Optimizing supportive care for clinical trials

Importance of studies to understand pathophysiology and to optimize clinical care and SOPs for outbreaks and public health emergencies

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Introduction

- *Standard of care (SOC)* is the care that is appropriate for specific disease or condition.
  - Disease characteristics, natural history/progression, complications and outcomes
  - Based on scientific evidence representing most effective and safest interventions/treatments
- *Optimized supportive care* is a subset of the SOC
  - Fundamental clinical interventions such as triage, monitoring, electrolyte management, nutrition and IV fluid therapy that need to be optimized and standardized in resource constrained environments

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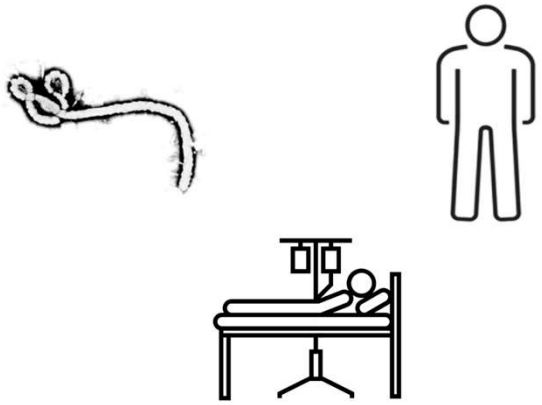
Complex interplay between host, pathogen and care



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What is optimized supportive care in clinical trial context?

ORIGINAL ARTICLE

Tecovirimat for Clade I MPXV Infection in the Democratic Republic of Congo

Author: The PALM007 Writing Group Author Info & Affiliations

Published April 16, 2025 | N Engl J Med 2025;392:1484-1496 | DOI: 10.1056/NEJMoa2412439 | VOL. 392 NO. 15

Methods

Patients were evaluated by site clinicians daily throughout hospitalization for mpox-related signs and symptoms, complications, and abnormalities in laboratory test results. Malnutrition status (severe acute, moderate acute, or none) was assessed at baseline and managed daily throughout hospitalization (Table S2 in the Supplementary Appendix, available at NEJM.org) by site clinicians and nutritionists.

All patients received supportive care, including symptom relief, nutritional support, skin care, and oropharyngeal care. When indicated, intravenous fluid, correction of hypoglycemia and electrolyte abnormalities, blood transfusion, antimalarial agents, broad-spectrum antibiotics, and antifungal treatment were provided. All participants who did not require treatment with broader-spectrum antibiotics received prophylactic treatment with cloxacillin.

- Overall mortality in study was 1.7% *regardless of whether they received the therapeutic intervention or not*, which was much lower than mpox case fatality rate in all reported mpox (4.6%)*
- Concluding that better outcomes can be achieved with high quality aggressive, supportive care delivered when patients were hospitalized in the study. May not be easily delivered in less constrained settings or in outpatient settings

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* case fatality rate as of end 2023
https://www.who.int/docs/default-source/coronaviruse/situation-reports/mpox_external-situation-report-30.pdf

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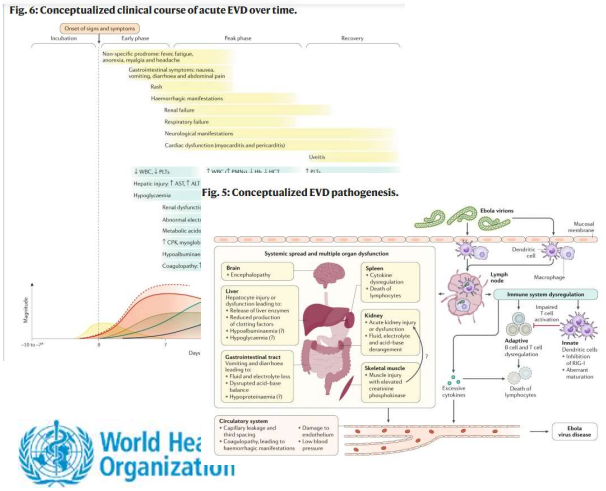
Developing the standard of care for FVD

Ebola virus disease | Nature Reviews Disease Primers

Case Series of Patients with Marburg Virus Disease, Equatorial Guinea, 2023



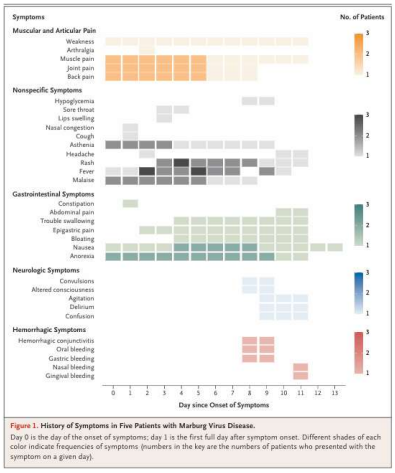


Figure 1. History of Symptoms in Five Patients with Marburg Virus Disease.
Day 0 is the day of the onset of symptoms; day 1 is the first full day after symptom onset. Different shades of each color indicate frequencies of symptoms (numbers in the key are the numbers of patients who presented with the symptom on a given day).

