Ebola Virus Disease (and Beyond):
A Critical Care Perspective

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Disclosures

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- Co-PI of the National Ebola Training and Education Center (funded by ASPR/CDC)

Objectives

- Review clinical presentation and management of EVD, with a focus on well resourced healthcare settings
- Discuss role of Critical Care in preparing for and responding to Ebola and other special pathogens
Ebola Virus

- Filovirus (enveloped RNA virus)

Ebola 1976 - 2016

<table>
<thead>
<tr>
<th>Year</th>
<th>Country</th>
<th>Cases</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>1976</td>
<td>South Sudan</td>
<td>284</td>
<td>151</td>
</tr>
<tr>
<td>1977</td>
<td>Dem. Rep. of Congo</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>1979</td>
<td>South Sudan</td>
<td>34</td>
<td>22</td>
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<tr>
<td>1994</td>
<td>Côte d’Ivoire</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>1994</td>
<td>Gabon</td>
<td>52</td>
<td>31</td>
</tr>
<tr>
<td>1996</td>
<td>South Africa</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>1996</td>
<td>Gabon</td>
<td>60</td>
<td>45</td>
</tr>
<tr>
<td>1996</td>
<td>Gabon</td>
<td>31</td>
<td>21</td>
</tr>
<tr>
<td>2000</td>
<td>Uganda</td>
<td>425</td>
<td>224</td>
</tr>
<tr>
<td>2001</td>
<td>Republic of Congo</td>
<td>57</td>
<td>43</td>
</tr>
<tr>
<td>2001</td>
<td>Gabon</td>
<td>65</td>
<td>53</td>
</tr>
<tr>
<td>2002</td>
<td>Republic of Congo</td>
<td>143</td>
<td>128</td>
</tr>
<tr>
<td>2003</td>
<td>Republic of Congo</td>
<td>35</td>
<td>29</td>
</tr>
<tr>
<td>2004</td>
<td>South Sudan</td>
<td>17</td>
<td>7</td>
</tr>
<tr>
<td>2007</td>
<td>Uganda</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>2011</td>
<td>Liberia</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>2012</td>
<td>Liberia</td>
<td>36</td>
<td>13</td>
</tr>
<tr>
<td>2012</td>
<td>Uganda</td>
<td>11</td>
<td>4</td>
</tr>
<tr>
<td>2014</td>
<td>Dem. Rep. of Congo</td>
<td>66</td>
<td>49</td>
</tr>
<tr>
<td>2014</td>
<td>Multiple Countries</td>
<td>28652</td>
<td>11325</td>
</tr>
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Adapted from CDC.gov
(https://www.cdc.gov/vhf/ebola/outbreaks/history/distribution-map.html)

Ebola Cases (United States)

- During this outbreak:
  - Seven persons (six healthcare workers and one journalist) infected in West Africa were transported to US hospitals
  - Six recovered, one died

- Ebola diagnosed in the United States in four people:
  - One who traveled to Dallas from Liberia
  - Two healthcare workers in Dallas
  - One healthcare worker who traveled to New York City from Guinea
  - Three recovered, one died

Information on U.S. Ebola cases available at

www.who.int accessed 11/1/2014
Early Clinical Presentation

- Acute onset
  - typically 8–10 days after exposure (range 2–21 days)
- Signs and symptoms
  - Initial: Fever, chill, myalgia, malaise, anorexia
  - After 3–5 days: nausea, vomiting, diarrhea, abdominal pain
  - Other: Headache, conjunctivitis, hiccups, rash, chest pain, shortness of breath, confusion, seizures
  - Hemorrhagic symptoms less common (usually occur late)
- Other possible infectious causes of symptoms
  - Malaria, typhoid fever, meningococcemia, dengue, influenza, Lassa fever and other bacterial infections (e.g., pneumonia)

Initial Signs and Symptoms of Ebola Are Non-Specific

- Starts as a non-specific febrile illness
- Usually rapid progression of intensity
- Some more unique features: Asthenia, Anorexia, Right upper quadrant pain, hiccups, Conjunctivitis, Rash, Oozing blood from gums, injections site

