL, Garside T, Adigbli D, Cavalcanti AB et al. Balanced crystalloids versus saline in critically ill adults - a systematic review with meta-analysis. NEJM Evid. 2022;1:EVIDoa2100010 (https://doi.org/10.1056/EVIDoa2100010).

52. Zampieri FG, Cavalcanti AB, Di Tanna GL, Damiani LP, Hammond NE, Machado FR et al. Balanced crystalloids versus saline for critically ill patients (BEST-Living): a systematic review and individual patient data meta-analysis. Lancet Respir Med. 2024;12:237–46 (https://doi.org/10.1016/S2213-2600(23)00417-4).

53. McIntyre L, Fergusson D, McArdle T, English S, Cook DJ, Fox-Robichaud AE et al. A crossover trial of hospital-wide lactated Ringer's solution versus normal saline. N Engl J Med. 2025;393:660–70 (https://doi.org/10.1056/NEJMoa2416761).

54. Jacquet-Lagrèze M, Pernollet A, Kattan E, Ait-Oufella H, Chesnel D, Ruste M et al. Prognostic value of capillary refill time in adult patients: a systematic review with meta-analysis. Crit Care. 2023;27:473 (https://doi.org/10.1186/s13054-023-04751-9).

55. Fleming S, Gill P, Jones C, Taylor JA, Van Den Bruel A, Heneghan C, et al. The diagnostic value of capillary refill time for detecting serious illness in children: a systematic review and meta-analysis. PLoS ONE. 2015;10:e0138155 (https://doi.org/10.1371/journal.pone.0138155).

56. Lamprea S, Fernández-Sarmiento J, Barrera S, Mora A, Fernández-Sarta JP, Acevedo L. Capillary refill time in sepsis: a useful and easily accessible tool for evaluating perfusion in children. Front Pediatr. 2022;10:1035567 (https://doi.org/10.3389/fped.2022.1035567).

57. Qin C, Ma D, Pang L, Hu M, Lin S, Zhou Z et al. Prognostic factors of sepsis: a systematic review and meta-analysis. BMC Infect Dis. 2025;25:1670 (https://doi.org/10.1186/s12879-025-12094-9).

58. Andersson M, Fröderberg Schooner K, Karlsson Werther V, Karlsson T, De Geer L, Wilhelms DB et al. Prehospital lactate analysis in suspected sepsis improves detection of patients with increased mortality risk: an observational study. Crit Care. 2025;29:38 (https://doi.org/10.1186/s13054-024-05225-2).

59. Hernandez G, Bellomo R, Bakker J. The ten pitfalls of lactate clearance in sepsis. Intensive Care Med. 2019;45:82–5 (https://doi.org/10.1007/s00134-018-5213-x).

60. Hernández G, Ospina-Tascón GA, Damiani LP, Estenssoro E, Dubin A, Hurtado J et al. Effect of a resuscitation strategy targeting peripheral perfusion status vs serum lactate levels on 28-day mortality among patients with septic shock: the ANDROMEDA-SHOCK randomized clinical trial. JAMA. 2019;321:654 (https://doi.org/10.1001/jama.2019.0071).

61. The ANDROMEDA-SHOCK-2 Investigators for the ANDROMEDA Research Network, Spanish Society of Anesthesiology, Reanimation and Pain Therapy (SEDAR), and Latin American Intensive Care Network (LIVEN), Pálizas F, Lattanzio B, Durandal N, Alonso ME, Duque J et al. Personalized hemodynamic resuscitation targeting capillary refill time in early septic shock: the ANDROMEDA-SHOCK-2 randomized clinical trial. JAMA. 2025;334:1988 (https://doi.org/10.1001/jama.2025.20402).

62. van Genderen ME, Paauwe J, de Jonge J, van der Valk RJP, Lima A, Bakker J et al. Clinical assessment of peripheral perfusion to predict postoperative complications after major abdominal surgery early: a prospective observational study in adults. Crit Care. 2014;18:R114 (https://doi.org/10.1186/cc13905).

