Pathogens of Concern
& Caring for the Patients who Harbor Them

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Bruce Ribner MD MPH
Learning Objectives

• Gain an appreciation for those pathogens that might warrant management in a BCU.

• Understand the principles of clinical care in high level isolation.

• Become familiar with clinical pearls gleaned from patients with serious communicable diseases.
Potential Candidates for Admission to a BCU

Persons Infected With:

- BSL-4 agents with person-to-person spread.
- Other highly hazardous communicable pathogens.
- Unknown diseases which appear highly hazardous.
  - The “Andromeda Strain” problem
- Diseases with public assuredness concerns.
Biosafety Levels

Biosafety terminology was NOT intended to apply to clinical facilities.

Experts agree that BSL-4 controls are not necessary in order to safely manage patients with diseases caused by BSL-4 pathogens.

<table>
<thead>
<tr>
<th>Biosafety Level</th>
<th>Laboratory</th>
<th>Clinical Correlate</th>
</tr>
</thead>
<tbody>
<tr>
<td>BSL-1</td>
<td>High School Biology Lab</td>
<td></td>
</tr>
<tr>
<td>BSL-2</td>
<td>Hospital Laboratory</td>
<td>Standard Room or Ward</td>
</tr>
<tr>
<td>BSL-3</td>
<td>State Health Lab</td>
<td>Isolation Room or Ward</td>
</tr>
<tr>
<td>*BSL-3+</td>
<td></td>
<td>BCU</td>
</tr>
<tr>
<td>BSL-4</td>
<td>CDC, USAMRIID</td>
<td>The “Slammer”</td>
</tr>
</tbody>
</table>

*This terminology is not widely recognized
The Downside of BSL-4-like Care

- Intense training needs
- Loss of tactile sense
- Loss of auditory sense
- Awkwardness & Clumsiness
- Claustrophobia
- Expense
The BSL-4 Pathogens

All except Variola cause VHF

- Filoviridae
  - Ebola
  - Marburg
- Arenaviridae
  - Lassa
  - Guanarito
  - Junin
  - Machupo
  - Sabia

- Flaviviridae*
  - RSSE & CEE
  - TBE Complex
  - Kyasanur Forest
  - Omsk

- Bunyaviridae
- Orthopoxviruses
  - Variola

*Vector-Borne; no known PTP transmission
The Arenaviruses

<table>
<thead>
<tr>
<th>Virus</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Old World Arenaviruses</td>
<td></td>
</tr>
<tr>
<td>Lassa</td>
<td>Lassa Fever</td>
</tr>
<tr>
<td>New World Arenaviruses</td>
<td></td>
</tr>
<tr>
<td>Guanarito</td>
<td>Venezuelan HF</td>
</tr>
<tr>
<td>Junin</td>
<td>Argentine HF</td>
</tr>
<tr>
<td>Machupo</td>
<td>Bolivian HF</td>
</tr>
<tr>
<td>Sabia</td>
<td>Brazilian HF</td>
</tr>
</tbody>
</table>
Mechanisms of Transmission

Contact or Fomites:
- Ebola
- Marburg
- Lassa
- Other VHF
- Variola
- Monkeypox

Droplets:
- Ebola
- Marburg?
- Nipah
- Hendra?
- Influenza
- Plague
- Monkeypox

Droplet Nuclei:
- Variola
- XDR-TB
- SARS?
- MERS?
Viral Hemorrhagic Fever

- Hantavirus Pulmonary Syndrome
- Dengue HF
- Venezuelan HF
- Bolivian HF
- Argentine HF
- Lassa
- Yellow fever
- Marburg
- Ebola
- Rift Valley Fever

Filoviruses
Flaviviruses
Bunyaviruses
 Arenaviruses

Courtesy of Mike Bray, NIAID
How contagious is Ebola?

How the Ebola virus compares with other contagious viruses. The reproduction rate or $R_0$, calculates the number of people likely to be infected by one person who has a disease.

