LET’S START WITH A CASE
Case Presentation

• 22 yo U.S. Army Active Duty male deployed to Afghanistan west of Kandahar presents with fever (102.5°F), headache, fatigue, chills, abdominal pain with non-bloody diarrhea (SEP 8, 2009)
  – Symptoms progressing over the previous 4 days

• Initially told he had a “gastroenteritis” at local clinic
  – Treated with Cipro and immodium
  – 48 hour quarters

• Returned the following day (SEP 9):
  – Symptoms worsening, now with nausea/vomiting and lethargy
  – Told he may have a “viral syndrome”
  – Referred to Kandahar for observation
Case Presentation

• Progressively worsened over the next several hours
  – Lethargy lead to somnolence
  – Bloody diarrhea and bleeding gums
  – Shortness of breath → intubated
  – Anemic, low platelets, developing organ failure

• Evacuated to LRMC with presumed diagnosis of pneumonia with septic shock (antibiotics started)
Case Presentation

• Upon arrival at the Landstuhl Regional Medical Center, he is found to be bleeding EVERYWHERE
  – Petechiae everywhere
  – Large ecchymotic lesions at IV sites
  – Extremely sick

• He requires emergent bronchoscopy for bleeding

• The ICU staff raises the concern for viral hemorrhagic fever
Case Presentation

• Co-located with Afghan army

• Potential exposures
  – Numerous outdoor activities to include sleeping outside
  – Recent tick exposures
    • Patient and battle buddy both with recent bites within a week of illness onset
    • This was a common occurrence (bragging rights)
  – Exposure to goat blood and undercooked goat meat
Case Presentation

• Blood sent to the Bernard Nocht Institute (BNI) in Hamburg within hours of admission

• Blood run overnight
  – SEP 10: PCR and IGM **POSITIVE** for CCHF
  – Infectious diseases consulted just prior to test results

• Within ~12 hours of diagnosis, treatment with oral ribavirin thru feeding tube
  – Dose given to match the standard IV dose

• Emergency IND approval for IV ribavirin from the FDA

• IV ribavirin started 12 hours after oral treatment (48 hours of hospitalization)
Case Presentation

- Renal and hepatic dialysis started
- Patient appeared to be improving

- However:
- SEP 14
  - Patient had a asystolic/PEA arrest
  - Declared brain dead
    - At time of death, viral load had declined and antibodies present
    - Cerebral edema on CT
Viral Hemorrhagic Fevers

Kris Paolino, MD
Chief, Clinical Trials Center
Walter Reed Army Institute of Research
July 2014
Thanks to:

COL Mark Kortepeter, MD, MPH
Will Cover Some Steps to Avoid....
The “Slammer”
1995 Kikwit Zaire ZEBOV Outbreak

Courtesy of Don Noah
Outline

• VHF已是 Overview of Syndrome

• Selected Pathogens:
  – Ebola
  – Crimean-Congo Hemorrhagic Fever
  – Lassa Fever
  – Hantaviruses

• Emerging Threats
This animal carries a deadly virus...and the greatest medical crisis in the world is about to happen.

OUTBREAK

Try to remain calm.

THE HOT ZONE

A TERRIFYING TRUE STORY

RICHARD PRESTON
Potential of VHF’s for Weaponization

• PRO
  – Many demonstrated as infectious by aerosol transmission
    • Exception is Dengue
  – Potentially high morbidity and mortality
  – Replicate well in cell culture
    • Exception are viruses in *Bunyaviridae* (e.g. CCHF)
  – Capability to overwhelm medical resources
  – Frightening effects of illness / terror value

• CON
  – Lack of treatment or vaccine to protect user’s own “troops”
    • May not be deterrent for some countries / non-state actors
  – Possible entry into local vector / reservoir population
  – Stabilizers must be used to enhance viability
Other Military Relevance: History of Weaponization

• Yellow fever and RVF were weaponized by the U.S. during their offensive program

• Former Soviet Union produced large quantities of Ebola, Marburg, Lassa, Junin, and Machupo

• Yellow fever may have been weaponized by North Koreans

• The Aum Shinrikyo cult unsuccessfully tried to obtain Ebola virus to create biological weapons

• Several studies have demonstrated ability to aerosolize Ebola, Marburg, Lassa, and some of the New World arenaviruses
United State Army Medical Research Institute of Infectious Diseases (USAMRIID)
Definition

• Viral hemorrhagic fever (VHF):
  • Fever
  • Malaise
  • Myalgia prostration
  • Bleeding diathesis
  • Severe multi-organ failure
  • Enveloped, single-stranded, RNA viruses

• Hemorrhagic fever virus (HFV) is a term used to generically identify those agents that cause VHF
Overview of VHF's

• Clinical Presentation
  – Variety of presentations
  – Prodrome
    • High fever, Headache, Malaise, Arthralgias, Myalgias
    • Nausea, Abdominal pain, Non-bloody diarrhea
  – Early signs
    • Fever, Tachycardia, Tachypnea, Conjunctivitis, Pharyngitis
    • Flushing, Skin Rash
  – Late
    • ↓ BP, Hemorrhagic diathesis, Petechiae, Mucous membrane
    • Conj. hemorrhage, Hematuria, Hematemesis, Melena
  – Severe Manifestations
    • DIC, Circulatory Shock, CNS dysfunction, Death
    • Mortality rates can be as high as 90%+
Overview of VHF

