Preparing an Institutional Response
Pharmacotherapy Frontiers

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Disclosures: Spouse works for Merck, Inc.
Nothing else to disclose

Objectives
- Describe the biology, virology, and pathogenesis of Ebola Virus Disease.
- Describe the epidemiology of Ebola, both in West Africa and in developed countries.
- Describe the US cases of Ebola Virus Disease, including the epidemiology, clinical signs and symptoms, clinical management, and outcome.
- Describe prevention strategies currently in use.
- Discuss the available information concerning Ebola Virus Disease medical countermeasures.

Overview
- Ebola Virus Disease Biology and Virology
- The Current West African Outbreak – Epidemiology
- Ebola Virus Disease and Western Medicine – Cases outside Africa
  - Epidemiology
  - Diagnosis
  - Clinical findings
  - Clinical management
  - Outcome
- Prevention
- Institutional Preparedness
- Infection Control
- Progress on the horizon – promising medical countermeasures

Ebola Virus
- Member of the Filovirus family – filamentous single-stranded negative-sense RNA viruses that are capable of causing severe disease in humans and nonhuman primates, and are often referred to as viral hemorrhagic fever viruses.
- Five species known.
  - Ebola bundibugyo
  - Ebola zaire
  - Ebola reston
  - Ebola sudan
  - Ebola tai forest

Ebola Virus Biology
Enzootic Cycle  Epizootic Cycle
Ebola Virus Transmission – 1

- Blood and Body Fluids
- Fomites
- Infected animals (e.g., fruit bats or primates [apes and monkeys]); clearly can be transmitted via contact with blood, fluids, or meat of infected animals.

Ebola Virus Transmission – 2

- Virus present in high quantity in blood, body fluids, and excreta of symptomatic EVD-infected patients.
- Transmission is thought to occur only after symptoms develop; the viral burden clearly rises at symptom onset.
- The risk of EVD transmission is more likely in severe illness (when the Ebola virus levels are highest).
- One study evaluated 31 environmental specimens from an Ebola isolation ward. All these specimens were negative by PCR.
- EVD among healthcare personnel is associated with direct contact with infected persons (or the bodies of persons who died from EVD), direct contact with body fluids from EVD patients, and occupational in from with needles, etc.

Ebola Virus Pathogenesis

- Immune response
- Cytokine release
- Inflammatory response
- Vascular leak
- Clinical course of Ebola (progressive disease)

Clinical Course of Ebola Virus Disease

- Incubation period: 2 to 21 days
- Symptoms: High fever, headache, muscle, weakness, vomiting, diarrhea, abdominal pain, jaundice, respiratory distress
- Mortality rate: 70% to 90%
- Recovery or death

Ebola Outbreak in West Africa – March 2014

Ebola Outbreak in West Africa – April 2014
Ebola Virus Disease Cases and Deaths*

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*Updated case counts available at http://www.who.int/demographic_health/outbreaks/2014_ebola/virus_cases_world_map/en/


Genomic Sequencing of the Ebola Outbreak

- 99 isolates from May-June 2014 sequenced (395 mutations)
- 50 fixed, non-synonymous changes, 4 of them in highly conserved areas of the genome
- No Evidence of significant functional change

Sequencing and Transmission Routes

Ebola in the air? A nightmare that could happen

Elizabeth Cohen, Medical Director, Center for Disease Control and Prevention, said it is the worst nightmare in her public health career: "If it were to happen in the US, it would be devastating, more devastating than any respiratory transmissible virus."
Medical Evacuations from West Africa

Source: The European Centre of Disease Prevention and Control (ECDC)

Cases Medically Evacuated to the U.S.


First US Ebola Case

First Ebola Case Diagnosed in the U.S.

Timeline

- September 19: Recorded a Brussels Airlines flight to Brussels.
- September 21: Returned to Brussels.
- September 22: Travelers on Brussels Airlines flight.
- October 8: Passed virus test in Brussels.
- October 9: Diagnosed in Texas.