**REPRODUCTION RATE ($R_0$)**

<table>
<thead>
<tr>
<th>$R_0$</th>
<th>1 to 4 people</th>
<th>2 to 4</th>
<th>4 to 7</th>
<th>5 to 7</th>
<th>5 to 7</th>
<th>6 to 7</th>
<th>12 to 18</th>
<th>12 to 17</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DISEASE</strong></td>
<td>Ebola</td>
<td>SARS</td>
<td>Mumps</td>
<td>Polio</td>
<td>Smallpox</td>
<td>Rubella</td>
<td>Measles</td>
<td>Pertussis (Whooping cough)</td>
</tr>
<tr>
<td><strong>HOW IT SPREADS</strong></td>
<td>Bodily fluids</td>
<td>Airborne droplets</td>
<td>Airborne droplets</td>
<td>Fecal-oral route</td>
<td>Airborne droplets</td>
<td>Airborne droplets</td>
<td>Airborne</td>
<td>Airborne droplets</td>
</tr>
</tbody>
</table>

Sources: Michigan Center for Public Health; WHO; Transmission Dynamics and Control of Severe Acute Respiratory Syndrome, Nature; Understanding the Dynamics of Ebola Epidemics, National Institute of Health

VHF Misperceptions

1. They all have the same features.
2. They all spread easily.
3. They are easily recognizable.
4. Bleeding is the primary cause of death.
## Distinguishing Features Among the VHF

<table>
<thead>
<tr>
<th>Feature</th>
<th>VHF</th>
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<tbody>
<tr>
<td>Jaundice</td>
<td>YF, RVF, CCHF</td>
</tr>
<tr>
<td>Renal Failure</td>
<td>Hantaviruses, YF</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>New-World Arenaviruses, Filoviruses, YF, Omsk, Kyasanur Forest</td>
</tr>
<tr>
<td>Rash</td>
<td>Dengue, Filoviruses, Lassa</td>
</tr>
</tbody>
</table>
Hemorrhagic signs near the end of the first week

- Bleeding doesn’t generally kill people; organ failure does.
## The Lethal VHFs

<table>
<thead>
<tr>
<th>Virus</th>
<th>Mortality Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ebola Zaire</td>
<td>65-90%</td>
</tr>
<tr>
<td>Marburg</td>
<td>25-90%</td>
</tr>
<tr>
<td>Lassa</td>
<td>15-20% of hospitalized</td>
</tr>
<tr>
<td>CCHF</td>
<td>3-30%</td>
</tr>
<tr>
<td>RVF</td>
<td>50% with hemorrhagic form</td>
</tr>
</tbody>
</table>
Providing Clinical Care in High-Level Containment

• Relatively limited diagnostic testing.
  o Laboratory tests
  o Imaging tests
    o Portable x-rays require advance planning/protocols.
    o Use of point of care ultrasound for diagnostic imaging and procedure guidance.

• Invasive procedures in PPE
  o Threshold may be different – response time to deteriorating patient is longer in isolation due to PPE donning.
  o Emergent procedures more likely to lead to exposures.
  o Consider simulation exercises of procedures – central line placement, endotracheal intubation.

• Consider telemedicine based consultations when possible.
  o Limit the number of providers who need to enter the patient room.
Caring for the VHF Patient: the Wide Range of Severity

- 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 a serious communicable disease is either confirmed or ruled out.
  - Additional considerations for range of ages possible from infants to older adults.
Caring for the VHF Patient: Emerging Critical Illness Phenotype

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

Courtesy of Michael Connor
Clinical Considerations

- Airway Management
- Central Line Placement
- Nutrition & Electrolytes
- Blood Product Support
- Renal Replacement
Caring for the VHF Patient: the Critical Role of Nursing

• Providing high-level nursing and supportive care essential.

• 24/7 one-on-one nurses allowed for rapid adjustment of care.