63. Claassen JAHR, Thijssen DHJ, Panerai RB, Faraci FM. Regulation of cerebral blood flow in humans: physiology and clinical implications of autoregulation. Physiol Rev. 2021;101:1487–559 (https://doi.org/10.1152/physrev.00022.2020).

64. Russell JA. Vasopressor therapy in critically ill patients with shock. Intensive Care Med. 2019;45:1503–17 (https://doi.org/10.1007/s00134-019-05801-z).

65. Liu L, Chao Y, Wang X, Chinese Critical Ultrasound Study Group. Shock resuscitation - the necessity and priority of renal blood perfusion assessment. Aging Dis. 2022;13:1056–62 (https://doi.org/10.14336/AD.2022.0105).

66. Varpula M, Tallgren M, Saukkonen K, Voipio-Pulkki L-M, Pettilä V. Hemodynamic variables related to outcome in septic shock. Intensive Care Med. 2005;31:1066–71 (https://doi.org/10.1007/s00134-005-2688-z).

67. Maheshwari K, Nathanson BH, Munson SH, Khangulov V, Stevens M, Badani H et al. The relationship between ICU hypotension and in-hospital mortality and morbidity in septic patients. Intensive Care Med. 2018;44:857–67 (https://doi.org/10.1007/s00134-018-5218-5).

68. Dünser MW, Takala J, Ulmer H, Mayr VD, Luckner G, Jochberger S et al. Arterial blood pressure during early sepsis and outcome. Intensive Care Med. 2009;35:1225–33 (https://doi.org/10.1007/s00134-009-1427-2).

69. Meng L, Sun Y, Rasmussen M, Libiran NBS, Naiken S, Meacham KS et al. Lassen's cerebral autoregulation plot revisited and validated 65 years later: impacts of vasoactive drug treatment on cerebral blood flow. Anesth Analg. 2025;140:1426–38 (https://doi.org/10.1213/ANE.0000000000007280).

70. Poukkanen M, Wilkman E, Vaara ST, Pettilä V, Kaukonen K-M, Korhonen A-M et al. Hemodynamic variables and progression of acute kidney injury in critically ill patients with severe sepsis: data from the prospective observational FINNAKI study. Crit Care. 2013;17:R295 (https://doi.org/10.1186/cc13161).

71. Badin J, Boulain T, Ehrmann S, Skarzynski M, Bretagnol A, Buret J et al. Relation between mean arterial pressure and renal function in the early phase of shock: a prospective, explorative cohort study. Crit Care. 2011;15:R135 (https://doi.org/10.1186/cc10253).

72. Reinikainen M, Delamarre L, Blaser AR, Hollenberg SM, Lobo SM, Rezende E et al. Association of noradrenaline dose with mortality in critically ill patients: a systematic review and dose-response meta-analysis. Crit Care. 2025;29:498 (https://doi.org/10.1186/s13054-025-05717-9).

73. Boyd JH, Forbes J, Nakada T, Walley KR, Russell JA. Fluid resuscitation in septic shock: a positive fluid balance and elevated central venous pressure are associated with increased mortality. Crit Care Med. 2011;39:259–65 (https://doi.org/10.1097/CCM.0b013e3181feeb15).

74. Sadaka F, Juarez M, Naydenov S, O'Brien J. Fluid resuscitation in septic shock: the effect of increasing fluid balance on mortality. J Intensive Care Med. 2014;29:213–7 (https://doi.org/10.1177/0885066613478899).

75. Sivapalan P, Ellekjaer KL, Jessen MK, Meyhoff TS, Cronhjort M, Hjortrup PB et al. Lower vs higher fluid volumes in adult patients with sepsis: an updated systematic review with meta-analysis and trial sequential analysis. Chest. 2023;164:892–912 (https://doi.org/10.1016/j.chest.2023.04.036).

76. National Heart, Lung, and Blood Institute Prevention and Early Treatment of Acute Lung Injury Clinical Trials Network, Shapiro NI, Douglas IS, Brower RG, Brown SM, Exline MC et al. Early restrictive or liberal fluid management for sepsis-induced hypotension. N Engl J Med. 2023;388:499–510 (https://doi.org/10.1056/NEJMoa2212663).

