Management of Patients with Ebola Virus Disease: Clinical and Operational Lessons Learned

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Disclosures

• Lisco – None
• Kraft – None
Learning Objectives

• Understand the history of Ebola Virus Disease
• Review and recognize the clinical concerns in patients infected with Ebola virus
• Describe the design, clinical workflow, and utilization of a biocontainment unit
• Recognize the logistical challenges presented by the care of patients infected with Ebola virus and other highly pathogenic contagions and implications for healthcare workers in the biocontainment unit environment
Recognize this Bill?
How about now?
Perhaps the only good news from the tragic Ebola epidemic in Guinea, Sierra Leone, and Liberia is that it may serve as a wake-up call: we must prepare for future epidemics of diseases that may spread more effectively than Ebola.
OUTBREAK
Deadliest Pandemics in History

Because a virus doesn’t care about state lines or national borders, it can wipe out millions and span multiple continents rapidly. Here is a look at the infectious diseases the world has battled throughout history.

What is a Pandemic?
Derived from the Greek word pandemos meaning “pertaining to all people,” a pandemic is a widespread disease that affects humans over a wide geographic area.

**Key:**
- **PANDEMIC YEAR**
- **DEATH TOLL**

**HIV/AIDS** 1985 - TODAY
- 25 million

**Plague of Justinian** 541 - 550
- 25 million

**Measles** 7th Century BC - 1963
- 200 million

**Smallpox** 1800 BC - 1979
- 300+ million

**Black Death** 1340 - 1377
- 75 million

**Typhus** 430 BC - TODAY
- 4 million

**Cholera** 1851 - TODAY
- 3 million

**Spanish Flu** 1918 - 1919
- 50-100 million

**Third Pandemic** 1855
- 12 million

**Hong Kong Flu** 1968 - 1969
- 1 million

**Honorable Mentions**
Although the following viruses do not have a figure for total amount of lives claimed, they continue to terrorize various areas around the world.

- **Malara** 1650 - Today
  - Common Symptoms: Chills, Headache, Fever, Jaundice, Muscle Pain, Nausea, Vomiting, Seizures
  - Death Toll: According to the World Health Organization’s 2010 “World Malaria Report,” an estimated 500,000 people are killed by the virus every year.

- **Tuberculosis** 700 BC - Today
  - Common Symptoms: Chest Pain, Cough, Fever, Chills, Fatigue
  - Death Toll: There are almost 2 million tuberculosis-related deaths worldwide every year.

- **Yellow Fever** 15th Century - Today
  - Common Symptoms: Bleeding, Fever, Nausea, Vomiting, Delirium, Seizures, Jaundice
  - Death Toll: Worldwide, 30,000 deaths are caused by the infection every year.

Sources: Mayo Clinic // Centers for Disease Control and Prevention // World Health Organization // New York Times // National Center for Biotechnology Information

http://awesome.good.is/transparency/web/1108/deadliest-pandemics/transparency.jpg (accessed 2.11.15)
Ebola: Virology

• Filovirus (Latin for ‘thread’): elongated structure, -ssRNA

• 6 subtypes
  • Zaire <<<< Currently active
  • Sudan
  • Bundibugyo
  • Cote d’Ivoire/Tai Forest
  • Reston (not pathogenic to humans)
  • Lloviu (no human infections identified)

• Viral Hemorrhagic Fever
  • One of four viruses
EBV Disease

- Ebola virus was discovered in 1976 near the Ebola River in what is now the Democratic Republic of the Congo.

- Outbreaks have appeared sporadically in Africa.

- The 2014 outbreak is the first in West Africa, and the largest outbreak ever recorded.

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<table>
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<th>Deaths</th>
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Ebola 2014
25,000 cases
10,000 deaths
CONTAGIOUS VS. INFECTIOUS

*Ebola is not very contagious, but it is dangerously infectious*

Center for Disease Control:

A **contagious disease** is a disease caused by a bacteria or virus that can be transmitted from **person to person** (a communicable disease).

