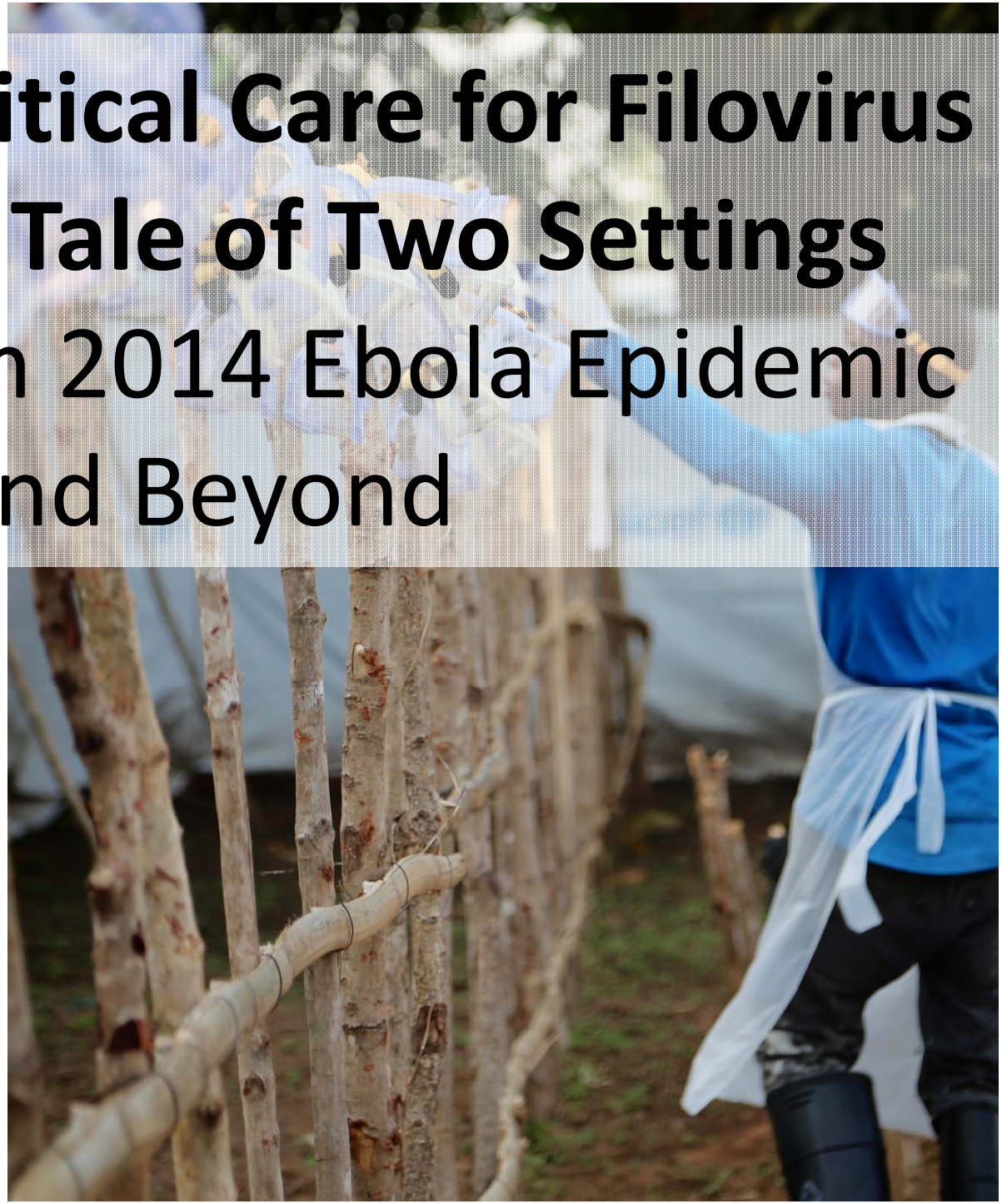
Improving Critical Care for Filovirus Patients: A Tale of Two Settings

