Ebola and Other Emerging Occupational Infections

AOHC
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2014 Disease of the Year
2014 Person (Heroes) of the Year

THE EBOLA FIGHTERS

Ebola Virus

Filovirus Family (Marburg and Lassa Fever)
5 distinct species in the Ebola genus
Enveloped, filamentous, ssRNA virus (- sense)
(Note: Lassa HF is an Arenavirus)
Ebola Virus

Multiple Ebola viruses can infect a single cell

Broad cell tropism (monocyte, macrophage, dendritic cells)

Surface Glycoprotein (GP) is responsible for attachment and fusion to cells

Soluble Glycoprotein (sGP) is secreted from infected cells and subverts the host immune system via pro-inflammatory cytokines and chemokines (SIRS or Cytokine Storm) and pro-coagulant protein tissue factors leading to lymphoid depletion and DIC

Ebola Virus Disease Transmission

No shedding prior to symptom onset

Very difficult to detect by PCR even up to 3 days of illness

Reference: http://www.cdc/vhf/ebola/

Ebola Virus Disease Transmission

Transmission

• Direct contact (through mucous membranes > broken skin) with bodily fluids (i.e. blood, urine, stool, breast milk, saliva, semen) of an infected patient

• Indirect contact (through mucous membranes > broken skin) with environments (fomites) contaminated with infected bodily fluids (can survive several days in blood, vomit and stool)

Reference: http://www.cdc/vhf/ebola/
Ebola Virus Disease Transmission

No airborne transmission (vs SARS, MERS-CoV, TB, Influenza)
• Neither through water nor food
• However, in Africa, Ebola may be spread as a result of handling bushmeat (wild animals hunted for food) and contact with infected bats.

Reference: http://www.cdc.gov/vhf/ebola/

Epidemiology of EVD

Incubation period clusters heavy around 8-10 days (2-21d)

Cause of death in the majority of EVD patients is due to hypovolemic shock (not hemorrhage)

The significance of survivors is that the victim can generate an effective immune response, if they can survive their viremia

Advanced medical care improves their odds of survival

Epidemiology of EVD

Ebola is an outbreak disease (in contrast to Malaria or HIV); only zero cases will end the outbreak

Confusion about the terms "bodily fluid," "droplet," & "aerosol"

Environmental contamination (fomites) or medical equipment

Animal reservoirs (bats, gorilla via bushmeat)
Detection of Ebola Virus in Body Fluids over Time

Ebola Virus Transmission is Overwhelmingly by Direct Contact

Absence of Airborne Ebola transmission in non-human primates

(Canadian Experiments, 2014)

Ebola Virus Transmission is Overwhelmingly by Direct Contact

Investigation of 173 contacts in 27 households in Kikwit, DRC, 1995

- Ebola transmission occurred only to those with direct physical contact or exposure to body fluids of the ill household member
- No transmission to the 78 household members who had no physical contact with the ill person
Ebola Virus Transmission is Overwhelmingly by Direct Contact

Investigation of three generations of EBV transmission in Uganda, 2003
Demonstrated that direct contact with patient body fluids was the strongest risk factor for transmission, with contaminated fomites as a possible lesser risk factor.

Severe and Acute Febrile Diseases in Ebola-endemic African Populations

- Malaria
- Typhoid Fever
- Shigellosis
- Meningococcemia
- Fulminant Viral Hepatitis
- Leptospirosis
- Typhus
- Murine Typhus
- Yellow Fever
- Chikungunya Fever
- Marburg
- Lassa Fever
- Plague
- Anthrax
- Relapsing fever (Borrelia recurrentis)

Clinical Presentation of EVD

- First symptoms
  - Day 7-9: Headache, fatigue, fever, muscle soreness
  - Day 10: Sudden high fever, vomiting, bleeding
- Final stages
  - Day 11: Loss of consciousness, seizures, massive internal bleeding, death

Source: World Health Organization, BBC Graphic Media Viewing © 2014 MCT
Time from Onset to Death for EVD

Ebola
Time from Onset to Death

Medical Management Breakthrough in EVD

A major breakthrough in understanding of the pathophysiology of Ebola virus disease occurred only during this 25th Epidemic of EVD.

It was only when EVD patients were given the opportunity to benefit from the advanced medical care available at “state of the art” hospitals that the key pathologic disturbances were identified and addressed to improve the survival of EVD patients.