Source: The New York Times
Travel from the Ebola Epidemic Region

On average, each day 150 to 250 individuals arrive in the U.S. from the three nations in which Ebola is epidemic.


Ebola Virus Diagnosis

- Real Time PCR (RT-PCR)
  - Used to diagnose acute infection
  - More sensitive than antigen detection ELISA
  - Identification of specific viral genetic fragments
  - Performed in select CLIA-certified laboratories

- RT-PCR sample collection
  - Volume: minimum volume of 4mL whole blood
  - Plastic collection tubes (not glass or heparinized tubes)
  - Whole blood preserved with EDTA is preferred
  - Whole blood preserved with sodium polyanethol sulfonate (SPS), citrate, or with clot activator is acceptable

Source: CDC Website - http://www.cdc.gov/ebola/healthcare providers.

Interpreting Negative Ebola RT-PCR Results

- If symptoms started ≥3 days before the negative result:
  - EVD is unlikely → consider other diagnoses
  - Infection control precautions for EVD can be discontinued unless clinical suspicion for EVD persists

- If symptoms started <3 days before the negative RT-PCR result:
  - Interpret result with caution
  - Repeat the test at ≥72 hours after onset of symptoms
  - Keep in isolation as a suspected case until a repeat RT-PCR ≥72 hours after onset of symptoms is negative

Source: CDC Website - http://www.cdc.gov/ebola/healthcare providers.

Clinical Observations

- Major issue is decreased vascular volumes and capillary leak syndrome due to both direct and indirect endothelial cell damage;
- Patients leak fluid into their 'third spaces' at an alarming rate
  - At Emory some of the patients gained as much as 40 pounds of water weight, yet remained profoundly hypovolemic
  - Their patients also lost as much as 10 L/day
- Electrolyte abnormalities are often profound, patients are often hypokalemic, hypocalcemic, hypomagnesemic, and hyponatremic


Clinical Observations

- Aggressive supportive care is crucial to success;
- Nursing care is labor-intensive
- Patients at all three centers have needed emotional support;
- Some patients have needed physical therapy as well as nutritional support (patients may be malnourished).

Clinical Prognosis

- Case-fatality rate to date is 71% for the 2014 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.
- Prolonged convalescence.
  - Includes arthralgia, myalgia, abdominal pain, extreme fatigue, and anorexia; many symptoms resolve by 21 months.
  - Significant arthralgia and myalgia may persist for >21 months.
  - Skin sloughing and hair loss has also been reported.

Organ System Involvement in West African Ebola Outbreak

<table>
<thead>
<tr>
<th>Organ System</th>
<th>Clinical Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal</td>
<td>Nausea, vomiting, diarrhea, anorexia, abdominal pain</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Chest pain, dyspnea, cough</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>Cough, dyspnea, sore throat</td>
</tr>
<tr>
<td>Hematological</td>
<td>Thrombocytopenia, leukopenia, neutrophilia</td>
</tr>
<tr>
<td>Neurological</td>
<td>Headache, confusion, coma</td>
</tr>
</tbody>
</table>

Laboratory Findings

- Thrombocytopenia (50,000–100,000/mL range).
- Initial leukopenia followed by neutrophilia.
- Elevations of transaminases: serum aspartate amino-transferase (AST) > alanine amino-transferase (ALT).
- Dramatic electrolyte abnormalities.
- Coagulation abnormalities – PT and PTT prolonged.
- Renal: proteinuria, increased creatinine.