Lessons from 2014 Ebola Epidemic and Beyond



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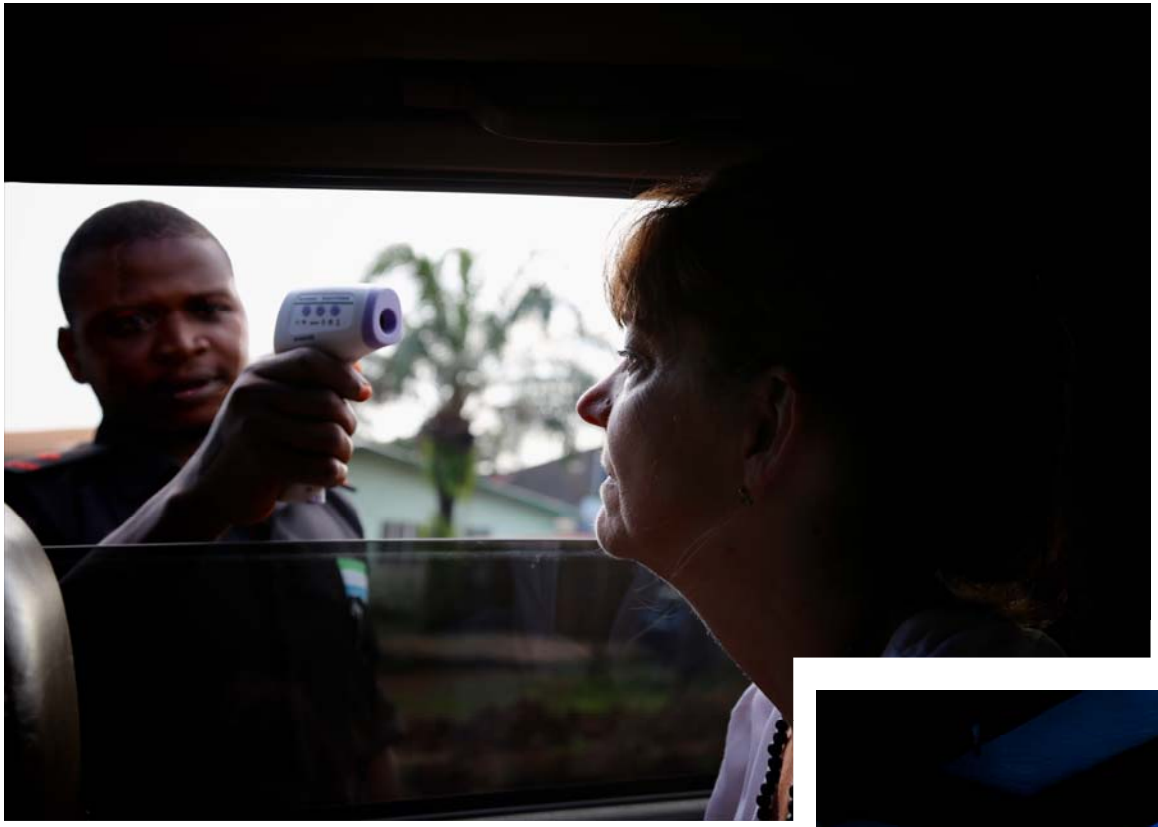


Learning objectives

- Describe both patient specific and health systems related factors affecting mortality in filovirus patients
- Outline factors impacting clinical Ebola response in West Africa and US during 2014 epidemic
- Identify practice strategies, treatments and technological innovations that can improve survival of Ebola patients

Disclosures

- None
- All images are mine unless otherwise stated

Do we still need to worry about Ebola?