R(o) quantifies how contagious a disease actually is

**Infectious** refers to how many bacteria, virions, or other pathogenic particles are needed to infect an exposed individual.
Basic Reproductive Rate (Ro) – The average number of persons infected by a single disease source. R(o) is affected by:

- Duration of infectivity
- Infectiousness of the organism
- Number of susceptible people with whom the infected person contacts

R(o) > 1, the disease will continue to spread
R(o) < 1, the disease will eventually disappear from a population

<table>
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<th>Disease</th>
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<th>Ro (# of secondary transmissions)</th>
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<td>Fecal-oral route</td>
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<tr>
<td>Rubella</td>
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<td>6-7</td>
</tr>
<tr>
<td>Small Pox</td>
<td>Airborne Droplet</td>
<td>5-7</td>
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</tbody>
</table>
EBOLA IS NOT THAT CONTAGIOUS

On average one EVD patient will infect two additional people.

To stop the chain of transmission health care workers must get the infected patient into isolation before signs / symptoms of EVD develop.

If R(0) drops to zero a geographic area will become free of Ebola.

Ebola is not very contagious.

Ebola is Highly Infectious


EVD is transmitted by contact with infected blood or bodily fluids with an infectious dose of <10 viruses and high virus concentrations in blood $10^8$ virus particles/mL
And Deadly

Death Rates for Pandemic Viruses

- **EBOLA**: 50–90%
- **Influenza-H1N1 Pandemic**: 0.01–0.3%
- **Marburg**: 23–90%
- **Polio**: 15–30%
- **Pertussis**: ≤4%
- **Measles**: 1–30%
- **Influenza Seasonal**: <1%
- **Lassa Fever**: 50%
- **Malaria**: ≤20%
- **SARS**: 13–43%
2014
Ebola Outbreak, West Africa


Total suspected, probable, and confirmed cases of Ebola virus disease in Guinea, Liberia, and Sierra Leone, March 29, 2015, WHO Situation Report, n=25178 cases; n=10445 deaths
Figure 4: Geographical distribution of new and total confirmed cases

The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

University of Nebraska Medical Center

Nebraska Medicine

Emory Medicine

Serious Communicable Diseases Unit

https://pbs.twimg.com/media/B_1oQxOWcAE6lAc.jpg:large accessed 3.14.2015
A BACK DOOR FOR EBOLA
SMUGGLED BUSHMEAT COULD SPARK A U.S. EPIDEMIC
Ebola virus Ecology

**Enzootic Cycle**

New evidence strongly implicates bats as the reservoir hosts for ebolaviruses, though the means of local enzootic maintenance and transmission of the virus within bat populations remain unknown.

**Ebola Viruses:**
- Ebola virus (formerly Zaire virus)
- Sudan virus
- Tai Forest virus
- Bundibugyo virus
- Reston virus (non-human)

**Epizootic Cycle**

Epizootics caused by ebolaviruses appear sporadically, producing high mortality among non-human primates and duikers and may precede human outbreaks. Epidemics caused by ebolaviruses produce acute disease among humans, with the exception of Reston virus which does not produce detectable disease in humans. Little is known about how the virus first passes to humans, triggering waves of human-to-human transmission, and an epidemic.

Following initial human infection through contact with an infected bat or other wild animal, human-to-human transmission often occurs.

Human-to-human transmission is a predominant feature of epidemics.
Disease Progression

**DISEASE PROGRESSION**

- **EXPOSURE**
  - Incubation period is 2-21 days following exposure. Symptoms appear on average 3-10 days following exposure. (CDC)

- **EARLY STAGES**
  - **SYMPTOM ONSET**
    - Weakness
    - Fever—greater than 101.5°F
    - Headache
    - Muscle Pain
    - Joint Pain
    - Conjunctivitis
    - Nausea
    - Throat Pain
    - Abdominal Pain
    - Diarrhea
    - Hiccups
  - **LATE STAGES**
    - Confusion
    - Irritability
    - Chest Pain
    - Diarrhea
    - Vomiting
    - Skin Rash
    - Internal/External Bleeding
    - DIC
    - Miscarriage
    - Respiratory Distress
    - Shock
    - Convulsions

- **POST-INFECTION**
  - Visual Complications
  - Joint Pain
  - Anemia
  - Risk for transmission up to 3 months in tears and semen

*Early and late stage symptoms may overlap; all symptoms may not manifest in all infected patients*

Source: Jonathan B. Perlin, MD, PhD and HCA Clinical Excellence Knowledge Center, 2014
Symptoms of Ebola

- Headache
- Red Eyes

Pharynx and lungs:
- Hiccups
- Sore throat
- Difficulty breathing
- Difficulty swallowing