77. Ahn C, Yu G, Shin TG, Cho Y, Park S, Suh GY. Comparison of early and late norepinephrine administration in patients with septic shock. Chest. 2024;166:1417–30 (https://doi.org/10.1016/j.chest.2024.05.042).

78. Harley A, George S, Phillips N, King M, Long D, Keijzers G et al. Resuscitation with early adrenaline infusion for children with septic shock: a randomized pilot trial. Pediatr Crit Care Med. 2024;25:106–17 (https://doi.org/10.1097/PCC.0000000000003351).

79. Parker MJ, Choong K, Fox-Robichaud A, Liaw PC, Thabane L, Canadian Critical Care Trials Group and the Canadian Critical Care Translational Biology Group. The SQUEEZE pilot trial: a trial to determine whether septic shock reversal is quicker in pediatric patients randomized to an early goal directed fluid-sparing strategy vs. usual care. Pilot Feasibility Stud. 2025;11:153 (https://doi.org/10.1186/s40814-025-01731-4).

80. Iramain R, Ortiz J, Jara A, Bogado N, Morinigo R, Cardozo L et al. Fluid Resuscitation and inotropic support in patients with septic shock treated in pediatric emergency department: an open-label trial. Cureus. 2022;14:e30029 (https://doi.org/10.7759/cureus.30029).

81. Braga A, De Melo HK, Paiva G, Rodrigues GM, Callado GY, Araujo Júnior E et al. Advances and challenges in obstetric intensive care medicine. J Clin Med. 2026;15:1487 (https://doi.org/10.3390/jcm15041487).

82. Leong TD, Mpofu R, Dadan S, Cohen K, Dawood H, Kredo T et al. A systematic review and meta-analysis of noradrenaline compared to adrenaline in the management of septic shock. Afr J Emerg Med. 2025;15:100881 (https://doi.org/10.1016/j.afjem.2025.05.005).

83. Banothu KK, Sankar J, Kumar UV, Gupta P, Pathak M, Jat KR et al. A randomized controlled trial of norepinephrine plus dobutamine versus epinephrine as first-line vasoactive agents in children with fluid refractory cold septic shock. Crit Care Explor. 2022;5:e0815 (https://doi.org/10.1097/CCE.0000000000000815).

84. Eisenberg MA, Georgette N, Baker AH, Priebe GP, Monuteaux MC. Epinephrine vs norepinephrine as initial treatment in children with septic shock. JAMA Netw Open. 2025;8:e254720 (https://doi.org/10.1001/jamanetworkopen.2025.4720).

85. Avni T, Lador A, Lev S, Leibovici L, Paul M, Grossman A. Vasopressors for the treatment of septic shock: systematic review and meta-analysis. PLoS One. 2015;10:e0129305 (https://doi.org/10.1371/journal.pone.0129305).

86. Cheng L, Yan J, Han S, Chen Q, Chen M, Jiang H et al. Comparative efficacy of vasoactive medications in patients with septic shock: a network meta-analysis of randomized controlled trials. Crit Care. 2019;23:168 (https://doi.org/10.1186/s13054-019-2427-4).

87. Evidence report central venous vs peripheral venous access. Geneva: World Health Organization; 2026 (https://files.magicapp.org/guideline/529d5810-e79e-4b7a-b0e8-5fd936d440cd/files/Evidence_report_central_versus_peripheral_venous_line_-_FINAL_r975880.docx).

88. Wu W, Yang X, Kou L. Extravasation, thrombosis, and infection with vasopressor infusion through peripheral intravenous catheters: a systematic review and meta-analysis. Cardiovasc Diagn Ther. 2025;15:847–60 (https://doi.org/10.21037/cdt-2025-290).