Medical Management of EVD

In addition to treating concurrent infections (e.g., malaria, typhoid), understanding the critical pathologic processes (capillary leak syndrome, SIRS, or Cytokine Storm) led to improved survival outcomes.
Medical Management of EVD

- Aggressive IV volume resuscitation
- Aggressive K+ replacement
- Broad spectrum antibiotics (GN Sepsis)
- Ventilator support (O2)
- Dialysis support
- ICU management of multi-organ failure

Medical Evacuations of EVD Patients to the USA and Europe (as of 3-29-15)

26 EVD Patients in Europe and USA
Demographics: Median age 37 (26-75)
- Male (70%)
- HCW (78%)
- Median Days from Sx Onset to Dx: 3.5 days
- Median Days from Sx to Hospitalization: 5 days
- Median Days from Sx to Medical evacuation: 7 days

“Initial” Symptoms of EVD Evacuees

- Fatigue 71%
- Fever 57%
- Weakness 48%
- Headache 39%
- Myalgia 35%
- Anorexia 19%
- Sore Throat 15%
- Pleuritic 10%
- Rhinorrhea 10%
- Arthralgia 10%
- Abd. Pain 5%
- Diarrhea 5%
- Nausea, vomiting or cough 0%
"Admitting" Symptoms of EVD Evacuees

- Fever 38.1°C (100.6°F) X 5-5 days 50%
- General Malaise 87%
- Diarrhea X 6 days 70%
- Nausea/Vomiting X 1.5 Days 70%
- Myalgias 57%
- Headaches 52%

Note: Median volume fluid loss = 250 ml/day
(range 100 ml –10,000 ml/day)

ICU Management of EVD Evacuees

- IV Fluids 96% (70% CVP, 30% PICC)
- Antiemetics 83%
- Loperamide 23%
- Anticonvulsants 5%
- WB/Plasma 27%
- Platelets 22%
- Antibiotics 83%
- Antifungals 26%
- Antimalarials 6% (empirically)

Laboratory Findings of Medical Evacuees

- Initial Mean Viral load: 27 X 10⁶/ml (0.0001-1.2 X10⁹)
- Peak Mean Viral Load: 65 X 10⁶
- Days to first negative Viral Load: 16 Days
- Lab findings:
  - \( K^+ \), \( Mg^{2+} \), \( Ca^{2+} \), Albumin
  - Transaminases (AST >> ALT), up to 3,000
Clinical Course of EVD Evacuees

Respiratory:
• Hypoxia 52%
• Pulmonary Edema 43%
• Pneumonia 17%
• Respiratory Failure 35%
• ARDS 27% (70% needed O2; 40% needed Ventilator support)

Clinical Course of EVD Evacuees

Renal:
• Oliguria 39%
• Anuria 22% (25% required dialysis)

Cardiac: Arrhythmias / ECG Abnormalities 17%

GI:
• Ileus 17%
• Intestinal paresis 17%
• Abdominal distention 39%

Clinical Course of EVD Evacuees

SIRS:
• Sepsis 26%
• Septic Shock 9%
• Cytokine Storm 61%
• (30% required vasopressors)
Clinical Course of EVD Evacuees

CNS:
- Delirium 35%
- Seizure 4%
- Coma 13%
- Encephalopathy / Encephalitis 35%

Infection: Malaria 4%

Prognosticating Biomarkers in EVD

Negative clinical laboratory biomarkers in fatal EVD cases:
- Elevated aspartate aminotransferase (AST)
- Elevated D-dimer
- Elevated blood urea nitrogen (BUN) and creatinine
- Reduced levels of calcium and albumin

Negative clinical laboratory biomarkers involved in immune function:
- Elevated cytokines and chemokines (interleukin 8 (IL-8) and GRO-alpha)
- Elevated C-reactive protein (CRP)
- Elevated serum amyloid antigen (SAA)
Prognosticating Biomarkers in EVD

Negative clinical laboratory biomarkers involved in coagulation and endothelial activation:

- Elevated ferritin and thrombomodulin levels (maintains the endothelium)

Clinical Outcomes of Medical Evacuees

A high viral load on admission was significantly correlated to a poorer response

- If patient was still ill at day 14 (13% case fatality)
- If patient was still ill at day 28 (22% case fatality)

Note: 50-70% case fatality in West Africa

Diagnostics Available to Most US ETCs

Currently, we are relying on Syndromic Surveillance (travel history and fever) for initial screening, as well as “direct active monitoring” following exposure

Within a few days after symptoms begin:
- ELISA
- IgM ELISA
- Polymerase chain reaction (PCR)
- Virus isolation
Diagnostics Available to Most US ETCs