<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, Dysrhythmia</th>
<th>Encephalopathy</th>
<th>Deafness</th>
<th>Eye Lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ARENAVIRIDAE</strong></td>
<td></td>
<td></td>
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<td></td>
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</tr>
<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>+</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>Lassa fever</td>
<td>+/S</td>
<td>+</td>
<td>0</td>
<td>++</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>+</td>
<td>+/S</td>
<td>++</td>
<td>0</td>
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<tr>
<td><strong>BUNYAVIRIDAE</strong></td>
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<tr>
<td>Rift Valley fever</td>
<td>+++</td>
<td>+++</td>
<td>≧</td>
<td>0</td>
<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>≧/↑</td>
<td>0</td>
<td>++</td>
<td>0</td>
<td>+</td>
<td>0</td>
<td>+</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>HFRS</td>
<td>+++</td>
<td>+++</td>
<td>≧</td>
<td>0</td>
<td>0</td>
<td>+++</td>
<td>+</td>
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<td>HPS</td>
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<td>+++</td>
<td>0</td>
<td>0</td>
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<td>0</td>
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<tr>
<td><strong>FILOVIRIDAE</strong></td>
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<td></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>Uveitis</td>
<td></td>
</tr>
<tr>
<td><strong>FLAVIVIRIDAE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Retina?</td>
<td></td>
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<tr>
<td>Yellow fever</td>
<td>+++</td>
<td>++</td>
<td>0/↓</td>
<td>0</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>++</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>DHF/DSS</td>
<td>++</td>
<td>+++</td>
<td>≧</td>
<td>+++</td>
<td>+</td>
<td>0</td>
<td>+</td>
<td>0</td>
<td>E</td>
<td>0</td>
<td>Retina</td>
</tr>
<tr>
<td>KFD/OHF</td>
<td>++</td>
<td>++</td>
<td>≧</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>E</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

+偶尔或轻微
++常见，并可能严重
+++特征，并且通常显著
S特征，仅在严重病例中

偶尔或轻微增加
∩∩∩∩偶尔或显著性增加，可能显著
∩∩∩∩∩∩∩∩∩∩特征性增加，并且通常显著

E发展为真性脑炎，但只在HF（KFD, Omsk）或其他患者（RVF）
Overview of VHF

- Lab Abnormalities
  - Leukopenia
    - Lassa with leukocytosis (WBC inc.)
  - Anemia
  - Hemoconcentration
  - Thrombocytopenia
  - Elevated liver enzymes
  - May have renal dysfunction
  - Coagulation abnormalities
Overview of VHF

- **Lab Abnormalities**
  - Coagulation abnormalities
    - Prolonged bleeding time
    - Prothrombin time
    - Activated PTT
    - ↑ fibrin degradation (i.e. increased D-dimer)
    - ↓ fibrinogen

- Urinalysis
  - Proteinuria
  - Hematuria
  - Oliguria
  - Azotemia
Overview of VHF

• Lab Abnormalities
  – These are not hard and fast rules.
  – There will be overlap with many of these infections
Argentine Hemorrhagic Fever
(Junin virus – New World Arenavirus)

Gingival hemorrhage
Bolivian Hemorrhagic Fever
(Machupo virus – New World Arenavirus)

Conjunctival injection & subconjunctival hemorrhage

Left arm. Ecchymosis, diffuse, severe.
(1 week after clinical onset)

Photo credit: Robert Swaneopoel, PhD, DTVM, MRCVS, National Institute of Virology, Sandringham, South Africa.
DENGUE
KOREAN HEMORRHAGIC FEVER (HANTAAN)
DENGUE
BOLIVIAN HEMORRHAGIC FEVER (MACHUPO)
KOREAN HEMORRHAGIC FEVER (HANTAAN)
Marburg Infection Human

Maculopapular rash

Overview of VHF

• General Summary of What is Known…
  – Pathogens
  – Geographic distribution
  – Animal hosts and vectors
  – Nosocomial and occupational risks
  – Estimated incubation periods
# Overview of Etiologic Agents of VHFs

<table>
<thead>
<tr>
<th>Family</th>
<th>Genus</th>
<th>Species</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Filoviridae</strong></td>
<td><em>Ebolavirus</em></td>
<td>Zaire, Sudan, Ivory Coast, Reston, Bundibugyo</td>
</tr>
<tr>
<td></td>
<td><em>Marburgivirus</em></td>
<td>Lake Victoria marburgvirus</td>
</tr>
<tr>
<td><strong>Arenaviridae</strong></td>
<td><em>Arenavirus</em></td>
<td>Lassa, Lujo (“Old World”)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Junin, Machupo, Guanarito, Sabia, (“New World”)</td>
</tr>
<tr>
<td><strong>Bunyaviridae</strong></td>
<td><em>Nairovirus</em></td>
<td>Crimean-Congo hemorrhagic fever</td>
</tr>
<tr>
<td></td>
<td><em>Phlebovirus</em></td>
<td>Rift Valley fever</td>
</tr>
<tr>
<td></td>
<td><em>Hantavirus</em></td>
<td>Hantaan, Seoul, Puumala, Dobrava, Sin Nombre</td>
</tr>
<tr>
<td><strong>Flaviviridae</strong></td>
<td><em>Flavivirus</em></td>
<td>Omsk HF</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Kyasanur forest disease (including Alkhurma)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dengue</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Yellow fever</td>
</tr>
</tbody>
</table>