89. Boulet N, Pensier J, Occean B-V, Peray PF, Mimoz O, Rickard CM et al. Central venous catheter-related infections: a systematic review, meta-analysis, trial sequential analysis and meta-regression comparing ultrasound guidance and landmark technique for insertion. Crit Care. 2024;28:378 (https://doi.org/10.1186/s13054-024-05162-0).

90. Brass P, Hellmich M, Kolodziej L, Schick G, Smith AF. Ultrasound guidance versus anatomical landmarks for internal jugular vein catheterization. Cochrane Database Syst Rev. 2015;1:CD006962 (https://doi.org/10.1002/14651858.CD006962.pub2).

91. Ricard J-D, Salomon L, Boyer A, Thiery G, Meybeck A, Roy C et al. Central or peripheral catheters for initial venous access of ICU patients: a randomized controlled trial. Crit Care Med. 2013;41:2108–15 (https://doi.org/10.1097/CCM.0b013e31828a42c5).

92. Delaney A, Finnis M, Bellomo R, Udy A, Jones D, Keijzers G et al. Initiation of vasopressor infusions via peripheral versus central access in patients with early septic shock: a retrospective cohort study. Emerg Med Australas. 2020;32:210–9 (https://doi.org/10.1111/1742-6723.13394).

93. Munroe ES, Co IN, Douglas I, Hyzy R, Khan A, Nelson K et al. Peripheral vasopressor use in early sepsis-induced hypotension. JAMA Netw Open. 2025;8:e2529148 (https://doi.org/10.1001/jamanetworkopen.2025.29148).

94. Stolz A, Efendy R, Apte Y, Craswell A, Lin F, Ramanan M. Safety and efficacy of peripheral versus centrally administered vasopressor infusion: a single-centre retrospective observational study. Aust Crit Care. 2022;35:506–11 (https://doi.org/10.1016/j.aucc.2021.08.005).

95. Asher E, Karameh H, Nassar H, Yosefy C, Marmor D, Perel N et al. Safety and outcomes of peripherally administered vasopressor infusion in patients admitted with shock to an intensive cardiac care unit - a single-center prospective study. J Clin Med. 2023;12:5734 (https://doi.org/10.3390/jcm12175734).

96. Munroe ES, Heath ME, Eteer M, Gershengorn HB, Horowitz JK, Jones J et al. Use and outcomes of peripheral vasopressors in early sepsis-induced hypotension across Michigan hospitals: a retrospective cohort study. Chest. 2024;165:847–57 (https://doi.org/10.1016/j.chest.2023.10.027).

97. The WHO AWaRe (Access, Watch, Reserve) antibiotic book. Geneva: World Health Organization; 2022 (https://iris.who.int/handle/10665/365135). Licence: CC BY-NC-SA 3.0 IGO.

98. Evidence report - antibiotics in filovirus disease. Geneva: World Health Organization; 2026 (https://files.magicapp.org/guideline/529d5810-e79e-4b7a-b0e8-5fd936d440cd/files/Evidence_report_antibiotics_FVD_-_FINAL_r975879.docx).

99. Aluisio AR, Perera SM, Yam D, Garbern S, Peters JL, Abel L et al. Association between treatment with oral third-generation cephalosporin antibiotics and mortality outcomes in Ebola virus disease: a multinational retrospective cohort study. Trop Med Int Health. 2020;25:433–41 (https://doi.org/10.1111/tmi.13369).

100. Kalema J, de Weggheleire A, de Smet B. Implementation of blood cultures in the Ebola virus disease care response in North Kivu, Democratic Republic of the Congo: results of a pilot study. 2021.

101. Curran J, Lo J, Leung V, Brown K, Schwartz KL, Daneman N, et al. Estimating daily antibiotic harms: an umbrella review with individual study meta-analysis. Clin Microbiol Infect. 2022;28:479–90 (https://doi.org/10.1016/j.cmi.2021.10.022).

102. Guidance on implementing patient blood management to improve global blood health status. Geneva: World Health Organization; 2024 (https://iris.who.int/handle/10665/380784). Licence: CC BY-NC-SA 3.0 IGO.