World Health Organization

- Crimean-Congo Hemorrhagic Fever (CCHF)
- Ebola Viral Disease and Marburg Viral Disease
- Lassa Fever
- Middle East respiratory syndrome coronavirus (MERS-CoV) and Severe Acute
- Respiratory Syndrome (SARS)
- Nipah and henipaviral diseases
- Rift Valley Fever (RVF)
- Zika disease
- Disease X

Global Health Security Agenda

Filovirus Disease

- Single stranded negative sense RNA viruses
- Causative agents for:
  - Ebola Virus Disease (EVD)
  - Marburg Virus Disease (MVD)
- Transmission
  - Human to human (mainly fluid contact)
  - Vector to human
    - Non-human primates
    - Fruit bats
- Range: West, East and Equatorial Africa
- Non targeted clinical management is similar to other viral hemorrhagic fevers- Arena viruses, Henipah viruses
- Diagnosis made by PCR (requiring biocontaiment settings)

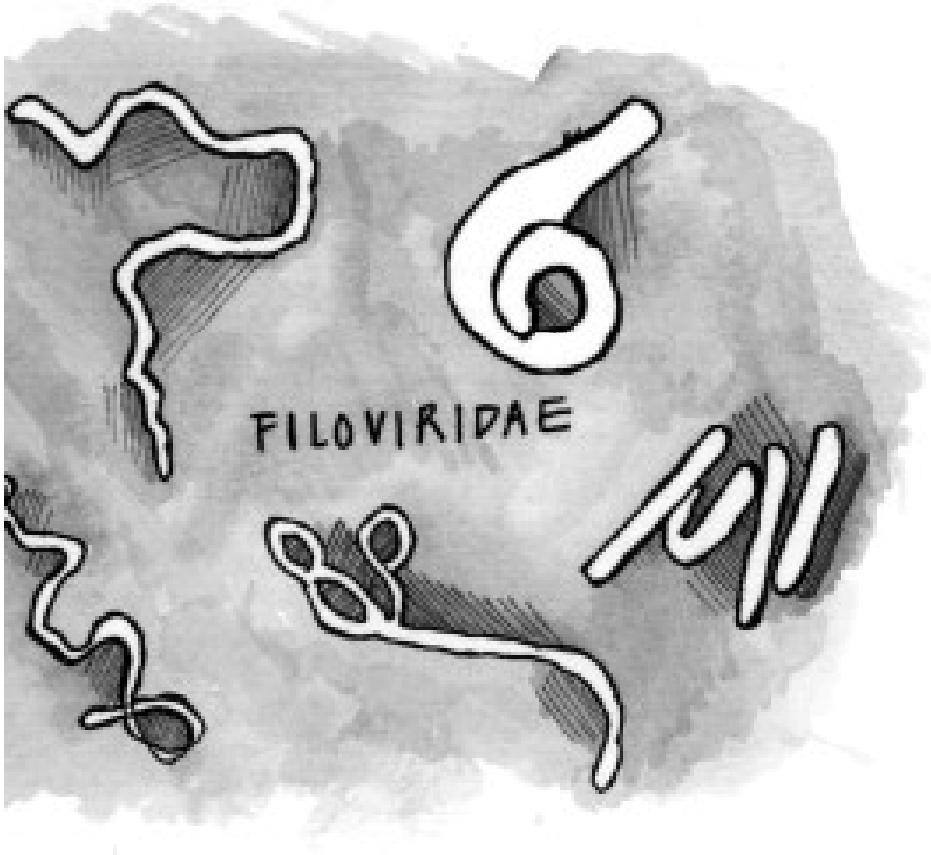


Illustration: Ruth Tam, PBS (2014)