Systemic:
- Fever
- Lack of appetite
- Internal bleeding

Muscular:
- Aches
- Weakness

Joints:
- Aches

Intestines:
- Diarrhea

Chest pain

Stomach:
- Pain
- Vomiting

Skin:
- Rash
- Bleeding
Virus’s typical path through a human

**First symptoms**
- Day 7-9: Headache, fatigue, fever, muscle soreness

**Day 10**
- Sudden high fever, vomiting, blood, passive behavior

**Day 11**
- Bruising, brain damage, bleeding from nose, mouth, eyes, anus

**Day 12**
- Loss of consciousness, seizures, massive internal bleeding, death

NOTE: Symptoms can start as early as two days after infection.

SOURCES: World Health Organization; BBC

Melina Yingling/McClatchy-Tribune
Detection of EVD in Different Human Body Fluids over Time
Caring for Ebola Patients in the USA

EBOLA VIRAL DISEASE 2015
USAMRIID

- DOD Lead Laboratory for medical biological defense research
  - Located in Fort Detrick, MD
  - Founded in 1969
  - One of the first biocontainment units in the USA built in 1972
    - BSL-4 patient isolation unit
  - Cared for one of the first EVD exposure patients in USA in 2004 for 21 days
    - Two bed unit nicknamed “the slammer”
• Rooms capable of providing an ICU level of care
• Autoclave
• Transportation device
Background: Civilian Biocontainment

Patient Care Units

• When the outbreak began in 2014, there were 3 biocontainment units in the United States designated to care for patients with Ebola.
  – Serious Communicable Diseases Unit (SCDU)
    • Located on-campus at Emory University Hospital in Atlanta, GA
  – Nebraska Biocontainment Unit (NBU)
    • Located on-campus at the University of Nebraska Medical Center in Omaha, NE
  – Special Clinical Studies Unit
    • Located at the National Institutes of Health (NIH) in Bethesda, MD
Background: Ebola in the Emory Serious Communicable Disease Unit (SCDU)

- July 30, 2014: *Emory University Hospital asked to accept as a transfer the first patient with confirmed Ebola virus infection to be treated in the United States*
- In total treated 4 patients:
  - August 2: 33 y/o male physician, day 11 of illness, admitted 19 days
  - August 5: 59 y/o female missionary, day 15 of illness, admitted 14 days
  - September 9: 44 y/o male physician, day 4 of illness, admitted 40 days
  - October 15: 30 y/o female nurse, day 2 of illness, admitted 12 days
Background: Ebola in the Nebraska Biocontainment Unit (NBU)

- September 5, 2014: The **Nebraska Biocontainment Unit** received a patient diagnosed with EVD, medically evacuated from Liberia
  - Day #8 of illness
  - Discharged on hospital day #21

- October 6, 2014: Received a patient diagnosed with EVD, medically evacuated from Liberia
  - Day #6 of illness
  - Discharged on hospital day #17

- November 15, 2014: Received a patient diagnosed with EVD, medically evacuated from Sierra Leone
  - Day #13 of illness
  - Multi-organ failure on admission
  - Died on hospital day #3
Initial Clinical Observations

- Fever
- Delirium
- Severe fatigue
- Nausea/vomiting
- Watery diarrhea
- Dehydration
- Rash
- Multi-organ failure (in later stage of illness)
Clinical Care of EVD: “Supportive Care”

• **What IS Supportive Care???:**

• **CDC’s Definition:**
  - Providing intravenous fluids and balancing electrolytes
  - Maintaining oxygen and blood pressure
  - Treating other infections if they occur

• **The provider’s simplified definition:**
  - “Keeping the patient alive long enough for them to develop the antibodies needed to resolve Ebola viremia”
Clinical Management: Day 1

- Evaluate the condition of the patient
  - Initial nursing and physician assessment
    - History and physical exam
    - Documentation in medical record
    - Initial labs ordered and drawn
- Establish IV access: Central venous catheter (CVC) placement
Clinical Management: Gastroenteritis

- Initial resuscitation
  - Intravenous fluids
  - Careful monitoring of fluid balance

- Replace electrolytes

- Supplemental oxygen if necessary

- Control nausea and vomiting
  - Anti-emetics administered

- Control of severe, watery diarrhea
  - +/- Anti-diarrheal agents
Clinical Management: Organ failure