Case Definition

- Person Under Investigation (PUI)
  - A person who has both consistent signs or symptoms and risk factors as follows should be considered a PUI:
    - Elevated body temperature or subjective fever or symptoms, including severe headache, fatigue, muscle pain, vomiting, diarrhea, abdominal pain, or unexplained hemorrhage; AND
    - An epidemiologic risk factor within the 21 days before the onset of symptoms.
- Confirmed Case
  - Laboratory-confirmed diagnostic evidence of Ebola virus infection.

http://www.cdc.gov/vhf/ebola/hcp/case-definition.html
http://www.cdc.gov/vhf/ebola/hcp/international/case-definitions.html
Clinical Features

- Nonspecific early symptoms may progress to:
  - Hypovolemic shock and multi-organ failure
  - Hemorrhagic disease
  - Death
- Non-fatal cases:
  - Typically improve 6–11 days after symptom onset if supportive care is provided promptly
- Fatal disease associated with more severe early symptoms:
  - Fatality rates of >70% have been reported in rural Africa
  - Intensive care, especially early intravenous and electrolyte management, may increase the survival rate

Ebola Virus Pathogenesis

- Direct infection of tissues
- Immune dysregulation
- Hypovolemia and vascular collapse
- Electrolyte abnormalities
- Multi-organ failure, septic shock
- Disseminated intravascular coagulation and coagulopathy
- Vascular leak / cytokine effect

Clinical Management of Ebola Virus Disease in the United States and Europe

Characteristics of patients in US and Europe

Clinical Management of Ebola:

- Hypovolemia and sepsis pathophysiology
- Aggressive intravenous fluid resuscitation
- Average max volume of diarrhea 3000ml (100ml to 10000ml). Average duration 6 days (1-20 days)
- Hemodynamic support and critical care management if necessary
- Electrolyte and acid-base abnormalities
- Aggressive electrolyte repletion
- Correction of acid-base derangements
Clinical Management of Ebola:

- Symptomatic management of fever and gastrointestinal symptoms
- Avoid NSAIDs, aspirin
- Anti-emetics and antidiarrheal agents may be needed
- Multisystem organ failure can develop and may require
  - Oxygenation and mechanical ventilation
  - Correction of severe coagulopathy
  - Continuous renal replacement therapy

Fowler RA et al. Am J Respir Crit Care Med. 2014

Clinical Care in High Level Isolation

- Relatively limited diagnostic testing
  - Laboratory tests
  - Imaging tests
  - Portable x-rays require advance planning/protocols
  - Use of point of care ultrasound for diagnostic imaging and procedure guidance
- Invasive procedures in PPE
  - Threshold may be different – response time to deteriorating patient longer in isolation
  - Consider simulation exercises of procedures – central line placement, endotracheal intubation
  - Consider telemedicine based consultations when possible
    - Limit the number of providers who need to enter the patient room

Central Line Placement

- Central vascular access often required
- Consider early placement
- Viral load may be lower earlier in course
- Planning/Simulation in PPE
- Ultrasound guidance
- Consider ultrasound confirmation of placement
- Safety and PPE considerations
  - Safety needles and catheters to replace any non-safety devices in the kit
Airway Management

- Prepare dedicated airway equipment/bundle
  - Standard blades/tubes/airway adjuncts
  - Induction/Emergency medications
  - Video laryngoscope
- Canadian EVD guidelines recommend video laryngoscopy
  - Increase distance from the patient
  - Consideration of rapid sequence induction (RSI) to reduce cough and possible aerosolization
- www.canadiancriticalcare.org
- Practice using simulation

PUIs may present with a range of severity of illness

- Some have presented relatively well with fever, prodromal symptoms
- Some have presented critically ill with multi-organ system failure
  - Need for emergent dialysis, intubation and mechanical ventilation
- Preparations should include plans for handling this range of illness until diagnosis of EVD is either confirmed or ruled out
  - Additional considerations for range of ages possible from infants to older adults

