The opinions or assertions contained herein are the private views of the author, and are not to be construed as official, or as reflecting true views of the Department of the Army or the Department of Defense. Research was conducted in an AAALACi accredited facility in compliance with the Animal Welfare Act and other federal statutes and regulations relating to animals and experiments involving animals and adheres to principles stated in the Guide for the Care and Use of Laboratory Animals, NRC Publication, 2011 edition.
AKA

Blood outside the body is bad
Outline

• Part I: VHF – General Summary of What is Known...
  • Overview of syndrome
  • Geographic distribution
  • Animal hosts and vectors
  • Nosocomial and occupational risks
  • Clinical Presentation and diagnosis
  • Management
  • Personal Protection Strategies
• Part II: Selected Pathogens and Emerging Threats
  • Crimean-Congo Hemorrhagic Fever
  • Hantaviruses (HFPS)
  • Lassa Fever
  • Marburg
  • Rift Valley Fever
OUTBREAK (1995)
3 weeks on top of US box office
Grossed: $190M ($50M budget)
Will Cover Some Steps to Avoid....

OR

Don’t be this guy/gal
The “Slammer”
“Hard-wired” Features of the Slammer

- External direct pass-thru entry
- Positive pressure “space” suits
- Intake/exhaust HEPA filtration
- Lab sewer system with steam sterilization
- UV light boxes
- Dunk tanks
- Autoclave
- Decon shower
- Telemetry, video monitoring
- On-site lab
1995 Kikwit Zaire ZEBOV Outbreak

Source: Don Noah
Military Relevance: Weaponization

- **Bioterrorism (BT)**
  - Hoaxes to mass casualties
  - Small attacks may be incredibly disruptive
  - 2001 Anthrax: ADLs, Commerce, Government, $$
- **VHF**s are important considerations in Bioterrorism (BT) preparedness
  - Reputation from popular literature, cinema
  - Media
  - Dramatic clinical syndrome(s) produced
- **Stability and infectivity of VHF viruses is sufficient (or could be enhanced) to produce effective WMD**
Sources: newsfortherevolution.wordpress.com; imgarcarde.com; Usatoday.com; Pixgood.com
History of Weaponization

- U.S.: Yellow fever and RVF
  - Ceased in 1968, weapons destroyed

- Former USSR: Ebola, Marburg, Lassa, Junin, and Machupo

- North Korea: ?Yellow Fever

- Japan: Ebola (Aum Shinrikyo). Unsuccessfully tried to obtain Ebola virus to create biological weapons

- Each step of the process has been tested and found to be feasible for inducing human disease

- Overall process has been tested at a practical level with experimental animals after open air exposure
Weaponization PROS

- **Stable**
- **Many demonstrated as infectious by aerosol transmission**
  - Exception is Dengue
  - Several studies have demonstrated ability to aerosolize Ebola, Marburg, Lassa, and some of the New World arenaviruses

- **Potentially high morbidity and mortality**
  - High case-to-infection ratio

- **Replicate well in cell culture**
  - Exception are viruses in *Bunyaviridae* (e.g. CCHF)
  - Titers fall short of ideal for WMD: state-sponsored programs?

- **Capability to overwhelm medical resources**
- **Frightening effects of illness / terror value**
- **Widely available in nature (exception: filoviruses)**
  - Select agent restrictions in the US have limited impact on their use

- **Difficult to control production equipment**
  - Multiple industrial uses, no unique signature
Weaponization CONS

• 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
• Large amounts needed to deploy (CCHF, hantavirus)
  – Applied research programs
• Stabilizers must be used to enhance viability
  – Marburg virus and glycerin
  – Liquid formulations (logistical constraints)
• Ultracold storage needed
  – Production of dried material that could maintain bulk infectivity for longer periods
That isn’t snow!

Check all gifts
Look for suspicious white powders
Report your friends and family

You better be good, for goodness sake!

The Department of Homeland Security
We don’t have to tell you why.