- Aggressive supportive care measures for critically ill patients
  - Intubation and mechanical ventilation
  - Dialysis
  - Blood pressure support
    - Vasopressors
  - Arterial line placement
Notable Laboratory Abnormalities

- Leukopenia
- Thrombocytopenia
- Transaminitis
- Coagulopathy
- Electrolyte disturbances
  - Hypokalemia
  - Hypomagnesemia
  - Hypocalcemia
  - Hypophosphotemia (with refeeding)
Nutrition

• Patients are unable to maintain oral intake due to nausea and vomiting
• Total parenteral nutrition (TPN) initiated
  • Continued until adequate oral intake possible
• Early consultation from Dietary service
• Calorie counts
Therapeutics

• No Proven Therapeutics
  – Unclear availability of experimental agents
  – Limited safety or efficacy data in humans
  – SIGNIFICANT support and advice from CDC, FDA, and medical and scientific colleagues throughout the world

• Therapeutic agents utilized in the care of our patients:
  • TKM-Ebola
  • Brincidofovir
  • ZMapp
  • Convalescent plasma
  • Favipiravir
Clinical Monitoring

- **Viral Load Monitoring**
  - Progressive declines in viral loads correlated with improvements in clinical condition
  - Had very low level of nucleic acid detection for several days despite resolution of symptoms
Recovery and Rehabilitation

- Encourage early ambulation
- Physical therapy consultation
- Family interaction
  - Through window or videoconferencing
- Emotional support
Post Ebola Syndrome

- Arthralgias and myalgias
- Abdominal Pain
- Extreme fatigue
- Anorexia
- Amenorrhea
- Parotitis
- Unilateral orchitis
- Visual problems
- Hair loss
- Hearing loss
Clinical and Operational Lessons Learned

Medical rounds in the NBU
Clinical Care: Lessons Learned

• Patients arrive critically ill
  • Fever, severe nausea/vomiting and diarrhea in initial stages
  • Multi-organ failure in later stage

• Early entry into therapy may halt progression of the illness, but this also likely depends on multiple factors
  • Host
  • Therapeutics
  • Viral load
Clinical Lessons Learned

• Careful monitoring of fluid balance
  • Aggressive rehydration can induce volume overload, including pulmonary edema

• Replacement of electrolytes is extremely important
  • Monitor on telemetry
  • Watch for QT prolongation
    • Electrolyte disturbance + medications
Clinical Lessons Learned

• Need for dedicated equipment
  • EKG
  • Portable X-ray machine
  • Ultrasound
    • CVC placement
    • TTE
    • Diagnostic ultrasound
  • Dialysis
  • Airway cart
  • Code cart

NBU portable X-ray machine
Clinical Lessons Learned

- It is unknown which treatment modalities play a role in recovery
  - supportive care
  - investigational drugs
  - convalescent serum
  - combination?

- Patients may recover clinically but still have detectible viral loads for several days

- Continued profound fatigue and other symptoms
Operational Lessons Learned

• Staffing
  • Multiple nurses and physicians are required to care for one patient with EVD
  • Nurses are needed at the bedside 24/7
  • Input from multiple specialties is necessary
Operational Lessons Learned

• Establishing a “Culture of Safety”
  – SHARED accountability
  – Need an open forum for Q & A from ANY team member

• The Daily Huddle
  – Clinical Update
  – Staffing issues
  – Feedback leads to modification of protocols
  – “The Family Rules”
    • Follow all Standard Operating Procedures
    • Ensure that others follow Standard Operating Procedures
    • Report all accidents and near-misses
    • Report any new symptoms via employee monitoring protocol
Operational Lessons Learned

• The administrative portion of caring for an Ebola patient requires a significant amount of time
  • Conference calls, media, etc.

Press conference at UNMC

Media at Emory University Hospital
Operational Lessons Learned

• Input from ancillary services is crucial
  • Radiology
  • Dialysis
  • Respiratory therapy
  • Nutrition
  • Physical therapy
  • Blood bank
Operational Lessons Learned

• Personal protective equipment
  • The most important aspect of utilizing appropriate PPE is the supervision of the donning and doffing process.
Operational Lessons Learned

• Waste disposal
  • Significant amount of waste generated for 1 patient
  • Need to establish method for safe waste disposal (solid and liquid)

• Laboratory support
  • Patients require intense laboratory monitoring
  • Need point-of-care laboratory capabilities
  • Establish protocols for the availability of a full complement of laboratory tests

University of Nebraska Medical Center

Nebraska Medicine

Emory Medicine

Serious Communicable Diseases Unit
Ebola Educational Initiatives

- UNMC/Emory/CDC Collaborative
  - On-site visits to other medical facilities preparing for Ebola
  - Team visits to UNMC and Emory for training
  - Phone consultations and webinars

- Goal: Enhance overall preparedness of healthcare facilities
EVD: Coming to a Hospital Near You!