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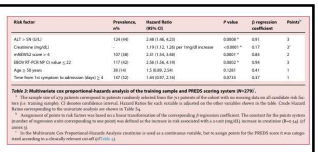
Independent risk factors for mortality?

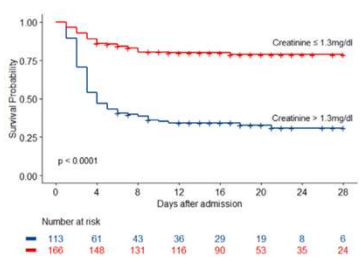


Development of the PREDS score to predict in-hospital mortality of patients with Ebola virus disease under advanced supportive care: Results from the EVISTA cohort in the Democratic Republic of the Congo

Organ Failure

ALT > 5N HR 2.48 (1.46, 4.23)

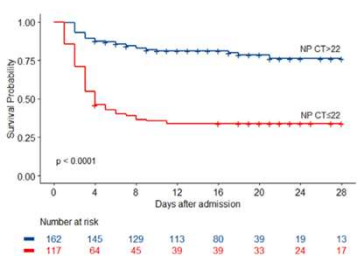
Creatinine (mg/dl)



Viral Load

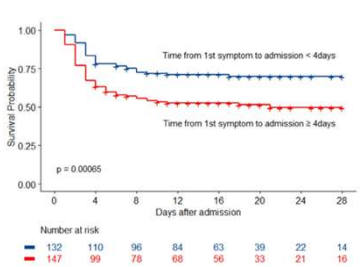
Ct < 22 HR 2.56 (1.56, 4.19)

EBOV Nucleoproteine (Ct value)



Time to admission

Time for 1st symptom to admission (days)



Slide courtesy of Dr William Fischer

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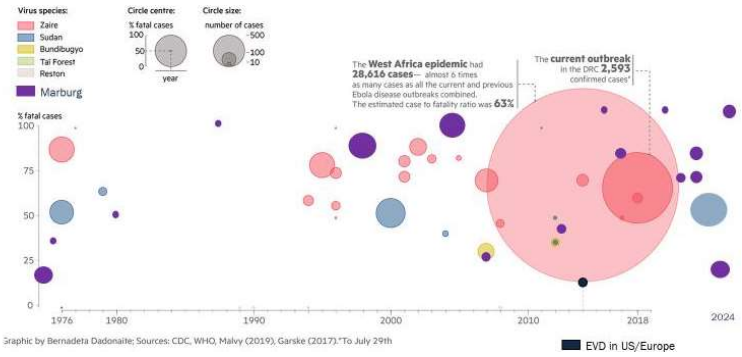
What is driving morbidity and mortality?

Case Fatality Ratio (CFR) during outbreaks can vary widely, not just between outbreaks but also within outbreaks

Adapted slide courtesy of Dr William Fischer
Filovirus outbreaks variability in size, frequency over time and mortality



WHO VHF tracker 2016 - 2025

Disease	CFR (95% CI)
EVD	65.1% (63.5 -66.6%)
MVD	55.6% (46.9 – 63.3%)
SVD	45.5% (38 – 53.1%)

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Deeper dive into morbidity and mortality

West Africa Ebola Virus Disease outbreak

Conakry, Guinea: CFR 43.2%

- 76% IV access, 3% received oxygen

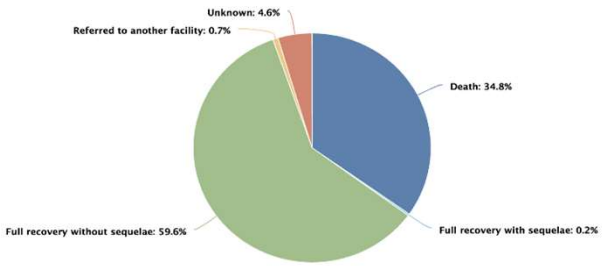
Clinical Presentation of Patients with Ebola Virus Disease in Conakry, Guinea