Source: oilempire.com
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
# Etiologic Agents of VHF

<table>
<thead>
<tr>
<th>Family</th>
<th>Genus</th>
<th>Species</th>
</tr>
</thead>
<tbody>
<tr>
<td>Filoviridae</td>
<td>Ebola virus</td>
<td>Zaire, Sudan, Ivory Coast, Bundibugyo,</td>
</tr>
<tr>
<td></td>
<td>Reston</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Marburgvirus</td>
<td>Lake Victoria marburgvirus</td>
</tr>
<tr>
<td>Arenaviridae</td>
<td>Arenavirus</td>
<td>Lassa, Lujo (&quot;Old World&quot;)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Junin, Machupo, Guanarito, Sabia, (&quot;New World&quot;)</td>
</tr>
<tr>
<td>Bunyaviridae</td>
<td>Nairovirus</td>
<td>Crimean-Congo hemorrhagic fever</td>
</tr>
<tr>
<td></td>
<td>Phlebovirus</td>
<td>Rift Valley fever</td>
</tr>
<tr>
<td></td>
<td>Hantavirus</td>
<td>Hantaan, Seoul, Puumala, Dobrava, Sin</td>
</tr>
<tr>
<td></td>
<td>Nombre</td>
<td></td>
</tr>
<tr>
<td>Flaviviridae</td>
<td>Flavivirus</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>
Family Features

• Small RNA viruses, fatty coating, acid sensitive
• Need a geographically restricted host (animal, insect) to live, multiply in. Humans are not a natural reservoir
• Human infection
  – Sporadic, irregular...i.e., cannot be easily predicted
  – Contact with infected hosts.
  – Some viruses, after the accidental transmission from the host, humans to human can occur.
• With a few noteworthy exceptions, there is no cure or established drug treatment for VHF.
• All aerosol infectious (except dengue)
<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>Nosocomial</td>
<td>5-16</td>
<td>15-80%</td>
</tr>
<tr>
<td>Junin</td>
<td>Argentina</td>
<td>Rodent</td>
<td>Nosocomial</td>
<td>7-14</td>
<td>10-30%</td>
</tr>
<tr>
<td>Machupho</td>
<td>Bolivia</td>
<td>Rodent</td>
<td>Nosocomial</td>
<td>9-15</td>
<td>5-30%</td>
</tr>
<tr>
<td>Guanarito</td>
<td>Venezuela</td>
<td>Rodent</td>
<td>Nosocomial</td>
<td>7-14</td>
<td>23%</td>
</tr>
<tr>
<td>Sabia</td>
<td>Brazil</td>
<td>Rodent</td>
<td>Nosocomial</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>2-5</td>
<td>1 - 50%</td>
</tr>
<tr>
<td>Hantaviruses</td>
<td>Worldwide</td>
<td>Rodent</td>
<td>Nosocomial</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

<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>Lujo</td>
<td>80%</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>
Geography of VHF
Distribution of RVF

Distribution of Junin

Distribution of CCHF

Distribution

- Virus and disease(s) are limited to where the host species live(s)
  - Geographically restricted: Rodent (New World arenaviruses)
  - Geographically diverse: Rodent (Hantavirus); common rat (Seoul virus)
- Occasionally, exported hosts can spread disease
  - Marburg (Germany, Yugoslavia)
  - Human travelers
  - Ebola
Overview of VHFs

Why do we even care?

Most of these infections are nowhere near the United States. Why should the U.S. use resources and risk personnel?
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
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.
Ebola Reston

Approximately 22 miles

Downtown DC
Overview of VHFs: Spread

- Inhaling or ingesting excretions/secretions from rodent hosts (urine, feces, saliva)
- Bite of an infected arthropod (tick, mosquito) or crushing infected arthropod
- Nosocomial/lab transmission – contact with human or animal blood/body fluids/tissue
- Artificially generated aerosols (biowarfare)
- Exposure to infected animals (Care, consumption, slaughter)
- Imported-Lassa is the most common imported VHF (if dengue not included)
- Fomites-implicated, not proven
Overview of VHFs: Spread