UNCLASSIFIED
<table>
<thead>
<tr>
<th>Disease (Virus)</th>
<th>Distribution</th>
<th>Host/Vector</th>
<th>Other risks</th>
<th>Incubation</th>
<th>CFR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ebola</td>
<td>Africa, Philippines (ER)</td>
<td>Bats/Pigs?</td>
<td>Nosocomial</td>
<td>2-21</td>
<td>25 - 88% (~67%)</td>
</tr>
<tr>
<td>Marburg</td>
<td>Africa</td>
<td>Bats?</td>
<td>Nosocomial</td>
<td>5-10</td>
<td>82%</td>
</tr>
<tr>
<td>Lassa (and Lujo)</td>
<td>Africa (Western)</td>
<td>Rodent</td>
<td>Nococomial</td>
<td>5-16</td>
<td>15-20%</td>
</tr>
<tr>
<td>Junin</td>
<td>Argentina</td>
<td>Rodent</td>
<td>Nococomial</td>
<td>7-14</td>
<td>10-30%</td>
</tr>
<tr>
<td>Machupo</td>
<td>Bolivia</td>
<td>Rodent</td>
<td>Nococomial</td>
<td>9-15</td>
<td>5-30%</td>
</tr>
<tr>
<td>Guanarito</td>
<td>Venezuela</td>
<td>Rodent</td>
<td>Nococomial</td>
<td>7-14</td>
<td>23%</td>
</tr>
<tr>
<td>Sabia</td>
<td>Brazil</td>
<td>Rodent</td>
<td>Nococomial</td>
<td>7-14</td>
<td>1 of 3</td>
</tr>
<tr>
<td>Crimean-Congo</td>
<td>Europe, Asia, Africa</td>
<td>Tick, herding animals, birds?</td>
<td>Nosocomial, slaughterhouse</td>
<td>3-12</td>
<td>3 - 70% (~20-30%)</td>
</tr>
<tr>
<td>Rift Valley Fever</td>
<td>Africa</td>
<td>Mosquito</td>
<td>slaughterhouse</td>
<td>2-6</td>
<td>1 - 50%</td>
</tr>
<tr>
<td>Hantaviruses</td>
<td>Worldwide</td>
<td>Rodent</td>
<td>Nosocomial (Andes virus)</td>
<td>9-35</td>
<td>1-15% (~50% HPS)</td>
</tr>
<tr>
<td>Omsk</td>
<td>Soviet Union</td>
<td>Tick</td>
<td></td>
<td>2-9</td>
<td>0.3-5%</td>
</tr>
<tr>
<td>Kyasanur</td>
<td>India</td>
<td>Tick</td>
<td></td>
<td>2-9</td>
<td>3-5%</td>
</tr>
<tr>
<td>Alkhumra</td>
<td>Middle East</td>
<td>Tick (Camels?)</td>
<td>Butchers</td>
<td>2-9</td>
<td>~30%</td>
</tr>
<tr>
<td>Yellow Fever</td>
<td>Africa, Americas</td>
<td>Mosquito</td>
<td></td>
<td>3-6</td>
<td>20-50%</td>
</tr>
</tbody>
</table>
# The “Deadly” VHF's

<table>
<thead>
<tr>
<th>VIRUS</th>
<th>Mortality Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ebola Zaire</td>
<td>75-90%</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>3-70% (typically 20-30%)</td>
</tr>
<tr>
<td>Rift Valley fever</td>
<td>50% of patients with hemorrhagic form</td>
</tr>
</tbody>
</table>
Overview of VHF

- Geography of VHF
AMERICA!!!!
WE'RE #1!!!!!

- MORE AMERICA!!
- uninhabited
- more evil-doers!!
- evil-doers!!
- tvs and cameras
- they make our stuff
- more evil-doers
- calls centers
- zoo animals come from here
- cold!
- coffee comes from here, i think
- cruise ships go here
- bombs go here
- don't drink the water
- santa!!

kangaroos
Approximately 22 miles

Ebola Reston

Downtown DC
Imported Case of Marburg Hemorrhagic Fever --- Colorado, 2008

Marburg hemorrhagic fever (MHF) is a rare, viral hemorrhagic fever (VHF); the causative agent is an RNA virus in the family Filoviridae, and growing evidence demonstrates that fruit bats are the natural reservoir of Marburg virus (MARV) (1,2). On January 9, 2008, an infectious disease physician notified the Colorado Department of Public Health and Environment (CDPHE) of a case of unexplained febrile illness requiring hospitalization in a woman who had returned from travel in Uganda. Testing of early convalescent serum demonstrated no evidence of infection with agents that cause tropical febrile illnesses, including VHF. Six months later, in July 2008, the patient requested repeat testing after she learned of the death from MHF of a Dutch tourist who had visited the same bat-roosting cave as the patient, the Python Cave in Queen Elizabeth National Park, Uganda (3). The convalescent serologic testing revealed evidence of prior infection with MARV, and MARV RNA was detected in the archived early convalescent serum. A public health investigation did not identify illness consistent with secondary MHF transmission among her contacts, and no serologic evidence of infection was detected among the six tested of her eight tour companions. The patient might have acquired MARV infection through exposure to bat secretions or excretions while visiting the Python Cave. Travelers should be aware of the risk for acquiring MHF in caves or mines inhabited by bats in endemic areas in sub-Saharan Africa. Health-care providers should consider VHF among travelers returning from endemic areas who experience unexplained febrile illness.
Domestically Acquired Seoul Virus Causing Hemorrhagic Fever with Renal Syndrome—Maryland, 2008

Christian Woods,¹ Rakhee Palekar,²³ Peter Kim,¹ David Blythe,² Olivier de Senarclens,¹ Katherine Feldman,² Eileen C. Farnon,⁴ Pierre E. Rollin,⁴ Cesar G. Albariño,⁴ Stuart T. Nichol,⁴ and Margo Smith¹

¹Washington Hospital Center, Washington, DC; ²Maryland Department of Health and Mental Hygiene, Baltimore, Maryland; ³Epidemic Intelligence Service, Office of Workforce and Career Development, and ⁴Special Pathogens Branch, Division of Viral and Rickettsial Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia
How are VHFs Spread?