Current Ebola Treatment Centers: 55 Hospitals as of 2/18/2015

- Maricopa Integrated Health Systems; Phoenix, Arizona
- University of Arizona Health Network; Tucson, Arizona
- Kaiser Los Angeles Medical Center; Los Angeles, California
- Kaiser Oakland Medical Center; Oakland, California
- Kaiser South Sacramento Medical Center; Sacramento, California
- University of California Davis Medical Center; Sacramento, California
- University of California Irvine Medical Center; Orange, California
- University of California Los Angeles Medical Center; Los Angeles, California
- University of California San Diego Medical Center; San Diego, California
- University of California San Francisco Medical Center; San Francisco, California
- Children's Hospital Colorado; Aurora, Colorado
- Denver Health Medical Center; Denver, Colorado
- Emory University Hospital; Atlanta, Georgia
- Grady Memorial Hospital; Atlanta, Georgia
- Ann & Robert H. Lurie Children's Hospital of Chicago; Chicago, Illinois
- Northwestern Memorial Hospital; Chicago, Illinois
- Rush University Medical Center; Chicago, Illinois
- University of Chicago Medical Center; Chicago, Illinois
- Johns Hopkins Hospital; Baltimore, Maryland
- University of Maryland Medical Center; Baltimore, Maryland
- National Institutes of Health Clinical Center; Bethesda, Maryland
- Baystate Medical Center; Springfield, Massachusetts
- Boston Children's Hospital; Boston, Massachusetts
- Massachusetts General Hospital; Boston, Massachusetts
- UMass Memorial Medical Center; Worcester, Massachusetts
- Allina Health’s Unity Hospital; Fridley, Minnesota
- Children's Hospitals and Clinics of Minnesota - Saint Paul campus; St. Paul, Minnesota
- Mayo Clinic Hospital - Rochester, Saint Marys Campus; Rochester, Minnesota
- University of Minnesota Medical Center, West Bank campus, Minneapolis, Minnesota
- Nebraska Medicine - Nebraska Medical Center; Omaha, Nebraska
- North Shore System LII/Glen Cove Hospital; Glen Cove, New York
- Montefiore Health System; New York City, New York
- New York-Presbyterian/Allen Hospital; New York City, New York
- NYC Health and Hospitals Corporation/HHC Bellevue Hospital Center; New York City, New York
- Robert Wood Johnson University Hospital; New Brunswick, New Jersey
- The Mount Sinai Hospital; New York City, New York
- MetroHealth Medical Center; Cleveland, Ohio
- Children's Hospital of Philadelphia; Philadelphia, Pennsylvania
- Hospital of the University of Pennsylvania; Philadelphia, Pennsylvania
- Lehigh Valley Health Network - Muhlenberg Campus; Muhlenberg, Pennsylvania
- Penn State Milton S. Hershey Medical Center; Hershey, Pennsylvania
- University of Texas Medical Branch at Galveston; Galveston, Texas
- Texas Children’s Hospital; Houston, Texas
- University of Virginia Medical Center; Charlottesville, Virginia
- Virginia Commonwealth University Medical Center; Richmond, Virginia
- Children’s Hospital of Wisconsin, Milwaukee; Milwaukee, Wisconsin
- Froedtert & the Medical College of Wisconsin – Froedtert Hospital, Milwaukee; Milwaukee, Wisconsin
- UW Health – University of Wisconsin Hospital, Madison, and the American Family Children’s Hospital, Madison; Madison, Wisconsin
- MedStar Washington Hospital Center; Washington, D.C.
- Children’s National Medical Center; Washington, D.C.
- George Washington University Hospital; Washington, D.C.
- Harborview Medical Center; Seattle, Washington
- Seattle Children’s Hospital; Seattle, Washington
- Providence Sacred Heart Medical Center; Spokane, Washington
- West Virginia University Hospital; Morgantown, West Virginia
Thank you