	2014-2015 West African ZEBOV Epidemic			Kikwit, DRC 1999	Bundibugyo, Uganda 2007-2008
Symptom (%)	Fitzpatrick (525)	Dallatomasina et al (489)	Yan et al (108)	Ndambi (23)	Roddy et al (26)
Fever	76.7	87	75.9	100	42
Fatigue	67.3	77	85.2	100	77
Vomiting/nausea	44.5	46	66.7	83	65
Diarrhea	49.5	48	65.7	96	81
Anorexia	71.2	72	84.3	96	58
Head ache	67.3	73	72.2	74	81
Muscle pain	45.5	NR	65.8	30	65
Abdominal pain	49.5	51	65.7	96	62
Chest pain	41.1	44	56.5	NR	27
Joint pain	55.4	56	67.6	22	
Difficulty breathing	17.8	20	50.9	39	19
Coma/confusion	9	9	53.7	13	15
Cough	36.6	40	51.9	NR	15
Dysphagia	25.2	26	40.7	48	58
Conjunctivitis	34.1	2	34.3	78	50
Sore throat	24.5	26	38	NR	NR
Hiccups	13.8	15	27.8	26	5
Jaundice	7.4	8	NR	NR	NR
Skin Rash	NR	3	19.4	NR	12
Unexplained bleeding	5.4	5	2.8	9-43%	27

EVD Clinical Course

Stage	Symptoms	Onset
Stage 1: early or mild	Non-specific features: fever, weakness, lethargy, myalgia, and arthritis	Day 0-2
Stage 2: gastrointestinal involvement	As above plus: diarrhea, vomiting or abdominal pain, or both	Day 3-5
Stage 3: complicated	As above plus: hemorrhage, shock, neurological involvement, or signs of organ failure	Day 7

Chertow et al (2014), Hunt et al (2015)

Demographic And Symptom-Based Mortality Predictors

- **Age**
  - Mean age:
    - Survivors 25 years vs Deaths 30 years* (Fitzpatrick et al)
    - Survivors 29 years vs Deaths 45 years* (Bah et al)
    - >45 with higher mortality* (Yan et al)

- **Gender:**
  - No statistical difference across 5 cohorts

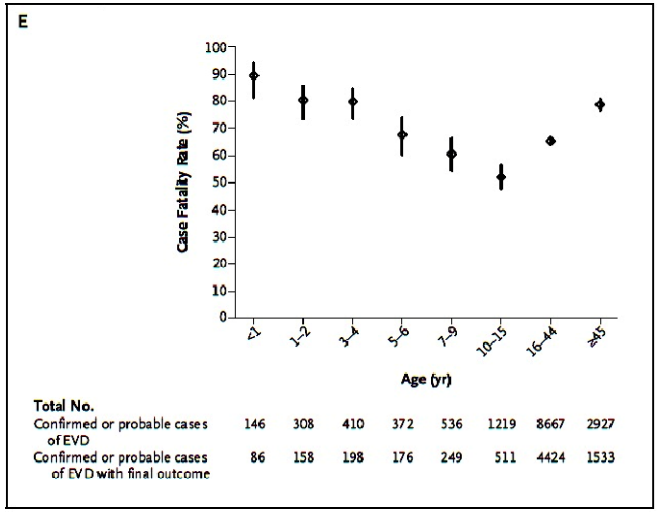
- **Statistically significant symptoms in non-survivors:**
  - Fever*, confusion, diarrhea, conjunctivitis, myalgia, headache, hiccups

- **Higher disease stage on admission was strongly associated with mortality**
  - (66·7%, 32·7%, and 25·8% for stage 3, 2, and 1, respectively; p=0·001) (Hunt et al)

- **Mortality rates ranged depending on site: 27-70%**

Special Populations

- Pediatric cases
  - Shorter incubation period in younger children (6.9din <1y, 9.8d in 10-15y)
  - More rapid progression to death
  - Higher case fatality <5 years
- Pregnant status:
  - Mortality has differed by outbreak but remains high
    - 2014-2015 Ebola epidemic aggregate mortality: **86%**
    - No neonatal survivors beyond the age of 19 days reported
  - Initial symptoms similar
    - Spontaneous abortion, vaginal bleeding reported
    - 2 cases presented without fever, ?blunting of pyrogenic response in pregnancy due to evolutionary immune tolerance (Akerlund et al 2015)
- Chronic symptoms/persistent viremia in survivors