1 - Inhaling or ingesting excretions/secretions from rodent hosts (urine, feces)

2 - Bite of an infected arthropod (tick, mosquito)

3 - Nosocomial/lab transmission – contact with human or animal blood/body fluids/tissue

4 - Artificially generated aerosols (biowarfare)
How are VHF spread?

Airborne?

- In monkeys, possible airborne transmission between cages 3 m
- Lung tissue, along with nares, pharynx, and conjunctiva w/virus
- Monkeys and guinea pigs able to be infected via airborne route

Arch Pathol Lab Med 1996;120: 140-5.
Arch Virol 1996(suppl);11:115-134.
Overview of VHF's

How are VHF's spread?

Human to Human?

Only dengue and yellow fever virus have adapted to efficient “human-to-human” transmission (via mosquitoes).

Typical story for nosocomial transmission:
- Patient Zero enters the health care facility
- VHF is not recognized or infection control not followed
- Unrecognized spread from blood/body fluid contact
- Health care personnel among the victims
- Victims carry infection to the community
- Close family members and those doing burial rites infected

No proven human to human respiratory transmission
Overview of VHFs

• How are VHFs spread?
  – Usually spread during patient care without appropriate barrier precautions
    • Contact with blood/tissue/body fluids
    • Includes re-use of syringes/needles
  – Epidemiologically, VHFs not readily transmitted person-to-person by airborne route
    • A possibility in only rare circumstances
  – Highest risk in later stages, when having vomiting, diarrhea, shock, hemorrhage
  – Not reported during incubation period (before fever)

Number of infected health care workers declined after barrier nursing practices were begun during the Ebola HF outbreak in Kikwit, DRC, 1995.

Overview of VHF's

How are VHF's spread?

Nosocomial

- Filoviruses – **Ebola** and **Marburg**
- Arenaviruses – **Lassa**, Junin/Machupo (rare)
- Bunyaviruses – **CCHF**, Andes virus (a cause of HPS)
- Flaviviruses – dengue (rare – from blood splash)

**Lassa** – most common **imported** VHF
(if dengue not included)

Transmission of VHF's rarely if ever occur prior to onset of symptoms
Overview of VHF

Differential Diagnosis

- Malaria
- Typhoid fever (*Salmonella*)
- Rocky Mountain Spotted Fever (*Rickettsia rickettsii*)
- Other rickettsioses
- Leptospirosis
- Meningococci
- Q fever (*Coxiella burnetti*)
- Plague
- Influenza

- Viral meningitis / encephalitis
  - Henipaviruses
- HIV / co-infection
- Hemorrhagic smallpox
- Vasculitis (i.e. autoimmune diseases)
- Thrombotic thrombocytopenic purpura (TTP)
- Hemolytic-uremic syndrome (HUS)
- Hemophagocytic syndrome

Clinical presentation: Fever, hemorrhage/purpura, thrombocytopenia, CNS signs, elevated LFTs, leukopenia, thrombocytopenia, DIC, multisystem / multi-organ failure
Overview of VHF

• Diagnosis
  – **High index of suspicion** (know what is in your AO)
  – Lab findings
    • Thrombocytopenia, low WBC, anemia, transaminitis, increased bilirubin, prolonged PT, PTT, increased D-dimer, decreased fibrinogen

  – Virus isolation (Gold Standard, but requires BSL-4 Lab)
  – Electron microscopy
  – Reverse transcription - polymerase chain reaction (RT-PCR)
  – Rapid ELISA techniques (most easily employed)
  – Immunohistochemistry (IHC) & in situ hybridization (ISH) of infected tissues

This stuff is all great, but in reality you may not have readily available basic labs let alone PCR capabilities.
Figure 1: Worldwide distribution of CCHF viruses.
Overview of VHF

- **Treatment**
  - **Supportive Care (the foundation of treatment)**
    - Careful management of fluid and electrolytes
    - Use of colloid
    - Hemodialysis as needed
    - Vasopressors and cardiotonic drugs (some do not respond to fluids)
    - Cautious sedation and analgesia
    - Watch for secondary infections
  
  - **Treatment of Disseminated Intravascular Coagulation (DIC)**
    - Coagulation studies and clinical judgment as guide
    - Replacement of coagulation factors / cofactors
    - Platelet transfusions
    - **No aspirin, NSAIDs, anticoagulant therapies, or IM injections**
Overview of VHF

- **Treatment**
  - Ribavirin
    - Investigational drug, compassionate use
    - Contraindicated in pregnancy
    - Arenaviridae (Lassa, Junin, Sabia, Lujo)
    - Bunyaviridae (Hantaan, CCHF) – not RVF
    - NO UTILITY FOR FILOVIRUSES OR FLAVIVIRUSES

- Immune (convalescent) plasma
  - Arenaviridae (Junin, Machupo; ?Lassa)
  - Passive immunoprophylaxis post-exposure?
  - Experimental studies in animals have not proven efficacy against filovirus infection
  - NOT READILY AVAILABLE
Overview of VHF

