VHF

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“We were at sea--there is no other adequate expression...To one hurrying through by stream there was a certain exhilaration in this spacious vacancy, this greatness of the air, this discovery of the whole arch of heaven, this straight, unbroken, prison-line of the horizon”

-Robert Louis Stevenson
Viral Hemorrhagic Fevers

Classified by CDC in 1999 as Category A bioweapon agents

- Potential to cause widespread illness / death
- Ease of dissemination or person-to-person transmission
- Potential for major special public health preparations
Viral Hemorrhagic Fevers

- Most already weaponized
  - Ebola Russia and former Soviet Union
  - Japan (attempted)
  - Marburg Russia and former Soviet Union
  - Lassa Russia and former Soviet Union
  - New World Arenaviridae (Junin and Machupo) Russia and former Soviet Union
  - Rift Valley Fever
  - Yellow Fever North Korea (reportedly)
  - Omsk hemorrhagic fever
  - Kyasanur Forest Disease
<table>
<thead>
<tr>
<th>Family</th>
<th>Genus</th>
<th>Virus</th>
<th>Disease</th>
<th>Vector in Nature</th>
<th>Geographic Distribution</th>
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<tbody>
<tr>
<td>Filoviridae</td>
<td>Filovirus</td>
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<td>Ebola hemorrhagic fever</td>
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<td>Lassa</td>
<td>Lassa fever</td>
<td>Rodent</td>
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<td></td>
<td></td>
<td>New World Arenaviridae†</td>
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<td>Bunyaviridae</td>
<td>Nairovirus</td>
<td>Crimean-Congo hemorrhag</td>
<td>Crimean-Congo hemorrhagic fever</td>
<td>Tick</td>
<td>Africa, central Asia, eastern Europe, M</td>
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<td></td>
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<td>ich fever</td>
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<td></td>
<td>Middle East</td>
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<tr>
<td></td>
<td>Phlebovirus</td>
<td>Rift Valley fever</td>
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<td>Hantavirus</td>
<td>Agents of hemorrhagic</td>
<td>Hemorrhagic fever with renal syndrome</td>
<td>Rodent</td>
<td>Asia, Balkans, Europe, Eurasia§</td>
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<td></td>
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<td>fever with renal system</td>
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<tr>
<td></td>
<td>Flaviviridae</td>
<td>Flavivirus</td>
<td>Dengue fever, Dengue hemorrhagic fever, and Dengue shock syndrome</td>
<td>Mosquito</td>
<td>Asia, Africa, Pacific, Americas</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Yellow fever</td>
<td>Yellow fever</td>
<td>Mosquito</td>
<td>Africa, tropical Americas</td>
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<td>Omsk hemorrhagic fever</td>
<td>Omsk hemorrhagic fever</td>
<td>Tick</td>
<td>Central Asia</td>
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<tr>
<td></td>
<td></td>
<td>Kyasanur Forest disease</td>
<td>Kyasanur Forest disease</td>
<td>Tick</td>
<td>India</td>
</tr>
</tbody>
</table>

*Bold indicates hemorrhagic fever viruses that pose serious risk as biological weapons (addressed in this consensus statement).
†There are 4 subtypes of Ebola: Zaire, Sudan, Ivory Coast, and Reston.
‡The New World Arenaviridae include Machupio, the cause of Bolivian hemorrhagic fever; Junin, the cause of Argentine hemorrhagic fever; Guanarito, the cause of Venezuelan hemorrhagic fever; and Sabia, the cause of Brazilian hemorrhagic fever. An additional arenavirus has been isolated following 3 fatal cases of hemorrhagic fever in California, 1999-2000.§
§Additionally, the agents of hantavirus pulmonary syndrome have been isolated in North America.
VHF - Epidemiology

- Reservoir – animals
- Spread by close contact
- Usually seen in Africa
- 20 outbreaks of Filoviruses (Marburg, Ebola) since 1967
Marburg Virus Infection

- Indigenous to Africa
- First seen in Europe in 1967.
- Spread to humans from African green monkeys from Uganda
- 7 of 32 infected persons died
- Some person-to-person spread (by needles, contact)
- Scattered cases in South Africa (1975), Kenya (1980s) and Russia (1990).
Marburg Virus Infection