Bebell et al (2017), WHO Ebola Response Team (2014)

Laboratory Findings in EVD

Table 2. Proportion of Patients with Abnormal Laboratory Values at Admission or at Any Time during Hospitalization in the United States or Europe.*

Abnormal Laboratory Result	At Admission	During Hospitalization	Treatment Received during Hospitalization†
	no./total no. tested (%)		*no./total no. (%)*
Hyponatremia (sodium <135 mmol/liter)‡	12/27 (44)	21/27 (78)	21/21 (100)
Hypokalemia (potassium <3.5 mmol/liter)	10/27 (37)	18/27 (67)	18/18 (100)
Hypocalcemia (total calcium <8 mmol/liter)	10/16 (62)	15/20 (75)	10/15 (67)
Hypomagnesemia (magnesium <0.85 mmol/liter)	9/10 (90)	14/17 (82)	10/14 (71)
Hypoalbuminemia (albumin <3.5 g/dl)	20/25 (80)	25/25 (100)	7/25 (28)
Elevated creatinine (>1.3 mg/dl)	5/27 (19)	11/27 (41)	
Elevated bilirubin (>1.5 mg/dl)	2/22 (9)	14/26 (54)	
Elevated aspartate aminotransferase (>98 U/liter)§	20/26 (77)	25/25 (100)	
Elevated alanine aminotransferase (>110 U/liter)¶	14/26 (54)	26/27 (96)	
Leukocytosis (white-cell count ≥15,000/μl)‖	3/25 (12)	17/27 (63)	
Leukopenia (white-cell count <3500/μl)‖	8/26 (31)	13/27 (48)	
Neutropenia (absolute neutrophil count <1500/μl)	3/23 (13)	4/23 (17)	
Lymphopenia (absolute lymphocyte count <1500/μl)	14/23 (61)	20/23 (87)	
Anemia (hemoglobin <11 mg/dl)**	1/27 (4)	16/27 (59)	3/16 (19)
Thrombocytopenia (platelet count <150,000/μl)	22/26 (85)	26/27 (96)	5/26 (19)
Thrombocytosis (platelet count >450,000/μl)††	0/26	9/27 (33)	2/9 (22)

Uyeki et al (2014)

Ideal Care And Management In The Field

- Oral and intravenous rehydration
- Electrolyte replacement
- Diagnosis and treatment of potential comorbidities
- Empiric treatment of secondary bacterial gut translocation
- Control of symptoms
  - Pain
  - Hiccups
  - Nausea
  - Diarrhea (not favored)
- Nutritional support

World Health Organization (2015), Viral Hemorrhagic Fevers Handbook


Dr. George

Actual care management in the field

- Poor baseline health system infrastructure
- Dearth of human and physical resources
- Limits of time in personal protective equipment (PPE)
- Inability to maintain infection control
- Dealing with shifting international guidelines on clinical care/PPE
- Lack of good options for care of sick healthcare workers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Systemic Challenges to Clinical Care Delivery During Ebola Epidemic

- Multiple, shifting epicenters
- Lack of timely lab results
- Poor data quality
- Community/patient distrust
- International media/public response often detrimental

Care and Management in Resource Rich Settings

Care and Management in The West

- Series of 27 patients evacuated from West Africa or acquired disease in US or Europe
- Mortality of 18.5%
- 7/26 had concurrent sepsis.
- Almost 70% had central line access
- 1/3 had delirium
- Only hemorrhagic signs were bleeding from IV site (52%), with frank hemorrhage in 7%

Uyeki et al (2014)