• Ability to support patients in: nutrition, physical therapy, self care

• Emotional support

• Family support

• Patient- and Family-Centered Model of Care
Licensed Therapy and Prophylaxis

Ribavirin for Lassa Rx

YF-Vax for Yellow Fever Prevention
Beyond the VHFs: Other Highly Hazardous Communicable Pathogens

- Coronaviruses
  - SARS
  - MERS
- Henipiviruses
  - Nipah
  - Hendra?
- Orthopoxviruses
  - Smallpox*
  - Monkeypox
- Highly Pathogenic Avian Influenza (HPAI)
- Other novel and pathogenic influenza viruses
- Pneumonic Plague
- XDR-TB

*included in the list of BSL-4 pathogens
The Coronaviruses

Causes of the Common Cold

- 229E
- NL63
- OC43
- HKU1
- MERS
- SARS
SARS

- Produces severe lower respiratory illness.
- Appeared in China in 2002
- No reported cases since 2004
- There have been 8273 total cases recorded.
  - 775 deaths
  - 27 US cases (no deaths)
- Overall mortality was 9.6%
The MERS virus

MERS-CoV  Middle East Respiratory Syndrome

Coronavirus: family of common viruses that affect humans and animals, including the SARS virus which killed nearly 800 people around the world in 2003

First detected April 2012  Not seen in humans before

Confirmed worldwide

1,179 cases
442 deaths
As of June 3

All cases have had some connection with the Middle East

Countries affected

SOUTH KOREA
Since May 2015
40 cases
4 deaths

Source: WHO
The Henipaviruses

Blue = Nipah
Red = Hendra
Nipah
Hemagglutinin
Allows the flu virus to adhere to the respiratory tract

Neuraminidase
Allows the flu virus to escape from respiratory cells after replication
Risk Factors for Novel Influenza or HPAI

- Pigs harbor human strains.
- Pigs harbor avian strains.
- Pigs thus serve as “mixing vessels”.
- Antigenic shift occurs in the pig.
- The fear: a new virus with human affinity and avian mortality.
The Orthopoxviruses:
Smallpox
Meschede Smallpox Outbreak, 1969

Pt 8 visits evening of 3rd day, stood in lobby for 15 minutes – not permitted to visit because flu outbreak

From Wehrle et al. 1970
Yugoslav Smallpox Outbreak, 1972

Single traveler returning from Hajj to Mecca through Iraq. Over 140 cases of smallpox were documented.

Nearly 7 million doses of vaccine needed to bring the outbreak under control.
Human Monkeypox
Democratic Republic of Congo
Human Monkeypox
Why we care in Nebraska

- 2003 Midwest Outbreak
- 71 reported cases
- Traced to Gambian Rats
  - Spread to Prairie Dogs
- No mortality in US
  - Traditionally, 1-10% fatal
- Widespread fear
  - Some clinicians refused care

**TABLE 1. Number and percentage of laboratory-confirmed monkeypox cases, by selected characteristics — United States, 2003**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No.</th>
<th>(%)</th>
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</thead>
<tbody>
<tr>
<td>State</td>
<td></td>
<td></td>
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<tr>
<td>Illinois</td>
<td>8</td>
<td>(23)</td>
</tr>
<tr>
<td>Indiana</td>
<td>7</td>
<td>(20)</td>
</tr>
<tr>
<td>Kansas</td>
<td>1</td>
<td>(3)</td>
</tr>
<tr>
<td>Missouri</td>
<td>2</td>
<td>(6)</td>
</tr>
<tr>
<td>Wisconsin</td>
<td>17</td>
<td>(49)</td>
</tr>
<tr>
<td>Age group (yrs)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6–18</td>
<td>11</td>
<td>(31)</td>
</tr>
<tr>
<td>19–51</td>
<td>24</td>
<td>(69)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>18</td>
<td>(51)</td>
</tr>
<tr>
<td>Male</td>
<td>17</td>
<td>(49)</td>
</tr>
<tr>
<td>Possible sources of monkeypox exposure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prairie dog(s)</td>
<td>14</td>
<td>(40)</td>
</tr>
<tr>
<td>Prairie dog(s) and human case(s)</td>
<td>14</td>
<td>(40)</td>
</tr>
<tr>
<td>Premises housing prairie dogs</td>
<td>6</td>
<td>(17)</td>
</tr>
<tr>
<td>Premises housing prairie dog(s) and human case</td>
<td>1</td>
<td>(3)</td>
</tr>
<tr>
<td>Clinical features</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash†</td>
<td>34</td>
<td>(97)</td>
</tr>
<tr>
<td>Fever</td>
<td>29</td>
<td>(86)</td>
</tr>
<tr>
<td>Respiratory symptoms§</td>
<td>27</td>
<td>(77)</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>24</td>
<td>(69)</td>
</tr>
<tr>
<td>Hospitalized‡</td>
<td>16</td>
<td>(46)</td>
</tr>
<tr>
<td>Previous smallpox vaccination**</td>
<td>8</td>
<td>(33)</td>
</tr>
</tbody>
</table>