- **Airborne (monkeys, guinea pigs)**
  - Monkeys: possible airborne transmission between cages 3 m
  - Lung tissue, along with nares, pharynx, and conjunctiva w/virus
- **Human to Human**
  - Only dengue and yellow fever virus have adapted to efficient “human-to-human” transmission (via mosquitoes).
  - No proven human to human respiratory transmission
  - ?later stages of disease, blood spatters
- **Nosocomial**
  - Filoviruses – Ebola and Marburg
  - Arenaviruses – Lassa, Junin/Machupo (rare)
  - Bunyaviruses – CCHF, Andes virus (a cause of HPS)
  - Flaviviruses – Dengue (rare – from blood splash)
Overview of VHFs: Spread

• 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
• Transmission of VHFs rarely if ever occur prior to onset of symptoms
Transmission cycle of CCHF
Pathogenesis

• Varying degrees of, singly or in combination:
  – Direct viral damage
  – Disseminated intravascular coagulation (DIC)
  – Hepatic damage
  – Vascular damage
  – Cytokine release
• Fatal cases
  – Lymphoid depletion (ex: hantavirus: immunopathology)
Clinical Presentation: Nonspecific, Wide Variety

• **Prodrome (3-4 days)**
  – Fever, Headache, Malaise, Arthralgias, Myalgias, fatigue
  – Nausea, Abdominal pain, Non-bloody diarrhea
• **Early signs**
  – High Fever, Tachycardia, Tachypnea, Conjunctivitis, Pharyngitis
  – Flushing, Skin Rash
  – Prostration, capillary leak (nondependent edema, effusions)
• **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%+**
Symptoms/Signs

- **Hemorrhage**
  - Most cases: South American hemorrhagic fevers
  - <50%: Lassa
  - Requires thrombocytopenia and capillary damage
- **Shock, florid hemorrhage, extensive CNS damage**
  - Poor prognosis
- **Physical signs early in the course may be suggestive**
  - Low BP
  - Postural hypotension
  - Petechial hemorrhage
  - Conjunctival injection common (ex: HPS)
<table>
<thead>
<tr>
<th>Disease</th>
<th>Clinical</th>
<th>Therapeutic Synopsis</th>
</tr>
</thead>
<tbody>
<tr>
<td>South American HF</td>
<td>Hemorrhage, dysarthria, tremor usual</td>
<td>Ribavirin, vaccine (limited availability)</td>
</tr>
<tr>
<td>Lassa fever</td>
<td>Prostration/shock/deafness: hemorrhage less so</td>
<td>Ribavirin</td>
</tr>
<tr>
<td>Rift Valley Fever</td>
<td>HF low; rapid course: DIC/hepatitis/retinal vasculitis/encephalitis</td>
<td>?Ribavirin Vaccine (limited availability)</td>
</tr>
<tr>
<td>Crimean Congo Hemorrhagic Fever</td>
<td>HF, hemorrhage, DIC</td>
<td>Ribavirin</td>
</tr>
<tr>
<td>Crimean Congo Hemorrhagic Fever</td>
<td></td>
<td>No vaccine</td>
</tr>
<tr>
<td>Hemorrhagic Fever with Renal Syndrome (HFRS)</td>
<td>Febrile prodrome, shock, renal failure, hemoconcentration</td>
<td>Supportive care, dialysis ?ribavirin Vax: China, Korea</td>
</tr>
<tr>
<td>Hantavirus Pulmonary Syndrome (HPS)</td>
<td>Similar to HFRS, but pulmonary edema vice renal failure</td>
<td>ICU management Ribavirin not useful</td>
</tr>
</tbody>
</table>

Adapted from: Peters CJ
## Clinical Features of VHFs

<table>
<thead>
<tr>
<th>Disease</th>
<th>Clinical Features</th>
<th>Therapeutic Synopsis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marburg/Ebola</td>
<td>Weight loss/prostration, rash, hepatitis, uveitis, orchitis, arthralgias common in convalescence</td>
<td>Supportive Vaccine in advanced clinical development</td>
</tr>
<tr>
<td>Yellow Fever</td>
<td>Severe HF with jaundice</td>
<td>Vaccine</td>
</tr>
<tr>
<td>Dengue</td>
<td>Need sequential infection with heterotypic serotypes</td>
<td>Supportive care Vaccines in clinical development</td>
</tr>
<tr>
<td>Tick-Borne Flavivirus</td>
<td>Biphasic: fever, thrombocytopenia, hemorrhage, followed by neurologic signs</td>
<td>No specific therapy or vaccine</td>
</tr>
</tbody>
</table>

