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?

- 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
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 biocontainment settings)

Illustration: Ruth Tam, PBS (2014)
<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>76.7</td>
<td>87</td>
<td>75.9</td>
</tr>
<tr>
<td>Fatigue</td>
<td>67.3</td>
<td>77</td>
<td>85.2</td>
</tr>
<tr>
<td>Vomiting/nausea</td>
<td>44.5</td>
<td>46</td>
<td>66.7</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>49.5</td>
<td>48</td>
<td>65.7</td>
</tr>
<tr>
<td>Anorexia</td>
<td>71.2</td>
<td>72</td>
<td>84.3</td>
</tr>
<tr>
<td>Head ache</td>
<td>67.3</td>
<td>73</td>
<td>72.2</td>
</tr>
<tr>
<td>Muscle pain</td>
<td>45.5</td>
<td>NR</td>
<td>65.8</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>49.5</td>
<td>51</td>
<td>65.7</td>
</tr>
<tr>
<td>Chest pain</td>
<td>41.1</td>
<td>44</td>
<td>56.5</td>
</tr>
<tr>
<td>Joint pain</td>
<td>55.4</td>
<td>56</td>
<td>67.6</td>
</tr>
<tr>
<td>Difficulty breathing</td>
<td>17.8</td>
<td>20</td>
<td>50.9</td>
</tr>
<tr>
<td>Coma/confusion</td>
<td>9</td>
<td>9</td>
<td>53.7</td>
</tr>
<tr>
<td>Cough</td>
<td>36.6</td>
<td>40</td>
<td>51.9</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>25.2</td>
<td>26</td>
<td>40.7</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>34.1</td>
<td>2</td>
<td>34.3</td>
</tr>
<tr>
<td>Sore throat</td>
<td>24.5</td>
<td>26</td>
<td>38</td>
</tr>
<tr>
<td>Hiccups</td>
<td>13.8</td>
<td>15</td>
<td>27.8</td>
</tr>
<tr>
<td>Jaundice</td>
<td>7.4</td>
<td>8</td>
<td>NR</td>
</tr>
<tr>
<td>Skin Rash</td>
<td>NR</td>
<td>3</td>
<td>19.4</td>
</tr>
<tr>
<td>Unexplained bleeding</td>
<td>5.4</td>
<td>5</td>
<td>2.8</td>
</tr>
</tbody>
</table>
# EVD Clinical Course

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

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 (6.9d in <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

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

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
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
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)
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
<table>
<thead>
<tr>
<th>Critical Care Challenges of EVD Management</th>
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<tbody>
<tr>
<td><strong>Dilemma</strong></td>
<td><strong>Solution/Compromise</strong></td>
</tr>
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</table>
| 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

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

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 and 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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