• Ribavirin Treatment
  – 33 mg/kg IV single loading dose
  – 16 mg/kg IV q 6 hr for 4 days
  – 8 mg/kg IV q 8 hr for 6 days

• Ribavirin Post-Exposure Prophylaxis
  – 500 mg PO q 6 hr for 7 days (different regimens)

Risks:
  - Upset stomach
  - Reversible hemolytic anemia
  - Arrhythmias
  - Teratogenic

Note: Parenteral (Rx) and oral Ribavirin (PEP) are investigational and available only through human use protocols (ahem….contact USAMRIID or LRMC through ID consult)

## Overview of VHFs

<table>
<thead>
<tr>
<th></th>
<th>Contained Casualty</th>
<th>Mass Casualty</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adults</strong></td>
<td>Same as previous slide</td>
<td>Load 2g po x 1, followed by 1.2g po qd divided in 2 doses (if &gt;75kg pt),</td>
</tr>
<tr>
<td></td>
<td></td>
<td>or 1g po qd in 2 doses (if pt &lt;75kg) for 10 days</td>
</tr>
<tr>
<td><strong>Pregnant</strong></td>
<td>Same as adults</td>
<td>Same as adults</td>
</tr>
<tr>
<td><strong>Children</strong></td>
<td>Same as Adults, dosed according to weight</td>
<td>Loading dose 30mg/kg po x1, followed by 15mg/kg qd in 2 divided doses for</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10 days</td>
</tr>
</tbody>
</table>
Prevention / Control

• YELLOW FEVER
  – Licensed 17D vaccine, highly efficacious
  – Live virus vaccine
  – Reports of vaccine associated deaths
  – Cannot be used in persons with egg allergy

• Junin Candid 1 – ARGENTINE HF
  – Live, attenuated
  – Safe and efficacious
  – Protects monkeys against Bolivian HF
  – **NOT AVAILABLE IN THE UNITED STATES**
Prevention / Control: None Licensed

• Rift Valley Fever
  – Formalin-inactivated
    • safe but requires 3 shots, intermittent booster
    • limited supply
  – Live, attenuated MP-12
    • Phase II testing

• Ebola
  – Adenovirus vectored +/- DNA prime
  – VEE replicons
  – VSV vectored
  – Virus-like particles (VLP)

• Marburg
  – Recent NHP study at USAMRIID: 100% survival following challenge w/ lethal dose of MBGV and then post-exposure treatment w/ recombinant VSV-GP Marburg vaccine
Overview of VHF

• Prevention
  – BACK TO THE INITIAL CASE PRESENTATION…
    • 18 HCPs identified as being HIGH risk exposures
    • Offered oral ribavirin post-exposure prophylaxis
    • 2 individuals had more significant symptoms to meds
    • Both were found to have developed antibodies to the CCHF virus
Overview of VHF

• CDC Recommendations - when to go “hot”
  – Standard Precautions in initial assessments
  – Private room upon initial hospitalization
    • “Barrier precautions” – including face shields, surgical masks, eye protection **within 3 feet** of patient (double glove, impermeable gown)

• Negative pressure room not required initially, but should be considered early to prevent later need for transfer

• Airborne precautions if prominent cough, vomiting, diarrhea, hemorrhage
  • E.g. HEPA masks, negative pressure isolation

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UNCLASSIFIED
Outbreak Management:
Isolation
Barrier precautions
Infection Control for Viral Haemorrhagic Fevers in the African Health Care Setting

World Health Organization

U.S. Department of Health & Human Services

CDC

www.cdc.gov/ncidod/dvrd/spb/mnpages/vhfmanual.htm
Overview of VHFIs

• Identify a minimum level of Standard Precautions
  – Establish routine hand washing
  – Establish safe handling and disposal of used sharps
    • Minimize the use of sharps if possible
  – Be prepared to intensify Standard Precautions and include VHF isolation precautions
  – Identify a VHF coordinator to oversee and coordinate activities associated with VHF isolation precautions
Overview of VHFIs

• Isolation Procedures
  – Isolate the patient in a pre-selected area
  – Wear protective clothing:
    • Scrub suit, gown, apron, two pairs of gloves, mask, headcover, eyewear, rubber boots
  – Clean/disinfect spills, waste, and reusable safety equipment, soiled linens, and laundry safely
  – Use safe disposal methods for non-reusable supplies and infectious waste
  – Counsel staff about the risk of transmission
  – Limit exposure to patient (use an “authorized” list and use a guard if necessary)
  – Provide information to families and the community about VHF prevention and care of patients

WHO VHF Africa Manual
Overview of VHFIs

• Isolation Area
  – Single room with adjoining toilet or latrine
    • Prefer to use chemical toilets if possible (5% sodium hypochlorite)
    • Changing area to don PPE
    • Hand washing stations
  – Separate building or ward for VHF patients only
  – An area in a larger ward that is separate and far away from other patients
  – An uncrowded corner of a large room or hall
  – Any area that can be separated from the rest of the health facility

WHO VHF Africa Manual
Overview of VHF Disinfection Solutions

- Disinfection solutions
  - 0.5% sodium hypochlorite (Dakin’s solution)
  - 2% glutaraldehyde
  - Phenolic disinfectants (0.5%-3.0%)
  - Soaps and detergents

WHO VHF Africa Manual
Overview of VHFs

Fig. 10. A sample layout for several patients
Identify a single lab personnel that will handle the samples
Overview of VHF s

• First Aid for Exposures
  – Anticipate in advance – be prepared
  – Wash / irrigate wound or site immediately