Pulmonary findings	
Hypoxemia‡	14 (52)
Pulmonary edema	12 (44)
Pneumonia	7 (26)
Respiratory failure	9 (33)
ARDS§	6 (22)
Supplemental oxygen¶	19 (70)
Noninvasive ventilation	4 (15)
Invasive mechanical ventilation	7 (26)
Renal findings	
Oliguria (urine <500 ml/day)	9 (33)
Anuria (urine <100 ml/day)	5 (19)
Dialysis catheter	5 (19)
CRRT	5 (19)
Cardiac findings	
Arrhythmia or electrocardiographic changes	11 (41)
Vasopressors or inotropes	8 (30)
Gastrointestinal findings	
Diarrhea‖	27 (100)
Vomiting	20 (74)
Ileus**	4 (15)
Intestinal paresis	4 (15)
Abdominal distention	10 (37)

Institutional Preparedness for EVD Care

- Physical infrastructure
- Staff training
- Extensive intradepartmental cooperation
- Institutional/in unit protocols
- Frequent drills, trainings
- Agreements with waste management companies
- Collaboration with public health bodies

Example of SPU Policies

- In Unit
  - Patient care
    - Surgical guidelines
    - Visitor Policy
    - Patient discharge
    - Laboratory sample collection
    - Spill and event based cleaning
    - Waste packaging and disposal
    - Advanced Resuscitation
  - Staff
    - PPE Donning and Doffing, PPE failure
    - Man down scenario
    - Occupational health/Staff exposure/illness
- At transfer
  - EMS Patient Transfer
  - Handling of deceased patients
  - Laboratory sample transport
  - Sterilization and terminal cleaning

Critical Care Challenges of EVD Management

Dilemma	Solution/Compromise
Mechanical ventilation	Elective intubation. Use of video laryngoscopy Use of substantial neuromuscular blockade
Renal replacement therapy	CVVH over HD- smaller footprint, less effluent fluid produced.
IV access/Blood draws	Elective early access placement if patient appears to be becoming critically ill. Preplanned and fewer blood draws.
Reduced diagnostic capacity	Preset menu of laboratory tests Use of bedside ultrasound Use of wireless stethoscopes
Risks associated with advanced resuscitation	If possible, preset discussion regarding altered level of care with patient/family. Some centers choose pharmacological resuscitation only.

Bhadelia (2015)

Targeted Medical Countermeasures

Therapeutic	NHP Efficacy studies	Human Safety Data available?	Human Efficacy Data available?
Antivirals			
BCX-4430	Yes	Yes	No
GS-5734	Yes	Yes	No
Brincidofivir	No	Yes	Yes (unpublished)
Favipiravir	None published	Yes	Yes (benefit in low viremia)
Small Interfering Molecules (siRNA)			
AVI-6002/7537	Yes	Yes	No
TKM 130803	Yes	Yes	Yes (trial terminated for futility)
Immunotherapeutics			
Convalescent plasma	Conflicting	Not available	Yes (no change in survival)

Lamontagne et al (2018)

When it comes to caring with patients with emerging infectious diseases, separation of research from care is a **false dichotomy.**

Positive Research Findings in 2014-2015 Epidemic

- Vaccines
  - Recombinant vesicular stomatitis virus–Zaire Ebola virus (rVSV-ZEBOV)- success in exposed contacts
- Therapeutics
  - ZMAPP- monoclonal antibodies- mortality benefit but not statistically significant
- Diagnostics
  - ReEBOV Ag test: good for those well into their disease (low sensitivity early)

Areas for Technological Innovation

- Data capture in clinical unit
  - Biological/Physiological
  - Clinical records
- Diagnostics
  - Imaging
  - Disease specific
- Infection control
  - Personal protective equipment
  - Patient isolation
  - Reusable/disposable clinical equipment
  - Environmental engineering
- Communication
- Transportation
  - Supplies
  - Biological samples
- Surveillance and case finding
  - Wearables?
- Platforms for easier delivery of vaccines an
  medical countermeasures

Key points

- Morbidity and mortality depends on quality of supportive care
- EVD clinical management requires extensive institutional planning
- Care of suspected/probable/confirmed cases is altered due to infection control constraints
- There are still no approved therapies for EVD
- Research and clinical care are inseparable for filovirus patients
- There is space for technological innovation to improve quality of care

THANK YOU!

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