† Totals might not add to 100 because of rounding.
‡ Excludes one patient who had a single atypical, plaque-like skin lesion and no further lesions.
§ One or more of the following symptoms: cough, sore throat, shortness of breath, and nasal congestion.
† Some persons were hospitalized for isolation precautions and not because of severe illness.
** Information was available for 26 (71%) of the laboratory-confirmed cases.
Pneumonic Plague

Note the Rose-colored ring around the neck
The Good News for Biocontainment Personnel

• Smallpox Vaccine
  – Prevents Smallpox
  – Also prevents Monkeypox
  – Effective 4 days post-exposure

• Antibiotics
  – Treat Plague
  – Can be given prophylactically
Tuberculosis

- **Standard TB**
  - Affects 1/3 of world
  - 1.5 million deaths/year
  - Contagious via droplet nuclei
  - Requires negative pressure room
  - Rx = INH + RIF + ETH + PZA

- **MDR-TB**
  - Resistant to INH & RIF

- **XDR-TB**
  - Resistant to INH & RIF +
  - Resistant to Quinolones or
  - Resistant to Aminoglycosides

Many believe that XDR-TB should be managed in a BCU
The Andromeda Strain

- Patients with unknown diseases could be admitted to a BCU or ETC.

- At the time of their initial outbreaks, these could have been “Andromeda Strains”
  - Nipah
  - Hendra
  - SARS
  - MERS
  - Sin Nombre
  - Many others
The next lecture will detail these “enhanced” precautions.
Questions?
Back-Up Slides
# Managing Potential Laboratory Exposure to Ebola Virus by Using a Patient Biocontainment Care Unit

Mark G. Kortepeter,* James W. Martin,* Janice M. Rusnak,* Theodore J. Cieslak,† Kelly L. Warfield,* Edwin L. Anderson,* and Manmohan V. Ranadive*

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Table 1. Admissions into the medical containment suite at the US Army Medical Research Institute of Infectious Diseases, 1972–2004