103. Guidance on ensuring a sufficient supply of safe blood and blood components during emergencies. Geneva: World Health Organization; 2023 (https://iris.who.int/handle/10665/366870). Licence: CC BY-NC-SA 3.0 IGO.

104. Safe blood and blood products. Guidelines and principles for safe blood transfusion practice - introduction. Geneva: World Health Organization; 2009 (https://cdn.who.int/media/docs/default-source/blood-transfusion-safety/guidelines-and-principles-for-safe-blood-transfudion-practice.pdf).

105. Fouche PF, Stein C, Nichols M, Meadley B, Bendall JC, Smith K et al. Tranexamic acid for traumatic injury in the emergency setting: a systematic review and bias-adjusted meta-analysis of randomized controlled trials. Ann Emerg Med. 2024;83:435–45 (https://doi.org/10.1016/j.annemergmed.2023.10.004).

106. Delgado LM, Pompeu BF, Martins GHA, Azevedo ML, Pasqualotto E, Chulam TC et al. Perioperative use of tranexamic acid in general surgery: a systematic review and meta-analysis. JAMA Surg. 2026;161:179–87 (https://doi.org/10.1001/jamasurg.2025.5498).

107. Ker K, Sentilhes L, Shakur-Still H, Madar H, Deneux-Tharaux C, Saade G et al. Tranexamic acid for postpartum bleeding: a systematic review and individual patient data meta-analysis of randomised controlled trials. Lancet. 2024;404:1657–67 (https://doi.org/10.1016/S0140-6736(24)02102-0).

108. Ali A, Gruen RL, Bernard SA, Burns B, Forbes AB, Gantner DC et al. Tranexamic acid timing and mortality impact after trauma. Ann Emerg Med. 2026;87:83–9 (https://doi.org/10.1016/j.annemergmed.2025.06.609).

109. Napolitano LM. Prehospital tranexamic acid: what is the current evidence? Trauma Surg Acute Care Open. 2017;2:e000056 (https://doi.org/10.1136/tsaco-2016-000056).

110. Vine V, Scott DP, Feldmann H. Ebolavirus: an overview of molecular and clinical pathogenesis. Methods Mol Biol. 2017;1628:39–50 (https://doi.org/10.1007/978-1-4939-7116-9_3).

111. Hunt BJ. Bleeding and coagulopathies in critical care. N Engl J Med. 2014;370:847–59 (https://doi.org/10.1056/NEJMra1208626).

112. Levi M, Toh CH, Thachil J, Watson HG. Guidelines for the diagnosis and management of disseminated intravascular coagulation. Br J Haematol. 2009;145:24–33 (https://doi.org/10.1111/j.1365-2141.2009.07600.x).

113. Consolidated guidelines for the prevention, diagnosis and treatment of postpartum haemorrhage. Geneva: World Health Organization; 2025 (https://iris.who.int/handle/10665/382923). Licence: CC BY-NC-SA 3.0 IGO.

114. Djoudjou T, Alamri O, Aljuwayr A, Fakieh A, Aljared A, Almalik A et al. Intravenous tranexamic acid in gastrointestinal bleeding: a systematic review and meta-analysis of randomized controlled trials. Am J Emerg Med. 2025;97:175–82 (https://doi.org/10.1016/j.ajem.2025.07.050).

115. CRASH-2 collaborators, Roberts I, Shakur H, Afolabi A, Brohi K, Coats T et al. The importance of early treatment with tranexamic acid in bleeding trauma patients: an exploratory analysis of the CRASH-2 randomised controlled trial. Lancet. 2011;377:1096–101, 1101.e1-2 (https://doi.org/10.1016/S0140-6736(11)60278-X).

116. Adepoju VA, Adnani QES, Adeniyi MO. Tranexamic acid for postpartum haemorrhage in low-, middle-, and high-income countries: an integrative review aligned with the WHO PPH Roadmap (2023–2030). Women. 2025;5:10 (https://doi.org/10.3390/women5010010).