Later in disease course or after recovery
• IgM and IgG antibodies

Retrospectively in deceased patients
• Immunohistochemistry testing
• PCR
• Virus isolation

Note: PCR tests at ETC’s must be approved by CDC (even if at State Health Lab)

Note: PCR tests have been shown to be negative up to 3 days after onset of illness

Novel “Point of Care” Diagnostic Tests

Multiplexed Protein Microarrays Technology
• Ability to screen for specific antibody responses to the six species of Ebola and Marburg
• Simple; quick; requiring only microliters of the patient’s blood
• A low-cost, point-of-care assay to expedite diagnosis and allow for serological surveillance in endemic countries

Tests used at the three USA (Tier 1) High Level Biocontainment Medical Facilities
• BioFire Defense – FilmArray Ebola PCR (1 hour) Test
• Cogenix – ReEBOV Rapid Antigen Diagnostic (15 min) Test

The Role of R & D in EVD
Novel Therapeutics in EVD

Antiviral Monoclonal Therapies

• zmAPP (a treatments originally developed for Anthrax) is a novel monoclonal therapy manufactured in tobacco plants.
• The cocktail of mAbs target different epitopes or virulence factors and may be useful in EBV post-exposure prophylaxis.
• Very limited supply
• LIMITATION: Requires 10-12 hour IV infusion

Small Interfering RNA compounds (e.g. TKM-Ebola)

RNA-polymerase inhibitors
Favipiravir (Japanese pandemic flu therapy)
Nucleotide analogue Brincidofovir (prodrug of Cidovir)

Amiodarone, a multi-ion channel inhibitor anti-arrhythmic that appears to also a potent inhibitor of filovirus cell entry

FX-06F, a fibrin-derived Peptide that combat the “Capillary Leak Syndrome”

Use of Investigational Therapeutics in EVD Evacuees

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>13%</td>
</tr>
<tr>
<td>Monotherapy</td>
<td>17%</td>
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<tr>
<td>Two drugs</td>
<td>34%</td>
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<tr>
<td>Three drugs</td>
<td>26%</td>
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<tr>
<td>Four drugs</td>
<td>4%</td>
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<tr>
<td>Overall</td>
<td>60%</td>
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Note: At NIH, Nina Pham received Brincidofovir, Z-MAPP, TKM-EBOLA, Convalescent Plasma
Vaccines in EVD

rVSV-ZEBOV (NewLink/Merck) Guinea, Sierra Leone
(Phase III)(Ring Trial/ Stepped Wedge)

ChAd3-ZEBOV (GSK/NIAID) Liberia (Phase III)
(Randomized Control Trial)

Convalescent Plasma/WB Guinea, Sierra Leone, & Liberia
(Phase II/III)

Purified glycoprotein (Novavax) U.K. (Phase II)

Ebola Virus PEP

Injection (via contaminated needles) is 100% efficient in
transmitting EVD compared with 80% for an exposure via skin
break or mucous membranes (Zaire [DRC], 1976)

The incubation period is shorter via percutaneous exposure
(6.3 days compared with 9.5 days)

Note: This would argue for the immediate transfer to a Tier 1
hospital and consideration for experimental therapies for any
Ebola needle stick exposure for receipt of VSV-EBOV and/or
TKM-EBOVA

Controversial Issues associated with EVD exposure:
1. Squeeze the puncture wound to express blood
disproven folklore treatment)
2. Cutting down to the base of the puncture site (e.g.
B-virus; Rabies PEP)
3. Decontamination of the surface with an "enveloped"
virus antiseptics
Current Ebola Virus US PEP Options

Immediate Treatment following a mucocutaneous exposure
- 15 minute copious irrigation of the mucous membranes with saline
- Additional surface decontamination following removal of PPE

“Observation” (Emory, NIH, & NMC)

- Immediate assessment
- “Observed” Temperatures BID X 21 Days
- Any symptoms require OMS evaluation
- Any travel out of area require approval

For High-risk Exposures (e.g. needle stick)
- VSV-ZEBOV (Emory, NIH, & NMC)
- TKM-EBOLA (Emory)

Conclusion

Risk assessment is essential and should be evidence-based (i.e. **only** high risk exposure is most concerning)

The face of Ebola is changing and expect other “hard lessons.”

Some things we are doing “out of an abundance of caution” are probably wrong and we must not allow irrational fears to hamper scientific advancement.

Medical Management of EVD

References