Adapted from: Peters CJ
## Clinical Features

<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>Nephritis, Dysarthria</th>
<th>Encephalopathy</th>
<th>Deafness</th>
<th>Eye Lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ARENAVIRIDAE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</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>0</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>
</tr>
<tr>
<td><strong>BUNYAVIRIDAE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<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>0</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>
<td>0</td>
<td>+</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>HPS</td>
<td>+</td>
<td>++</td>
<td>⊀☉☉☉</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>+++</td>
<td>0</td>
<td>+</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>FILOVIRIDAE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marburg and Ebola</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>Retina?</td>
</tr>
<tr>
<td>HF</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>FLAVIVIRIDAE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<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>+</td>
<td>0</td>
<td>0</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>E</td>
<td>0</td>
<td>Retina</td>
<td></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)
Lab Abnormalities

- WBC
  - Leukopenia
  - Esp. South American HF
  - Lassa with low, normal or increased WBC
  - Hantavirus: leukemoid counts
- RBC/Hct/Hb
  - Anemia
  - Hemoconcentration
  - Extreme: hantavirus
- PLT
  - Thrombocytopenia
- AST/ALT, Cr, PT/PTT
Lab Abnormalities

- Coagulation abnormalities
  - No patterns diagnostic
  - Prolonged bleeding time
  - Prothrombin time
  - Activated PTT
  - ↑ fibrin degradation (i.e. increased D-dimer)
  - ↓ fibrinogen
- DIC: CCHF, filoviruses, severe RVF, early HFRS
- AST, amylase
- Urinalysis: reflects circulatory status
  - Proteinuria: reflecting capillary leak?
  - Hematuria
  - Oliguria
  - Azotemia
Lab Abnormalities and Disease Presentations

- These are not hard and fast rules.
- There will be overlap with many of these infections
- Nonspecific initial presentations
- Mimic many common syndromes
- Must have SA
- Ask the question!
Differential Diagnosis

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

- Malaria, Malaria, 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
- Shigella
Bolivian Hemorrhagic Fever
(Machupo virus – New World Arenavirus)

Conjunctival injection & subconjunctival hemorrhage

Crimean-Congo Hemorrhagic Fever (CCHF)

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

Source: Robert Swaneopoel, PhD, DTVM, MRCVS, National Institute of Virology, Sandringham, South Africa.
Crimean-Congo Hemorrhagic Fever (CCHF)

Source: healthierpakistan.com
Crimean-Congo Hemorrhagic Fever (CCHF)

Source: glogster.com
Crimean-Congo Hemorrhagic Fever (CCHF)

Source: data.fao.org
KOREAN HEMORRHAGIC FEVER (HANTAAN)

Source: emedecine.medscape.com
Argentine Hemorrhagic Fever

Source: telemedicine.org
Dengue Hemorrhagic Fever

Source: magnustoday.net
Marburg Infection

Maculopapular rash

Hemorrhagic Fever with Renal Syndrome (HFRS)

Source: lookfordiagnosis.com
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

• Acute phase: detection of RNA by RT-PCR, finding viral proteins by ELISA, or viral isolation (BSL-4)

• As patients improve, markers of acute infection disappear and IgM appears

• Hantaviruses: antibodies present in serum at time of onset of disease (IgM capture ELISA)
Lab Diagnosis

• 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
Management

- **General Strategy**
- **Rapid atraumatic hospitalization**
- **ICU admission if available**
- **Early Supportive Care (the foundation of treatment)**
  - Careful management of fluid and electrolytes
  - Blood transfusions as needed (whole blood if available)
  - Hemodialysis as needed
  - Vasopressors and cardiotonic drugs (some do not respond to fluids)
  - Monitor for signs of hypotension and shock
  - Cautious sedation and analgesia
  - Watch for secondary infections (add broad spectrum antibiotics, malaria RDTs vs. empiric treatment)
- **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**
  - Use acetaminophen for pain or fevers
Management