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Date of admission</th>
<th>Days in isolation</th>
<th>Virus †</th>
<th>Reason for admission</th>
<th>Therapy ‡</th>
<th>Comments §</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1972 Oct</td>
<td>18</td>
<td>Machupo</td>
<td>Cut finger</td>
<td>IP</td>
<td></td>
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<tr>
<td>2</td>
<td>1975 Oct</td>
<td>42</td>
<td>Machupo</td>
<td>Cut finger</td>
<td>IP, IG</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1976 Oct</td>
<td>21</td>
<td>JEB</td>
<td>Fingerstick</td>
<td>IP</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>1977 Sep</td>
<td>14</td>
<td>Machupo</td>
<td>Vial leak</td>
<td>IP</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>1977 Sep</td>
<td>14</td>
<td>Machupo</td>
<td>Vial leak</td>
<td>IP</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>1978 May</td>
<td>11</td>
<td>Dengue</td>
<td>Not specified</td>
<td>IP</td>
<td>Modified CC</td>
</tr>
<tr>
<td>7</td>
<td>1978 May</td>
<td>8</td>
<td>Dengue</td>
<td>Not specified</td>
<td>IP</td>
<td>Modified CC</td>
</tr>
<tr>
<td>8</td>
<td>1978 Jun</td>
<td>17</td>
<td>Lassa</td>
<td>Dropped vial</td>
<td>LIG</td>
<td></td>
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<tr>
<td>9</td>
<td>1978 Jun</td>
<td>17</td>
<td>Lassa</td>
<td>Dropped vial</td>
<td>LIG</td>
<td></td>
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<tr>
<td>10</td>
<td>1978 Jul</td>
<td>8</td>
<td>Lassa</td>
<td>Field exposure</td>
<td>LIG</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>1978 Nov</td>
<td>14</td>
<td>Lassa</td>
<td>Suit seam failed</td>
<td>IP</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>1979 May</td>
<td>20</td>
<td>Lassa</td>
<td>Fingerstick</td>
<td>IP</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>1979 Jul</td>
<td>21</td>
<td>Lassa</td>
<td>Fingerstick</td>
<td>IP</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>1979 Nov</td>
<td>20</td>
<td>Lassa</td>
<td>Fingerstick</td>
<td>IP, Rib</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>1981 May</td>
<td>14</td>
<td>Ebola/Lassa</td>
<td>Field exposure</td>
<td>IP, Rib</td>
<td>Modified CC</td>
</tr>
<tr>
<td>16</td>
<td>1982 Oct</td>
<td>14</td>
<td>Junin</td>
<td>Defective suit seal</td>
<td>IP</td>
<td>Conventional</td>
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<td>17</td>
<td>1982 Dec</td>
<td>21</td>
<td>Junin</td>
<td>Fingerstick</td>
<td>IP</td>
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<td>18</td>
<td>1983 Jan</td>
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<td>Waste exposure</td>
<td>IP</td>
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<td>Conventional</td>
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<td>20</td>
<td>1985 May</td>
<td>4</td>
<td>Junin</td>
<td>Fingerstick</td>
<td>IP</td>
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<tr>
<td>21</td>
<td>2004 Feb</td>
<td>21</td>
<td>Ebola</td>
<td>Fingerstick</td>
<td>IP</td>
<td></td>
</tr>
</tbody>
</table>

*Modified from Cieslak et al. (8) with permission.
†JEB, Japanese encephalitis virus B; Ebola/Lassa, potential exposure to these viruses.
‡IP, immune plasma from previously infected survivors; IG, immune globulin; LIG, Lassa immune globulin; Rib, ribavirin.
§CC, containment care; modified CC, provided by converting a separate physical facility into a Biosafety Level 4–like suite; conventional, Biosafety Level 3 isolation was permitted for lower risk exposures.
‖Not noted in previous reports (7,8).
# Clinical Features of the VHFs