Detection of Ebola Virus in Different Human Body Fluids over Time

Immunological Findings

Challenges to Successfully Managing Imported Ebola-Infected Patients – Institutional Preparedness

- Effective exit and entrance screening of individuals arriving from the epidemic areas.
- Effective identification of patients in Emergency Rooms and other acute care settings.
- Assurance that institutions can provide safe care for patients.
- Appropriate use of PPE, routine use of trained monitors.
- Managing the waste stream.
**Airport Screening**

**Exit Screening**
- Fever
- Presence of symptoms
- History of contact with known Ebola patient
- Refuse exit if screen positive

**Entry Screening**
- Instituted October 2014
- Fever
- Presence of symptoms
- History of contact with known Ebola patient
- Refer for further evaluation, and quarantine, if warranted

**Managing Ebola-Infected Patients**

- All institutions –
  - Must have effective strategies for screening for exposure/travel history of emergency room and outpatients, at the initial interaction – this interaction must be focused, precise and clear (CDC checklist);
  - For patients who have any symptoms and positive exposure/travel histories, institutions (CDC checklist), Must have:
    - The ability to place patients safely on empiric isolation precautions immediately;
    - Streamlined procedures for urgent interaction with public health authorities to determine next steps;
    - Strategy to assure that all staff interactions include full PPE.

**Managing Ebola-Infected Patients**

- All institutions –
  - Must work with local and national public health authorities to determine whether or not to provide comprehensive care for EVD patients.
  - For institutions that plan to refer patients to regional or tertiary centers, procedures for safe transport/transfer of patients to a location where comprehensive care can be provided must be developed and implemented;

**Institutional Planning for Managing Ebola-Infected Patients Comprehensively**

- An institutional effort – involves every department.
- Components include (but not limited to):
  - Effective early screening for infection;
  - Safe transport – both to the hospital and within the hospital (staff and infrastructure);
  - Effective containment and PPE;
  - Training (and retraining) of staff (physicians, nurses, technologists, trained observers, etc.);
  - Simulation for procedures and intensive care;
  - Refresher training;
  - Standard operating procedures to assure safe care and safe laboratory practices;
  - Internal and external communication –
    - Keeping staff informed; managing hysteria, fear and dissention.

**Planning for Managing Ebola-Infected Patients**

- An institutional effort – involves every department
  - Physician staff
    - Infectious Diseases
    - Critical Care
  - Anesthesiology
  - Medical and surgical subspecialty consultants
  - Nursing
  - Clinical laboratory leadership and staff
  - Facilities management
  - Environmental services
  - Communications
Planning for Managing Ebola-Infected Patients

- Strategies for safe transport

Effective Containment – Emory University Medical Center Containment Unit

Effective Containment – NIH Clinical Center Special Clinical Studies Unit

Institutional Infection Control Considerations

- Guidelines are far too complex for detailed description.
- Prudence mandates an abundance of caution.

Specific CDC guidelines are available at the following sites:

- Information about Personal Protective Equipment (including donning and doffing) – http://www.cdc.gov/vhf/ebola/hcp/procedures-for-ppe.html

Source: CDC Website – http://www.cdc.gov/vhf/ebola/hcp/index.html

Institutional Infection Control Considerations

- Key issues for consideration – 1
  - High-level containment units not required, but do offer advantages.
  - Care is labor-intensive and requires many staff
    - Use of the “buddy” system is key to success
    - In our experience use of an independent, trained observer (a “watchman”) is key to safe use of PPE
  - Development of (and rigid adherence to) Standard Operating Procedures
    - SOP’s are a moving target
    - SOP’s should be tailored to the individual institution
Key Issues for consideration – 2

- Highest level of risk is likely associated with 'doffing' and management of needles and sharp objects.
- Crucial to anticipate laboratory needs; laboratory guidance not yet clear; where possible, point-of-care testing is optimal.
- Dedicated equipment is also important.
- We have aggressively used hydrogen peroxide vapor decontamination of equipment and the environment.
- Practice, practice, practice—full dress rehearsals.

Risk Levels for People (including HCW’s) who may have been Exposed to Ebola’s — 1*


Risk Levels for People (including HCW’s) who may have been Exposed to Ebola’s — 2*

Risk Mitigation

- **Standard Operating Procedures Should be a Constant “Work in Progress”**
  - Procedures should be constantly reevaluated for risk-points;
  - Failure mode and effects analysis (FMEA) is a powerful prospective tool for such assessments;
  - Instances of protocol violation should precipitate Root Cause Analyses (RCAs);
  - Creativity is key to risk mitigation;
  - Encourage questioning: "How can we do this better or safer?"
  - What kinds of quality care can be delivered without having the physician enter the room?
  - All team members have an equal voice
  - Practice.