- **Congo (1998-1999)**
  - 128 of 154 died (83%)
  - First cases in gold miners
  - 4 cases occurred after infection control measures

- **Angola (2004-2005)**
  - 227 of 252 died (90%)
  - Local burial practices a contributing factor
  - ? source is the fruit bat
Ebola Virus Infection - History

- First seen in 1976 in 2 places in Africa
- 290 of 318 died (91%) in Zaire
- 150 of 284 died (53%) in Sudan
- Seen in imported monkeys in Virginia in 1989
- Seen in monkeys (imported from Philippines) in Texas, 1996
Ebola Virus Infection - History

- In Congo in 1995
  - 245 of 317 died (77%)

- In Uganda 2000-2001
  - 425 cases, 224 deaths (53%)
Ebola Virus Epidemiology

- Contact with patients or body fluids a risk factor
- Virus found in saliva, stool, blood, semen, breast milk, tears and skin.
- Wild animal deaths (eg, gorilla) precede human deaths
- Aerosol spread possible in primates
Lassa Fever - History

- First described in 1969

- Outbreaks in Nigeria (1970) and Liberia (1972)
  - 39 cases (50% mortality), nosocomial spread

- Sierra Leone outbreak in 1972-1973
  - 441 cases (16% mortality)
Lassa Fever

- Causes estimated 200,000-400,000 cases per year in West Africa
- Causes 5000 deaths per year in Africa
- 4% of survivors are deaf, and up to 1/3 have some hearing loss
- Fever, sore throat and vomiting associated with a fatal outcome
- IV ribavirin begun in the first 6 days reduces mortality
Lassa Fever - Epidemiology

- Virus found in many rats
- Spread to humans by rat urine
- Spread person-to-person by direct contact
- About 20 imported cases from Africa have been seen
- Isolate with strict barrier precautions
- No secondary cases noted
- Consider ribavirin prophylaxis for exposures
VHF--Other important diseases

- **Yellow fever**
  - Seen in Africa, South America
  - Mosquito-borne
  - Monkeys are the main reservoir
  - Vaccine available

- **Dengue**
  - Found in tropical areas
  - Mosquito-borne
  - Called "breakbone fever"
  - 2008: over 40,000 cases in Brazil

- **Rift valley fever**
  - A disease of livestock
  - Mosquito-borne
  - Increasing outbreaks in Africa
  - Can cause liver failure, blindness
VHF--Other important diseases

- **Crimean-Congo hemorrhagic fever**
  - Found in animals in Europe, Asia and Africa
  - Tick-borne
  - Nosocomial spread is common

- **Chikungunya**
  - Causing outbreaks in India, Indian Ocean islands, Italy
  - Mosquito-borne
  - Named for contorted posture due to severe joint pain

- **Others**
  - Hantavirus infection
  - Ross river virus
  - Sabia virus
  - Whitewater Arroyo virus
  - Argentinian HF
  - Bolivian HF
  - Venezuelan HF
  - Omsk HF
  - Kyasanur forest disease
Ebola virus is discovered in imported monkeys in Reston, Virginia
VHF: Clinical Presentation

- Other signs/symptoms
  - Prostration
  - Pharyngeal, chest, or abdominal pain
  - Mucous membrane bleeding, ecchymosis
  - Shock

- Usually improving or moribund within a week (exceptions: HFRS, arenaviruses)

- Bleeding, CNS involvement, marked SGOT elevation indicate poor prognosis

- Mortality: agent dependent (10 to 90%)
VHF Signs and Symptoms

- Fever (≥38.3°C or 101°F)
- Fatigue
- Dizziness
- Headache
- Malaise
- Myalgia
- Arthralgia
- CNS Dysfunction

- Thrombocytopenia
- Skin rash (hemorrhagic)
- Encephalitis
- N,V,D
- Conjunctivitis
- Pharyngitis
- DIC
- Shock
Viral Hemorrhagic Fevers

Diagnosis

– Appropriate clinical presentation
  - Acute fever, life-threatening illness, bleeding manifestations without predisposing factors

– With risk factors
  - travel, insect bite, animal handling

– Specimens must be sent to CDC or USAMRIID
DIAGNOSIS OF VHF: LABORATORY CONFIRMATION

- Nucleic acid hybridization and ELISA
  - Electron microscopy can provide definitive evidence