<table>
<thead>
<tr>
<th>DISEASE</th>
<th>Hemorrhage</th>
<th>Thrombocytopenia</th>
<th>Leucocyte count</th>
<th>Rash</th>
<th>Icterus</th>
<th>Renal Disease</th>
<th>Pulmonary Disease</th>
<th>Tremor, Dysarthria</th>
<th>Encephalopathy</th>
<th>Deafness</th>
<th>Eye Lesions</th>
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</thead>
<tbody>
<tr>
<td>ARENAVIRIDAE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>South American HF</td>
<td>++</td>
<td>++</td>
<td></td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>++</td>
<td>+/S</td>
<td>++</td>
<td>0</td>
</tr>
<tr>
<td>Lassa fever</td>
<td>+/-</td>
<td>+</td>
<td>0</td>
<td>++</td>
<td>0</td>
<td>0</td>
<td>++</td>
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<td>+/S</td>
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<tr>
<td>BUNYAVIRIDAE</td>
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<td></td>
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<tr>
<td>Rift Valley fever</td>
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<td>++</td>
<td>+</td>
<td>0</td>
<td>E</td>
<td>0</td>
<td>++</td>
<td>Retina</td>
</tr>
<tr>
<td>Crimean Congo HF</td>
<td>+++</td>
<td>+++</td>
<td>0/&gt;|</td>
<td>++</td>
<td>0</td>
<td>+</td>
<td>0</td>
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<td>HFRS</td>
<td>+++</td>
<td>+++</td>
<td>(\text{\textcolor{red}{\textbullet}})</td>
<td>0</td>
<td>+++</td>
<td>+</td>
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<td>(\text{\textcolor{red}{\textbullet}})</td>
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<tr>
<td>FILOVIRIDAE</td>
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<tr>
<td>Marburg and Ebola HF</td>
<td>++</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
<td>0</td>
<td>+</td>
<td>0</td>
<td>++</td>
<td></td>
<td>++</td>
<td>Uveitis?</td>
</tr>
<tr>
<td>FLAVIVIRIDAE</td>
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<td></td>
<td></td>
<td></td>
<td>Retina?</td>
</tr>
<tr>
<td>Yellow fever</td>
<td>+++</td>
<td>++</td>
<td>(0/0)</td>
<td>0</td>
<td>+++</td>
<td>++</td>
<td>+</td>
<td>0</td>
<td>++</td>
<td>0</td>
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</tr>
<tr>
<td>DHF/DSS</td>
<td>++</td>
<td>+++</td>
<td>(\text{\textcolor{red}{\textbullet}})</td>
<td>+++</td>
<td>+</td>
<td>0</td>
<td>+</td>
<td>0</td>
<td>++</td>
<td>0</td>
<td>Retina</td>
</tr>
<tr>
<td>KFD/OHF</td>
<td>++</td>
<td>++</td>
<td>(0/0)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>++</td>
<td>0</td>
<td>E</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

* + occasional or mild
  + + commonly seen, may be severe
  + +++ characteristic and usually marked
  S characteristic, seen in severe cases

* / occasionally or mildly increased
  “/ commonly increased, may be marked
  “/” characteristically increased and usually marked

* E Develop true encephalitis but either after HF (KFD, Omsk) or in other patients (RVF)
Bolivian Hemorrhagic Fever (Machupo)
Disease 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
Disease Transmission

• Opportunities for human-to-human transmission:
  
  o Direct contact (through broken skin or unprotected mucous membranes) with an infected patient’s blood or body fluids
  
  o Sharps injury with virus-contaminated needle or other sharp
  
  o Direct contact with the remains of a person who died
  
  o Indirect contact with an infected patient’s blood or body fluids via a contaminated object (soiled linens)
  
  o Possibly from contact with semen from a man who has recovered
  
  o Droplets in aerosol generating procedures
  
  o Airborne transmission for select agents (variola, coronavirus)
Human-to-Human Transmission

• Infectiousness of Ebola Virus Disease
  o Infected persons are not contagious until onset of symptoms
  o Infectiousness of body fluids increases as patients become more ill
  o Remains from deceased infected persons are highly infectious

• Human-to-human transmission of Ebola virus via inhalation has not been demonstrated
  o However, respiratory protection (e.g. N-95, PAPR) are recommended in case there is an unexpected need to perform an aerosol-generating procedure (e.g. emergency intubation)
Early Clinical Presentation

• Acute onset
  o typically 8–10 days after exposure (range 2–21 days)

• Signs and symptoms
  o Initial: Fever, chills, myalgia, malaise, anorexia
  o After 5 days: GI symptoms, such as nausea, vomiting, diarrhea, abdominal pain
  o Other: Headache, conjunctivitis, hiccups, rash, chest pain, shortness of breath, confusion, seizures
  o Hemorrhagic symptoms in 18% of cases (usually occur late)

• Other possible infectious causes of symptoms
  o Malaria, typhoid fever, meningococccemia, dengue, influenza, Lassa fever and other bacterial infections (e.g., pneumonia) –very common in Africa
  o PCR testing may be negative early in the course of illness
  o Prepare to care for patients for up to 72 hours prior to confirmation (or refutation) of serious communicable disease
Clinical Features