  – Mucous membrane (eye, mouth, nose)
    • Continuous irrigation with rapidly flowing water or sterile saline for > 15 minutes

  – Percutaneous
    • Scrub for at least 15 minutes while copiously soaking the wound with soap or detergent solution
      – Fresh Dakin's solution (0.5% hypochlorite)
Overview of VHF

- **Casual contacts:**
  - Remote contact (same airplane/hotel)
  - No surveillance indicated

- **Close contacts:**
  - Housemates, nursing personnel, shaking hands, hugging, handling lab specimens
  - Place under surveillance when diagnosis confirmed
  - Record temperatures twice daily x 3 wks
  - Notify for temperature >= 101

- **High-risk:**
  - Mucous membrane contact (kissing, sex) or needle stick or other penetrating injury involving blood/body fluid
  - Place under surveillance as soon as diagnosis is considered
  - Immediately isolate for temperature >= 101

If you are dealing with something where ribavirin may be of benefit consider it as a post-exposure prophylaxis option

MMWR 1988;37:1-16
Ebola
Ebola

• Filovirus (Marburg virus is related)
• Several different strains
  – Zaire, Sudan, Ivory Coast, Bundibugyo, (Reston)
• First identified in 1976
• Has become the “prototypical” VHF
  – Classic bleeding diatheses
  – High case fatality rates
  – Significant nosocomial risk
  – Incubation typically 8 – 10 days (up to 3 weeks)
Ebola

• Current Outbreak
  – Affecting Sierra Leone and Liberia
    • No new cases in Guinea recently where it started in March
  – A record number of cases
    • Cases = 1048 (632 deaths; 60% CFR)
    • In the past week alone there are 67 new cases (19 deaths)
  – The current situation is far from stable
Ebola

• Treatment is primarily supportive
• In the works…
  – Recombinant human monoclonal antibodies against the envelope glycoprotein
  – Vaccine still in pre-clinical stage
    • DNA vaccines
    • Live viral vector vaccines
  – Medications:
    • Pyrazinecarboxamide derivative, T-705 (favipiravir)
    • Broad-spectrum nucleoside analogue (BCX4430)
    • Recombinant nematode anticoagulant protein (NAP)
      – inhibits activated factor VII-tissue factor complex
Crimean-Congo Hemorrhagic Fever
Crimean-Congo Hemorrhagic Fever

• Geographic regions
  – 12th Century: Tajikistan
    • HF syndrome: blood in urine, rectum, gums, vomit
  – 1944-45: First clinical description
    • Soviets (N=200, CFR = 10%) assisting peasants in Crimea
  – 1956: febrile patient in Belgian Congo
  – Common antigenic structure: Crimea & Congo viruses = CCHF
Figure 5. Number of Etioman-Congo hemorrhagic fever cases and deaths in Turkey between 2002-2008. 

- **Number of cases and death**
  - Cases: 17, 133, 249, 266, 438, 717, 1315
  - Deaths: 6, 13, 13, 27, 33, 63
Crimean Congo Hemorrhagic Fever cycle:

- Ungulates
- Man
- Hospital

Tick cycle:
- Eggs
- Larvae
- Nymph
- Imago (Adult)
Crimean-Congo Hemorrhagic Fever

• Exposure Risks
  – Ticks (*Hyalomma* sp.) – primary vector
    • Bite (increased exposure in Spring and Summer)
    • Crushed against skin
  – Animals
    • Rabbits, small mammals and birds – reservoir
    • Hoofed mammals (ungulates) – may be infected but won’t show evidence of illness
    • Contact with dead animals (farmers, slaughterhouse, undercooked meat)
  – Nosocomial risk (many HCP have died)

• Mortality Rates: 3-70% (typically 20-30%)
Crimean-Congo Hemorrhagic Fever

• Diagnosis
  – ELISA (antigen capture as well as antibody)
  – RT-PCR (blood or tissue)
  – Virus isolation
  – Immunohistochemical staining

• Some predictors for severity in literature
Crimean-Congo Hemorrhagic Fever

• Containment & Prevention
  – Several reports in the literature indicating high risk of nosocomial transmission to HCPs
    • One report of a patient acquiring CCHF from being in same hospital room
  
  – Turkish study of HCPs in setting with high number of cases showed high rates of PPE use was associated with only a 0.53% seroprevalence rate
  
  – The 2 HCP who seroconverted in our initial case admitted to accidental mask slippage during care where aerosolization was a high risk

IntJ Infect Dis. 2009; 13: e105-7
Crimean-Congo Hemorrhagic Fever

• Containment & Prevention
  – Ribavirin
    • High risk contacts can be considered
    • Use oral ribavirin
  – The CCHF case from Afghanistan recommended 600 mg PO twice daily for 14 days (only took meds for 7 days in all cases)
Crimean-Congo Hemorrhagic Fever

• Treatment
  – Supportive Care
  – Ribavirin controversy
    • In-vitro activity against CCHF
    • No randomized controlled trials
    • Many case reports and case series indicating efficacy
    • Several others indicate no significant benefit
    • CDC does not “fully” recommend it’s use
    • WHO recommends its use for CCHF (as well as Lassa, Junin, and hantavirus with renal syndrome)
    • DoD has a phase 2 open label study for ribavirin treatment of Lassa and CCHF (clinicaltrials.gov - NCT00992693)
Crimean-Congo Hemorrhagic Fever