US and Europe: CFR 18. 5%

- All patients had IV access, 70% received oxygen, 30% vasopressors, 19% renal replacement therapy, 33% mechanical ventilation

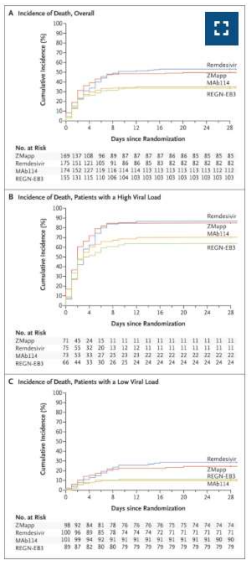
Clinical Management of Ebola Virus Disease in the United States and Europe | New England Journal of Medicine

North Kivu 2018-19 EVD outbreak



A Randomized, Controlled Trial of Ebola Virus Disease Therapeutics
New England Journal of Medicine

- All enrollees received standard of care (IV fluids, correction electrolytes)
- Treatment with REG-EB3 and MaB114 reduced mortality.
- As low as 10% in patients treated with low viral load.



Cumulative Incidence of Death.

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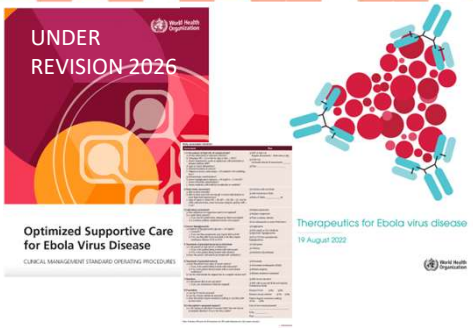
What is optimized standard of care for FVD?



Aims to optimize, standardize and reduce variability in care across the treatment units and outbreaks

Includes fundamental/ foundational principles such as:

- Triage
- Clinical monitoring (i.e. vital signs)
- Clinical laboratory monitoring
- Treatment of dehydration, hypoglycemia, hyperkalemia, nutrition, etc.
- Intravenous access (IV) and fluids

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What is optimized standard of care for FVD?

- More advanced supportive care interventions largely based on indirect evidence generated from sepsis, not pathogen specific, and include:
  - Management of septic shock (fluid type and quantities, vasopressors)
- Areas of uncertainty:
  - amount of fluid therapy in shock and severe dehydration,
  - timing and dose of RRT,
  - escalation of oxygen therapy,
  - role of corticosteroids

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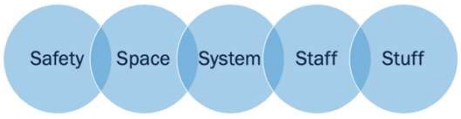
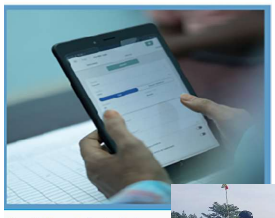
Enabling the delivery of optimized standards of care…health workforce and logistics





Strategic stockpile of medical, IPC and research kits for FVD

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INITIATE²

Infectious disease treatment module (IDTM) rapidly deployable

Infection prevention and control guideline for Ebola and Marburg disease

August 2023

26 March 2025 | Departmental update

WHO Launches Online Training to Strengthen Filovirus Outbreak Response

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Lesson 1: Generate evidence , collect standardized data

- Understanding of symptoms, risk factors, disease progression, complications and outcomes
- Identifies areas to focus our outbreak efforts (clinical management, health logistics, etc.)
- Identifies areas that need further investigation
- Enables monitoring and quality improvement (KPIs)
- Supports implementation of MEURI of investigational product use
- Serves “on-ramp” to randomized clinical trials

WHO Global Clinical Platform for Viral hemorrhagic fever

Data for public health response

How to register

The WHO Global Clinical Platform

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Lesson 2: Standards evolve over time…living guidelines stay up to date with evidence generation

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Conclusion

- Optimizing the standard of care aims to bring equity in access to quality (safe and effective) care during outbreaks and or health emergencies.
- Any use of investigational products, including clinical trials, should ensure optimized supportive care to maximize patient survival and ensure the best conditions for comparing treatment alternatives (through reducing inter-site variability of outcomes)

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Optimizing supportive care:

Updated WHO clinical guidelines with OSoC interventions

Guidelines that can be adapted into national protocols, trainings and tools.