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

• **Ribavirin Treatment**
  - 30 mg/kg IV single loading dose
  - 15 mg/kg IV q 6 hr for 4 days
  - 7.5 mg/kg IV q 8hr for 6 days

• **Ribavirin Post-Exposure Prophylaxis**
  - 500 mg PO q 6 hr for 7 days
  - 35 mg/kg x 1, then 15 mg/kg Q8hrs x10 days (WHO)

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

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

# Ribavirin Dosing

<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), 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 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 in the U.S.

- **Rift Valley Fever**
  - Formalin-inactivated
  - Safe but requires 3 shots, intermittent booster
  - Limited supply

  - Live, attenuated MP-12
- **Phase II testing**

- **Ebola**
  - Adenovirus (Ad3) vectored +/- DNA prime
  - Vesicular Stomatitis Virus (VSV) vectored
  - VEE replicons
  - 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
Experimental Products in the Pipeline

- Recombinant human monoclonal antibodies
  - MB-003, ZMAb, ZMapp
- Vaccines mostly in pre-clinical stage (few human studies)
  - DNA vaccines
  - Live viral vector vaccines
  - Virus-like particles vaccines
- Drugs:
  - Pyrazinecarboxamide derivative, T-705 (favipiravir)
  - Broad-spectrum nucleoside analogue (BCX4430)
  - Recombinant nematode anticoagulant protein (NAP)
  - AVI-6002 (antisense oligomers)
  - Clomiphene/Toremiphene
  - Retanizone (Vit A derivative)
Ebola starts with flu-like symptoms, then fever and shaking. Finally you bleed out and die.

There's a promising drug in America. Why not try it?

It might make you sick.
Experimental Products

• Why don’t we just test these products on the sick?
  • The story of TGN1412…
    — CD28-monoclonal antibody
    — Intended for treatment of B-cell CLL and rheumatoid arthritis
    — Tested in animals previously and noted to be safe
    — Clinical Trial (2006)
      ➢ First in humans study
      ➢ Given at a fraction of the dose found safe in animals
      ➢ All 6 human volunteers were hospitalized that same day
        ➢ Multi-organ failure
        ➢ Cytokine storm
        ➢ Prolonged hospitalization

Bottom line: We don’t know if they are safe
vVSV-ZEBOV

• Attenuated, replication-competent, recombinant VSV-based vaccine expressing the glycoprotein of a Zaire strain of ZEBOV
• Two Phase 1 trials (26 x 2 participants)
  — WRAIR and NIH
• Placebo-controlled, double-blind, dose escalating studies
  — 20 million PFU vs. 3 million PFU
• Adverse events
  — Injection site pain, myalgias, fatigue
• Seroconversion (Day 28): 100%
  — GMT 4079 (20 million) vs 1300 (3 million); P<0.001
VSV viremia detected for short duration

The Problem

• At peak infection, virus in the blood or secretions
  – Up to 100,000,000+ virions per ml

• Number needed to infect:
  – 1-10 virions

• There is no room for error

• Like the BSL-4 lab, redundancy is key
PPE Evolution

Per Mike Kurilla

Dbl Gloves

Headgear

Leggings

Booties
Personal Protective Equipment (PPE)

• 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)
  – Have your VHF “battle buddy” double check you

• 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

Outbreak Management:
Isolation
Barrier precautions
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

WHO VHF Africa Manual
Overview of VHFs

• 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 waste
  – Counsel staff about the risk of transmission
  – Limit exposure to patient (use an “authorized” list and use a guard)
  – Provide information to families and the community about VHF prevention and care of patients
  – Consider all samples **highly infectious**
  – Surgical mask for patient for any patient movement

WHO VHF Africa Manual
Overview of VHFs

• Isolation Area
  – Single room with adjoining toilet or latrine
    • Prefer to use chemical toilets if possible (5% sodium hypochlorite)
    • Changing area to put on 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
Overview of VHF