117. Roberts I, Murphy MF, Moonesinghe R, Grocott MPW, Kalumbi C, Sayers R et al. Wider use of tranexamic acid to reduce surgical bleeding could benefit patients and health systems. BMJ. 2024;385:e079444 (https://doi.org/10.1136/bmj-2024-079444).

118. WHO recommendation on tranexamic acid for the treatment of postpartum haemorrhage. Geneva: World Health Organization; 2017 (https://iris.who.int/handle/10665/259374). Licence: CC BY-NC-SA 3.0 IGO.

119. WOMAN Trial Collaborators. Effect of early tranexamic acid administration on mortality, hysterectomy, and other morbidities in women with post-partum haemorrhage (WOMAN): an international, randomised, double-blind, placebo-controlled trial. Lancet. 2017;389:2105–16 (https://doi.org/10.1016/S0140-6736(17)30638-4).

120. Comprehensive mental health action plan 2013-2030. Geneva: World Health Organization; 2021 (https://iris.who.int/handle/10665/345301). Licence: CC BY-NC-SA 3.0 IGO.

121. Arroll B, Elley CR, Fishman T, Goodyear-Smith FA, Kenealy T, Blashki G et al. Antidepressants versus placebo for depression in primary care. Cochrane Database Syst Rev. 2009;2009:CD007954 (https://doi.org/10.1002/14651858.CD007954).

122. Hengartner MP, Plöderl M. Estimates of the minimal important difference to evaluate the clinical significance of antidepressants in the acute treatment of moderate-to-severe depression. BMJ Evid Based Med. 2022;27:69–73 (https://doi.org/10.1136/bmjebm-2020-111600).

123. Mental Health Gap Action Programme (mhGAP) guideline for mental, neurological and substance use disorders. Geneva: World Health Organization; 2023 (https://iris.who.int/handle/10665/381088). Licence: CC BY-NC-SA 3.0 IGO.

124. Muwonge H, Nasimiyu C, Bakamutumaho B, Elyanu P, Joloba ML, Situma S et al. Long-term clinical sequelae among Sudan ebolavirus disease survivors 2 years post-infection: a matched cohort study. BMC Med. 2025;23:432 (https://doi.org/10.1186/s12916-025-04271-z).

125. Thorson AE, Deen GF, Bernstein KT, Liu WJ, Yamba F, Habib N, et al. Persistence of Ebola virus in semen among Ebola virus disease survivors in Sierra Leone: a cohort study of frequency, duration, and risk factors. PLoS Med. 2021;18:e1003273 (https://doi.org/10.1371/journal.pmed.1003273).

126. Lieberman Lawry L, Stroupe Kannappan N, Canteli C, Clemmer W. Cross-sectional study of mental health and sexual behaviours for Ebola Survivors in Beni, Butembo and Katwa health zones of the Democratic Republic of Congo. BMJ Open. 2022;12:e052306 (https://doi.org/10.1136/bmjopen-2021-052306).

127. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008;336:924–6 (https://doi.org/10.1136/bmj.39489.470347.AD).

128. Hirano Y, Miyoshi Y, Kondo Y, Okamoto K, Tanaka H. Liberal versus restrictive red blood cell transfusion strategy in sepsis or septic shock: a systematic review and meta-analysis of randomized trials. Crit Care. 2019;23:262 (https://doi.org/10.1186/s13054-019-2543-1).

129. Kotani Y, Belletti A, D'Amico F, Bonaccorso A, Wieruszewski PM, Fujii T et al. Non-adrenergic vasopressors for vasodilatory shock or perioperative vasoplegia: a meta-analysis of randomized controlled trials. Crit Care. 2024;28:439 (https://doi.org/10.1186/s13054-024-05212-7).

130. Permpikul C, Tongyoo S, Viarasilpa T, Trainarongsakul T, Chakorn T, Udompanturak S. Early Use of Norepinephrine in Septic Shock Resuscitation (CENSER). A randomized trial. Am J Respir Crit Care Med. 2019;199:1097–105 (https://doi.org/10.1164/rccm.201806-1034OC).

World Health Organization
Avenue Appia 20
CH-1211 Geneva 27
Switzerland