Predictors of Clinical Outcomes in EVD

<table>
<thead>
<tr>
<th>Nonlethal Infection</th>
<th>Lethal Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prominent CD8+ T cell activation</td>
<td>No CD8+ T cell activation</td>
</tr>
<tr>
<td>Above-normal numbers of T cells</td>
<td>Below-normal numbers of T cells</td>
</tr>
<tr>
<td>10^7 viral genome copies/ml serum</td>
<td>10^10 viral genome copies/ml serum</td>
</tr>
<tr>
<td>Detectable antibodies in blood at onset of symptoms</td>
<td>No detectable antibodies in blood at onset of symptoms</td>
</tr>
<tr>
<td>Low Nitric Oxide</td>
<td>High Nitric Oxide levels</td>
</tr>
<tr>
<td>High sCD40L levels</td>
<td>Low sCD40L levels</td>
</tr>
</tbody>
</table>

Predictors of Clinical Outcomes in EVD

Patient Recovery

- Overall case-fatality rate approximately 40% in the 2014-2016 Ebola outbreak
- Case-fatality rate is likely much lower with access to intensive care
- Patients who survive often have signs of clinical improvement by the second week of illness
- Associated with the development of virus-specific antibodies
- Antibody with neutralizing activity against Ebola persists greater than 12 years after infection

ICU Care Makes a Difference

- Ability to provide high-level nursing care and supportive care is essential
- 24/7 one-on-one nurses allowed for rapid response to changes and adjustment of care
- Ability to support patients in nutrition, physical therapy, and self-care
- Emotional support
- Family support
- Patient- and Family-Centered Model of Care
Clinical Pearls

- Patients will be hypovolemic even while their body weight increases (15-20 kg)
- Low albumin
- Vascular damage
- May not be a factor in underdeveloped healthcare systems due to inability to match fluid losses
- Large volume losses: 5-10 liters/day

Impact of Nutrition and Electrolytes

- Patients may have marked electrolyte abnormalities and nutritional deficiencies
- Hypokalemia, hypocalcemia and hyponatremia
- Both intravenous and oral replacement
- Used oral nutritional supplements including nutritional drinks high in easily absorbed proteins, minerals and vitamins
- Laboratory testing for chemistries was critical to provide supportive care

Monitoring Virologic Status

- CDC assistance in monitoring EBOV viral loads in blood by PCR and antibody titers
- Increased IgG levels correlated with decreased viral loads
- Progressive decline in viral load correlated with improvements in clinical condition
- May have very low level of nucleic acid detection for several days despite resolution of symptoms
Critical Illness Phenotype

- Day 8-11
- Gastroenteritis/hepatitis & febrile phases may be improving
- Pulmonary
  - Progressive hypoxemia + multifocal/diffuse interstitial infiltrates
- Renal
  - Acute kidney injury – rapid loss of small solute clearance
  - Metabolic acidosis
- Encephalopathy
  - Often severe & may develop earlier in course of illness

Critical Illness Phenotype

- No proven EVD-specific organ support beyond established CCM “best” practices
- Lung protective ventilation & minimizing sedation as possible
- Target euvoelemia
- Nutrition support – early & aggressive
- Delivery of critical care requires special consideration/planning

Renal Placement Therapy

- CRRT generates less spent effluent than conventional
  - 48-96 L/day CRRT vs 192 L/4h IHD session
- All RRT effluent should be non-infectious (for Ebola virus)
  - Virus/RNA too big to fit through membrane
- Tested effluent multiple days by PCR to confirm
- Disposed in same manner as local guidelines required for stool/urine
Lessons Learned

- Patients with Ebola can be safely cared for in our healthcare system with good preparation
- We do expect a lower mortality rate than in underdeveloped healthcare systems
- Communication is critical
- Critical and advanced care can be delivered if appropriately planned
- Comprehensive, multidisciplinary patient- and family-centered models of care can be delivered even in extreme circumstances
What about other diseases/pathogens?

Why do we care as critical care clinicians?