Compilation of research gaps and questions to energize more collaborative research in this space

Impact improved quality of life and lives saved in patients with filovirus

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Developing the standard of care for FVD

[Ebola virus disease | Nature Reviews Disease Primers]

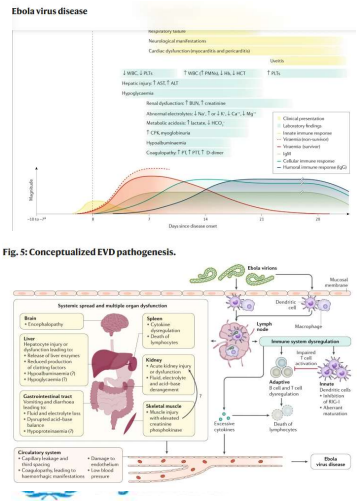
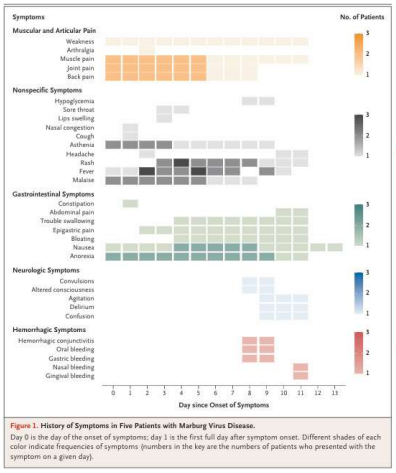


Fig. 5: Conceptualized EVD pathogenesis.

[Case Series of Patients with Marburg Virus Disease, Equatorial Guinea, 2023]



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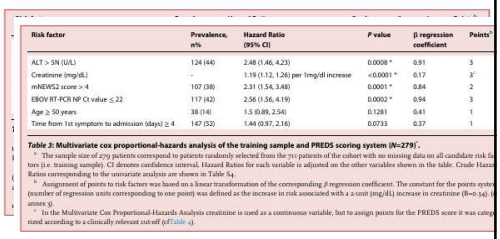

Risk factor	Prevalence, n%	Hazard Ratio (95% CI)	P value	β regression coefficient	Points*
ALT > SN (ULN)	124 (44)	2.48 (1.46, 4.23)	0.0008 *	0.91	3
Creatinine (mg/dL)	-	1.19 (1.12, 1.26) per 1mg/dl increase	<0.0001 *	0.17	3^
mNEWS2 score > 4	107 (38)	2.31 (1.54, 3.48)	0.0001 *	0.84	2
EBOV RT-PCR NP Ct value ≤ 22	117 (42)	2.56 (1.56, 4.19)	0.0002 *	0.94	3
Age ≥ 50 years	38 (14)	1.5 (0.89, 2.54)	0.1281	0.41	1
Time from 1st symptom to admission (days) ≥ 4	147 (52)	1.44 (0.97, 2.16)	0.0733	0.37	1

Table 3: Multivariate cox proportional-hazards analysis of the training sample and PREDS scoring system (N=279)[†].

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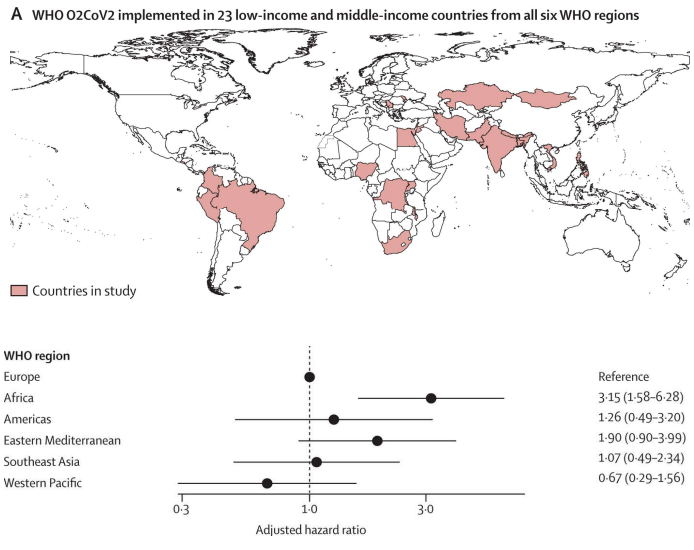
Uncertainties in optimizing supportive care

- COVID-19 example:
  - Oxygen therapy for hypoxemia but variability in mortality in patients on oxygen across different regions and times
  - O2COV2 study showed in LMIC, specifically AFRO
  - WHO Go2Repsiratory collaborative addressing these uncertainties through research…

JR1



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Slide 18

JR1 [@DIAZ, Janet Victoria] - wasn't sure what this meant, but have put forest plot of mortality by region on the right
Jamie Rylance, 2026-04-21T16:19:29.817