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

Fig. 10. A sample layout for several patients
Separate high/low risk entrances

Flow from low to high risk

Triage patients to suspected +EVD

Perimeter security

Chertow SW. NEJM Nov 2014 epub
4 High Level Containment Care Facilities in the US

NIH – Bethesda, MD
Emory Univ – Atlanta, GA
St. Patrick’s Hospital, Missoula, MT
Univ of Nebraska Medical Center, Omaha, NB

Why do specialized units make sense?
Caring for Patients With Ebola: A Challenge in Any Care Facility

Mark G. Kortepeter, MD, MPH; Philip W. Smith, MD; Angela Hewlett, MD; and Theodore J. Cieslak, MD

- Rare Infection – clinicians and staff unfamiliar
- High mortality rate
- No proven effective vaccine or therapies
- Propensity to infect health care providers
- Many infection control challenges – mitigated by special units:
  - Highly trained staff/continually reinforced
  - Training, policies, procedures, logistics ready in advance
  - Disposal of significant volumes of waste and human waste

- Added reassurance to the public
- Still can’t engineer out human error or sharps injuries
Identify a single lab personnel that will handle the samples.
-lab testing may not be available at all.
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

• 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 VHFs

• 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 >= 100.4°F

• 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 >= 100.4°F

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
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
Emerging threats

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

• **Alkhurma hemorrhagic fever (Saudi Arabi, 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 (10 cases, 2 deaths; in Missouri, Oklahoma, and Tennessee)
    • Lone star tick may transmit this virus
Emerging Threats

• Chapare Virus
  – Small cluster of cases occurred
  – Hemorrhagic fever symptoms
  – Novel arenavirus found in 1 pt
    • 22 yo male, died on DOI 14

Overview of VHF\textsubscript{S}

- Summary for the Deploying Provider
  - Identify the potential KNOWN risks in your AO
  - Identify your unit’s VHF coordinator
  - Keep track of all patient contacts
  - Identify your evac plan BEFORE you need it
  - Identify nearest medical support that can handle such patients
    - Could your patient benefit from ribavirin? Other meds?
    - Have your nearest infectious disease and prev med support on speed dial

- If going in support of the Ebola outbreak, familiarize yourself with the WHO handbooks and OTSG Clinical Practice Guidelines (in draft form)
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, **NOT EBOLA**) 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

• Experimental drugs and vaccines for selected VHFIs are working their way into human clinical trials
Detailed information on CDC's Safety Training Course for Healthcare Workers Going to West Africa in Response to the 2014 Ebola Outbreak

CDC's Safety Training Course for Healthcare Workers Going West Africa in Response to the 2014 Ebola Outbreak is intended to provide the first step in training that will help prepare healthcare personnel (HCP) to provide medical care to Ebola patients in an Ebola Treatment Unit (ETU) that has been established and is staffed by MSF personnel, or in a facility that maintains MSF standards of care, or in an ETU established and staffed by WHO personnel. Further training (see below), under the direct supervision of qualified personnel in an ETU, should follow this course.

Participants should understand that providing care or conducting activities in other ETUs (e.g., a non-MSF, non-WHO Ebola treatment center or a general hospital) may not offer the same level of engineering and/or administrative infection control measures that an MSF- or WHO-ETU provides. This course may not provide sufficient training to work safely in such environments.

Participants intending to take this course should be currently licensed by a recognized professional agency to provide clinical care in some jurisdiction (e.g., hold a medical license to provide care in a state in the United States) and have recent relevant experience providing direct care to patients. The course is intended for licensed medical doctors (MD, DO degrees), licensed nurses (RN, BSN, LPN, etc.), and other licensed clinical care providers (e.g., paramedics, physician assistants, and other clinical providers). This course is designed to instruct practitioners on how to protect themselves from infection while providing basic clinical care to Ebola patients, and assumes clinical proficiency and familiarity with standard infection control as practiced at this time in North American healthcare facilities. This course will not provide general medical training or instruction on advanced medical topics.
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
YOU HAVE MUCH TO LEARN, GRASSHOPPER!
United States Army Medical Research Institute of Infectious Diseases (USAMRIID)
Questions?