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Global travel is increasing

<table>
<thead>
<tr>
<th>International Travelers</th>
<th>2008 (Millions)</th>
<th>2014 (Millions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Worldwide</td>
<td>948</td>
<td>1,161</td>
</tr>
<tr>
<td>Europe/Central Asia</td>
<td>505</td>
<td>588</td>
</tr>
<tr>
<td>US</td>
<td>58</td>
<td>75</td>
</tr>
<tr>
<td>France</td>
<td>79</td>
<td>84</td>
</tr>
<tr>
<td>Thailand</td>
<td>15</td>
<td>25</td>
</tr>
<tr>
<td>China</td>
<td>53</td>
<td>56</td>
</tr>
<tr>
<td>New York City</td>
<td>8.8</td>
<td>12</td>
</tr>
<tr>
<td>Seattle</td>
<td>2.78 (2015)</td>
<td></td>
</tr>
</tbody>
</table>

Source: World Bank (data.worldbank.org), nyc.gov, visitseattle.org

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What is a “special pathogen”?

- No set criteria, some considerations
  - Pathogen causes high mortality
  - Pathogen with high likelihood of secondary cases
  - Pathogen with absence of an effective vaccine or prophylaxis or treatment
  - Pathogen for which clinical or public assuredness concerns might prompt the use of a biocontainment unit
Healthcare workers are at risk of infection with emerging pathogens: SARS

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>GTA (%)</th>
<th>Tarim (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatal cases</td>
<td>275</td>
<td>NA</td>
</tr>
<tr>
<td>Probable</td>
<td>247 (66)</td>
<td>668</td>
</tr>
<tr>
<td>Suspected</td>
<td>128 (33)</td>
<td>NA</td>
</tr>
<tr>
<td>Total</td>
<td>541</td>
<td>734</td>
</tr>
</tbody>
</table>

1. Healthcare-related cases: 271 (77)
2. Healthcare workers: 144 (44)

1-27% of cases in HCP (varies by region/hospital)

Source: WHO.int

Emerging Infectious Diseases, 2004. 10(5)

MERS and Health Care Workers

1-27% of cases in HCP (varies by region/hospital)

Source: WHO.int

Curr Opin Infect Dis, 2015. 28:349-361

What effect do events like SARS/MERS/Ebola/Pandemic influenza have on health care workers?

- **Challenges**
  - High Resource Demand
  - Low Resource Capacity
  - High Risk Perception - Staff, public
  - Clinical Care in Isolation

- **Strategies**
  - Preparation
  - Communication
  - Cooperation
  - Collaboration


Physicians and Professionalism in the SARS outbreak

Qualitative interviews with 14 attending physicians from Toronto involved in care of patients with SARS

- 4 became ill during the outbreak

Issues

- Fear and stress
- Balance of patient care and personal risk
  - Set point for risk varies
  - Response of colleagues varied
- Patient and staff confidentiality
- Physician – patient (and family) relationship in high level isolation


Take Home Points

Even if you aren’t involved in international health, you may be called upon to respond to a disease/disaster in your own community

Health care workers are at risk of infection in outbreaks of disease

This risk can be reduced through training and preparation (personal, environmental and organizational), but may not be eliminated

This risk to health care providers creates challenges in response

- Fear and stress
- Differing risk thresholds

National Ebola Training and Education Center (NETEC)

Mission: To increase the capability of United States public health and health care systems to safely and effectively manage individuals with suspected and confirmed special pathogens

For more information, visit www.netec.org or email us at info@netec.org
Role of NETEC

Through the 5 year project period and in collaboration with ASPR, CDC and other stakeholders, the NETEC will:

• Create readiness metrics.
• Conduct peer review readiness assessments of regional and state ETCs as well as assessment centers
• Provide technical assistance to public health departments and healthcare facilities.

Role of NETEC (continued)

• Create, conduct, and maintain a comprehensive suite of onsite and online education courses and helpful resources and tools.
• Develop a repository for education resources, announcements, links to key information, exercise templates at www.netec.org
• Provide technical assistance to public health departments and healthcare facilities.
• Create a research infrastructure across the 10 regional ETCs.

Thank you