Table 1. Characteristics of SSI Parameters for Crimean-Congo Hemorrhagic Fever

<table>
<thead>
<tr>
<th>SSI Parameter</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet count, $\times 10^3$ platelets/mm$^3$</td>
<td></td>
</tr>
<tr>
<td>$&gt;150$</td>
<td>0</td>
</tr>
<tr>
<td>$150–50$</td>
<td>1</td>
</tr>
<tr>
<td>$49–20$</td>
<td>2</td>
</tr>
<tr>
<td>$&lt;20$</td>
<td>3</td>
</tr>
<tr>
<td>aPTT, sec</td>
<td></td>
</tr>
<tr>
<td>$\leq 34$</td>
<td>0</td>
</tr>
<tr>
<td>$35–45$</td>
<td>1</td>
</tr>
<tr>
<td>$46–59$</td>
<td>2</td>
</tr>
<tr>
<td>$&gt;60$</td>
<td>3</td>
</tr>
<tr>
<td>Fibrinogen level, mg/dL</td>
<td></td>
</tr>
<tr>
<td>$\geq 180$</td>
<td>0</td>
</tr>
<tr>
<td>$179–160$</td>
<td>1</td>
</tr>
<tr>
<td>$159–120$</td>
<td>2</td>
</tr>
<tr>
<td>$&lt;120$</td>
<td>3</td>
</tr>
<tr>
<td>Bleeding</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>0</td>
</tr>
<tr>
<td>Petechia</td>
<td>1</td>
</tr>
<tr>
<td>Ecchymosis</td>
<td>2</td>
</tr>
<tr>
<td>Bleeding</td>
<td>3</td>
</tr>
<tr>
<td>Somnolence</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>0</td>
</tr>
<tr>
<td>Yes</td>
<td>1</td>
</tr>
</tbody>
</table>

Abbreviation: aPTT, activated partial thromboplastin time; SSI, severity scoring

- Severity Scoring Index
  - 0-2 = mild disease
  - 3-9 = moderate
  - 10-13 = severe

- Those with moderate disease had significantly better outcomes when receiving ribavirin

- Individuals with severe disease did better with corticosteroids added

CID 2013; 57:1270-4
Crimean-Congo Hemorrhagic Fever

• Treatment
  – Ribavirin appears to be beneficial to overall survival in at least moderate to severe disease
  
  – Earlier the therapy the better (within first 4 days of illness)

  – Corticosteroids in severe illness in addition to ribavirin may be beneficial to survival
Lassa
Lassa

• Geographic regions
  – *Arenavirus* first described in Nigeria in 1969 with distribution primarily in West Africa

  – Outbreaks have occurred in:
    • Central African Republic
    • Guinea
    • Liberia
    • Nigeria
    • Sierra Leone (1987)
      – 10-16% of all adult medical admissions
      – 30% of adult deaths
      – 25% of all maternal deaths

  – Serological evidence found in Democratic Republic of the Congo, Mali, and Senegal
Lassa

Map showing the countries where Lassa fever outbreaks and serological evidence of human infection have been reported:

- Senegal
- Guinea
- Sierra Leone
- Liberia
- Mali
- Nigeria
- Central African Republic
- Congo

Legend:
- Red Circle: Outbreaks of Lassa Fever
- Blue Circle: Serological evidence of human infection

Ratio 0 km 800
Lassa

• Exposure Risks
  – Reservoir: *Mastomys* rodents
    • Rodent-to-human:
      – Inhalation of aerosolized virus from rodent urine and feces
      – Ingestion of food or materials contaminated by infected excreta
      – Catching and preparing *Mastomys* as a food source

  – Human-to-human:
    • Direct contact with blood, tissues, secretions or excretions
    • Needle stick or cut
    • Inhalation of aerosolized virus suspected

  – Mortality Rates: 15-20% of hospitalized
Lassa

• Exposure Risks
  – Nosocomial Outbreaks
    • Dry season (JAN to APR)
    • All age groups and both sexes
  
  – Pregnant women and fetus at high risk

  – The Kenema Government Hospital
    • January to April 2004
    • 95 pediatric cases admitted
    • 50% of all cases aged under 15 years
      – CFR was 30–50% in children <5
      – CFR was 71% in children <1

(UNCLASSIFIED) Slide 102

Dr. Conteh attempted femoral venipuncture and sustained a needlestick.

(WHO, Weekly Epi Record, MAR 2005)
Lassa

• Diagnosis
  – Clinical diagnosis is tough
    • May present with nonspecific symptoms
    • Hemorrhagic manifestations may not be evident
    • Neurologic symptoms (hearing loss, tremors, encephalitis)
  – ELISA (antibody or antigen)
  – Viral culture (wouldn’t do this unless you have BSL-4)
  – Immunohistochemical staining of tissue
  – RT-PCR
Lassa

• Containment & Prevention
  – Rodent control (food storage is key)
  – Use of VHF barrier precautions can limit or eliminate healthcare worker risks
  – Isolation of patients as discussed
  – Lassa vaccine
    • USAMRIID had a vaccine based on a live viral platform that protected monkeys against a lethal challenge of Lassa

• Monkeys did not have symptoms, BUT were found to have circulating virus

Lassa

• Containment & Prevention
  – Ribavirin
    • High risk contacts can be considered
      – Needle sticks or sharp injury
      – Mucous membrane or broken skin with blood/secretions
      – Participation in emergency procedures without PPE
      – Prolonged contact in enclosed space (e.g. med evac)