• Nonspecific early symptoms may progress to:
  o Hypovolemic shock and multi-organ failure
  o Hemorrhagic disease
  o Death

• Non-fatal cases:
  o Typically improve 6–11 days after symptom onset if supportive care is provided promptly

• Fatal disease associated with more severe early symptoms:
  o Fatality rates of 70% have been reported in rural Africa
  o Intensive care, especially early intravenous and electrolyte management, may increase the survival rate
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
Airway Management

• Prepare dedicated airway equipment/bundle
  o Standard blades/tubes/airway adjuncts
  o Induction/Emergency medications
  o Video laryngoscope

• Canadian EVD guidelines recommend video laryngoscopy
  o Increase distance from the patient
  o Consideration of rapid sequence induction (RSI) to reduce cough and possible aerosolization
    ▪ www.canadiancriticalcare.org

• Practice using simulation
Central Line Placement

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

• Patients may have marked electrolyte abnormalities and nutritional deficiencies
  o Hypokalemia, hypocalcemia and hyponatremia
  o Both intravenous and oral replacement
  o 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 (to be covered in another session)
Blood Product Support

• Packed red blood cells as needed
  o May need to use O- blood if blood typing not available

• Correction of Coagulopathy
  o FFP if INR > 2 with serious bleeding
  o Cryo if fibrinogen low with serious bleeding
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

*Courtesy of Harold Franch and Michael Connor*
Monitoring Virologic Status

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

- Consider secondary infections
- Nosocomial infections
- Malaria
  - Co-infection up to 30-50% in current EVD outbreak
  - Check 2-3 rapid malaria screens
  - Always complete malaria prophylaxis
Emerging Critical Illness Phenotype

- No proven EVD-specific organ support beyond established CCM “best” practices for most infections
- Lung protective ventilation & minimizing sedation as possible
- Target euvolemia
- Nutrition support – early & aggressive
- Delivery of critical care requires special consideration/planning
Clinical Management: Supportive but Aggressive

- Hypovolemia and sepsis pathophysiology
  - Aggressive intravenous fluid resuscitation
  - Hemodynamic support and critical care management if necessary

- Electrolyte and acid-base abnormalities
  - Aggressive electrolyte repletion
  - Correction of acid-base derangements

Fowler RA et al. Am J Respir Crit Care Med. 2014
• Symptomatic management of fever and gastrointestinal symptoms
  o Avoid NSAIDs, aspirin
  o Anti-emetics and antidiarrheal agents may be needed

• Multisystem organ failure can develop and may require
  o Oxygenation and mechanical ventilation
  o Correction of severe coagulopathy
  o Continuous renal replacement therapy

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

• Case-fatality rate between 50%-70% in the 2014 Ebola outbreak
  o Case-fatality rate is likely much lower with access to intensive care- 18% in resource-rich environments

• Patients who survive often have signs of clinical improvement by the second week of illness
  o Associated with the development of virus-specific antibodies
  o Antibody with neutralizing activity against Ebola persists greater than 12 years after infection

Patient Recovery

• Prolonged convalescence in Ebola
  o Includes arthralgia, myalgia, uveitis, abdominal pain, extreme fatigue, and anorexia; many symptoms resolve by 21 months
  o Significant arthralgia and myalgia may persist for >21 months
  o Depression, headache, skin sloughing, and hair, vision, and hearing loss have also been reported

Viral persistence in immune privileged sites:
- Semen
- Central nervous system
- Eye
- Amniotic fluid