Safe Clinical Laboratory Practices

- CDC developed interim guidance for laboratory workers and healthcare personnel who collect or handle specimens
- The guidance includes information about the appropriate steps for collecting, transporting, and testing specimens from patients who are suspected to be infected with Ebola
- Specimens should NOT be shipped to CDC without consultation with CDC and local/state health departments
- Not all authorities are comfortable with these recommendations; for example the American Society for Microbiology has recommended that only "point-of-care" testing be used

Ebola – Medical Countermeasures: Therapeutics

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<th>Agent</th>
<th>Mechanism of Action</th>
<th>Evidence of Efficacy</th>
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<tbody>
<tr>
<td>Drug</td>
<td>Combination of three humanized mouse monoclonal antibodies directed against Ebola glycoprotein</td>
<td>Documented efficacy in primate studies</td>
</tr>
<tr>
<td>Vaccines</td>
<td>Small, interfering RNA</td>
<td>Human Phase 1 trials in progress</td>
</tr>
<tr>
<td>EID-12A</td>
<td>Nucleoside analog; RNA polymerase inhibitor</td>
<td>Prophylactic efficacy in systemic model of Marburg Virus infection</td>
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<td>Breincovirin</td>
<td>Broad-spectrum antiviral acting as a viral RNA polymerase inhibitor</td>
<td>in vivo activity against flaviviruses in late-stage disease trials evaluating efficacy against other viruses</td>
</tr>
<tr>
<td>Favipiravir</td>
<td>RNA-polymerase inhibitor; already licensed in Japan for influenza</td>
<td>Therapeutic efficacy in a murine model of Ebola</td>
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Ebola – Medical Countermeasures: Vaccines

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<th>Vaccine</th>
<th>Mechanism of Action</th>
<th>Evidence of Efficacy</th>
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<tr>
<td>NIAID/GSK Vaccine</td>
<td>Replication incompetent chimpanzee adenovirus vector containing gene for Ebola glycoprotein</td>
<td>Efficacy in animal trials; now in Phase 1 human testing; Phase 2 trials are complete; awaiting results</td>
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<tr>
<td>K01 Vaccine</td>
<td>Replication competent adenovirus vector containing gene for Ebola glycoprotein</td>
<td>Human Phase 1 trials in progress</td>
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Phase I Trial of NIAID/GSK Candidate Ebola Vaccine Now Fully Enrolled

2079 participants have received the vaccine; no immediate safety issues; formal data about safety and immunogenicity should be available in late November 2014
Chimpanzee adenovirus vaccine generates acute and durable protective immunity against ebolavirus challenge

John C

Annie W  C

limitation, have fied virus have been evaluated as vaccine vectors In primates and human clinical trials 5 -'

low worldwide are not human sera 4 Here evaluated monovalent (EBOV GP) or bivalent (EBOV plus ebolavirus ChAd- ebolavirus vaccines protection against acute EBOV challenge and durable protection using and approaches.

* Protected 4/4 rhesus macaques from lethal Ebola inoculation

Going Forward...

- Improved public health infrastructure.
- Humanitarian assistance.
- Careful implementation of safe and effective care strategies.
- Meticulous attention to infection control.
- Public health interventions – contact tracing and follow-up.
- Effective internal and external communication.

Obtaining CME/CE Credit

If you would like to receive continuing education credit for this activity, please visit:

http://nih.cds.pesgce.com

Phase I Trial of Canadian VSV-Based Candidate Ebola Vaccine to Begin

The Washington Times

HOME NEWS OPINION SPORTS MEDIA MARKET

By: Joseph J. Viola, The Washington Times

Early trials in the US, Canada, Gabon, and Kenya

Decisions usually involve risk.....