• Use oral ribavirin
  – 800 mg daily for 10 days (EID article)
  – 35 mg/kg x 1 (up to 2.5 g) then 15 mg/kg (up to 1 g)
    TID x 10 d

CID 2010; 15;51(12):1435-41
EID 2010; 16 (20): 2009-2011
Lassa

• Treatment
  – Supportive Care
  – Ribavirin
    • If used early (within 6 days) may significantly reduce mortality (76% to 9%)
      – If you wait to start ribavirin after 6 days, rate goes up to 47%

• WHO recommends use (CDC also promotes its use)
• DoD use via the open label study (see CCHF info above)

Antiviral Res. 1994;23:23
Rev Infect Dis. 1989;11:S750
Hantaviruses
Hantaviruses

• History
  – 1934: First published case of HFRS
  – 1951-1953
    • United Nation’s troops in Korean War (near Hantaan River)
    • 3000 cases of fever + hemorrhage in 33%
  – 1978: virus isolated
    • 14 cases of HFRS among 3,754 US Marines
    • 10 were hospitalized & 2 died (CFR = 14%)
    • Cases confirmed by serologic testing

MMWR Feb 19, 1988/37(6);87-90,95-6
Hantaviruses

• Geographic regions
  – “Old World”:
    • Hantaan (Korea, China, Eastern Russia)
    • Dobrava (Balkans)
    • Seoul (Asia)
    • Puumala (Scandinavia, Western Russia, Europe)
  – “New World”: Sin Nombre (U.S.), Andes
Hantavirus Pulmonary Syndrome (HPS) Cases, by State of Exposure

HPS Cases per State:
- 1 - 15
- 16 - 50
- > 50
- Zero Cases

Total Cases: (N=624 in 34 States)
28 Cases With an Unknown State of Exposure. Cumulative Case Count Per State Valid as of July 9, 2013.

Source: Viral Special Pathogens Branch, CDC
Hantaviruses

• Exposure risks
  – Rodent excreta (aerosolized)
  – Reservoir
    • *Apodemus agrarius*: striped field mouse (Hantaan)
    • *Aedes flavicollis*: yellow necked mouse (Dobrava)
    • *Clethrionomys glareolus*: bank voles (Puumala)
    • *Rattus norvegicus*: rat (Seoul)

• Demographic
  • Farmers, forest workers, soldiers in the field
  • Opening and utilizing previously unused buildings
  • 20 to 50 years in age
  • Male > Female

• Human to Human (very rare, with Andes virus)
Hantaviruses

- **Diagnosis**
  - **Presentation:**
    - Hemorrhagic Fever with Renal Syndrome (Old World)
      - Incubation period may be 2-4 weeks
      - Flu-like symptoms, flushing or rash, red eyes, hemorrhagic symptoms possible
      - Acute renal failure
        - Puuma has a milder presentation
    - Hantavirus Pulmonary Syndrome (New World)
      - Early = nonspecific, flu-like symptoms
      - Late = severe shortness of breath and cough secondary to pulmonary edema
  - Lab diagnosis similar to other VHF's mentioned
Hantaviruses

• Containment & Prevention
  – Rodent control and maintain adequate food storage
  – Person-to-person transmission has only been identified with the Andes virus (causes HPS)
  – Vaccines are being developed
    • Recently completed a phase 1 study at WRAIR
Hantaviruses

• Treatment
  – Supportive care
  – Dialysis frequently required for “Old World”
  – Ribavirin appears to be of benefit in “Old World” cases, by decreasing mortality and improving renal morbidity
    • A double-blind, RCT of ribavirin in New World HPS did not indicate effectiveness

JID 1991;164(6):1119-27
Antiviral Res. 2009 Jan;81(1):68-76
Emerging Threats

“There are known knowns; there are things we know that we know.

There are known unknowns; that is to say, there are things that we now know we don't know.

But there are also unknown unknowns – there are things we do not know we don't know.”

DONALD RUMSFELD
United States Secretary of Defense
February 12, 2002
Be on alert for emerging infections…

• Lujo hemorrhagic fever (Zambia, South Africa)
  – 4 out of 5 patients died
  – The lone survivor received ribavirin

• Alkhurma hemorrhagic fever (Saudi Arabia, Egypt)
  – Case fatality rate ~30%
  – Considered to be tick born
  – Hemorrhagic fever +/- encephalitis (similar to Kyasanur Forest Disease)

• Novel bunyaviruses (likely tick borne)
  – Severe Fever with Thrombocytopenia Syndrome virus (China)
  – Heartland virus (2 cases, no deaths; found in Missouri)
Emerging Threats

• Chapare Virus
  – Small cluster of cases occurred in rural Bolivia (2003-2004)
  – Hemorrhagic fever symptoms
  – Novel arenavirus found in 1 pt
    • 22 yo male, died on DOI 14

Summary

• VHF will start as flu-like illness and progress to organ failure (bleeding may not be evident)

• Have high concern for the nosocomial risk as the treating provider

• Masks, gloves, gowns, and eye protection at a minimum

• Have isolation plan, post-exposure plan, and evac plans ready

• Ribavirin may be of benefit to some (not all VHFs) if given early
Summary

• Ribavirin is an investigational drug for VHF, thus you need to use it on a **research protocol**

• Avoid rodents

• If you are in a remote tropical locale with little epidemiologic data, and there are cases of something that appears hemorrhagic in nature, consider the unknown
Final Thoughts

• Any fever in a traveler to a malaria endemic region is malaria until proven otherwise

• Any traveler with fever **AND** bleeding out of their eyeballs is VHF until proven otherwise
Questions?