Implications for infection control??
## Experimental Interventions

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Mechanism</th>
<th>Status</th>
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</thead>
<tbody>
<tr>
<td>Convalescent plasma</td>
<td>Provide anti-EBOV antibodies</td>
<td>• Studies have not shown a clear benefit</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Has been used in multiple evacuated patients in this outbreak</td>
</tr>
<tr>
<td>Hyperimmune globulin from immunized animals or previously</td>
<td>Concentrated plasma to provide high titers of neutralizing antibody</td>
<td>• Not currently available.</td>
</tr>
<tr>
<td>infected humans</td>
<td></td>
<td>• Work in horses and cattle are underway</td>
</tr>
<tr>
<td>ZMapp (Mapp Biopharmaceutical Inc.)</td>
<td>Cocktail of three chimeric mouse human monoclonal antibodies targeting the GP envelope protein</td>
<td>• Very promising data in macaques</td>
</tr>
<tr>
<td>TKM-100802 Lipid (TKM-Ebola; Tekmira)</td>
<td>Nanoparticle Small interfering Ribonucleic acid (siRNA) Targets two essential viral genes to stop the virus from replicating</td>
<td>• single-dose phase 1 study in healthy volunteers found side effects including headache, dizziness, chest tightness and raised heart rate at high doses.</td>
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<tr>
<td></td>
<td></td>
<td>• A limited number of treatment courses</td>
</tr>
<tr>
<td>Therapy</td>
<td>Mechanism</td>
<td>Status</td>
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<tr>
<td>AVI 7537 (Sarepta)</td>
<td>Phosphorodiamidate oligonucleotide</td>
<td>• Monkey studies showed 60-80% when given at the time of infection&lt;br&gt;• Tolerability has been demonstrated in early studies.&lt;br&gt;• No human grade availability until late October</td>
</tr>
<tr>
<td>Favipiravir/T-705</td>
<td>Selective inhibition of viral RNA-dependent RNA polymerase&lt;br&gt;Does not inhibit RNA or DNA synthesis in mammalian cells</td>
<td>• Effective against EVD in mice, but in animal monkey study only 1/6 survived&lt;br&gt;• Approved in Japan for influenza treatment under special circumstances.&lt;br&gt;• ~10 000 treatment courses may available</td>
</tr>
<tr>
<td>BCX4430 (Biocryst)</td>
<td></td>
<td>• 83-100% survival in rodents with EVD&lt;br&gt;• Effective in animals 48 hours after infection with the lethal Marburg virus&lt;br&gt;• Testing for EVD in monkeys is underway</td>
</tr>
<tr>
<td>Brincidofovir (CMX001)</td>
<td>lipid conjugate of the nucleotide analog, cidofovir (CDV) uses endogenous lipid uptake uses endogenous lipid uptake pathways to achieve high intracellular concentrations</td>
<td>• In vitro data at CDC showing good anti-EBOV activity&lt;br&gt;• Has been used in 4 patients</td>
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## Vaccine Candidates

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<tr>
<th>Therapy</th>
<th>Mechanism</th>
<th>Status</th>
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| **Chimpanzee adenovirus serotype 3 (ChAd3) vaccine**          | Uses a chimpanzee adenovirus that does not grow                             | • 16/16 monkeys were protected from a lethal dose by a single dose of the vaccine  
• Trials in humans ongoing  
• Approximately 15,000 doses might be available by the end of 2014 |
| **Recombinant Vesicular Stomatitis Virus (rVSV) vaccine**     | Recombinant VSV vector expressing ebola GP protein to induce EBOV-specific immune responses | • 20/20 monkeys protected from a lethal dose of EVD  
• Animals with weakened immunity were not harmed by rVSV-EVD  
• Unknown if rVSV-EVD will grow in humans, which would affect immunogenicity and safety  
• Phase 1 trials underway  
• ~800 doses available |
Origin of “Swine-Origin” H1N1
Garten et al Science, 2009
Smallpox
the only Disease thus far Eradicated*

• Last natural V. major- 1975
• Last natural V. minor- 1977
• Two lab-acquired cases- 1978
• Declared eradicated- 1980
• 1:10 deaths throughout history
• 1:3 pediatric deaths
• case fatality rate: 30%
• >600,000,000 victims?
• The weapon- Vaccine
“Ordinary Type” Smallpox