- Polymerase chain reaction (PCR)
  - Increasingly important tool; undergoing further development

- Viral culture is still the gold standard for diagnosis
VHF Treatment

- Supportive therapy
- Ribavirin
TRANSMISSION TO HUMANS

- Aerosols: usually through rodent excreta
- Contaminated food / water
- Arthropod vectors:
  - Mosquitoes
    - Bunyavirus: RVF
    - Flaviviruses: Dengue, yellow fever
  - Ticks
    - Bunyavirus: CCHF
    - Flaviviruses: Kyasanur Forest disease, Omsk HF
  - Hematophagous flies:
    - Bunyavirus: RVF
PERSON-TO-PERSON TRANSMISSION

Blood and body fluids

- Arenaviruses
- Bunyaviruses
  - CCHF, RVF

- Filoviruses
- Flaviviruses
  - Yellow Fever

Respiratory droplet or airborne (?)

- Arenaviruses
  - (Lassa, Bolivian HF)

- Bunyaviruses
  - (CCHF)

- Filoviruses ??
  - (Ebola Reston: monkey-human)
What is wrong with this picture?
VHF – Nosocomial Risk

- 1976: 27% of Ebola cases in Zaire spread by injection
- 2000: 14 of 22 infected personnel in Uganda infected after isolation was instituted.
  - Poor compliance?
  - Airborne spread?
- Lassa: nosocomial transmission due to needlestics, contact
VHF:

Patient Isolation

- Single room w/ adjoining anteroom (if available)
  - Handwashing facility with decontamination solution
- Negative air pressure
- Strict barrier precautions including protective eyewear/faceshield
- Disposable equipment /sharps in rigid containers with disinfectant then autoclave or incinerate
- All body fluids disinfected
VHF-Infection Control

- HICPAC guideline (2007): Droplet and Contact isolation

- 2002 Consensus Paper (JAMA) recommends: Droplet, Contact and Airborne isolation
  - Single room
  - Double gloves
  - Impermeable gowns
  - Face shields
  - Eye protection
  - Leg and shoe coverings
  - Restricted access
  - Dedicated medical equipment
  - AII (6-12 air exchanges per hour) plus N95s or PAPRs
  - Disinfection with bleach
  - May autoclave linens
VHF: Contact Management

- **Casual contacts** - No known risk

- **Close contacts**
  - Household, physical, nursing, handle lab specimens
  - Record temp b.i.d. for 3 weeks post-exposure
  - **Consider** prophylaxis (Ribavirin) if temp > 101°F or other systemic symptoms within 3 weeks

- **High-Risk contacts**
  - Mucous membrane, penetrating injury with exposure to body fluids or tissue
  - **Consider** post-exposure prophylaxis
EXPOSURES
FIRST AID

- **Wash/irrigate wound / site immediately**
  - Within 5 minutes of exposure

- **Mucous membrane (eye, mouth, nose)**
  - Continuous irrigation with rapidly flowing water or sterile saline for ≥ 15 minutes

- **Skin**
  - Scrub for at least 15 minutes while copiously soaking the wound with soap or detergent solution
    - Fresh Dakin's solution (0.5% hypochlorite):
      - 1 part standard laundry bleach (5.25% hypochlorite)
      - 9 parts tap water
No way out
Viral Hemorrhagic Fevers

- Infections acquired percutaneously are associated with shortest incubation and highest mortality
- Person-to-person airborne transmission is normally rare, but possible
- Incubation period is 2-21 days
Viral Hemorrhagic Fevers

Four families of viruses
- All are single-stranded RNA with lipid envelopes
- Arenaviruses, flaviviruses, bunyaviruses, filoviruses
- All restricted to specific geographic locations
- Usually transmitted via contact with infected animals or arthropods
- Human to human spread seen Ebola/Marburg, CCHF, Lassa fever, Junin
- Transmission via physical contact and mucosal spread
- Airborne spread may be possible with Marburg/Ebola
  - All outbreaks contained without airborne precautions
  - Virus is stable and highly infectious as an aerosol
Viral Hemorrhagic Fevers

Pathogenesis

- Vary by organism but most act on endothelium causing increased permeability and platelets causing dysfunction
- Hallmark is microvascular injury
- Some act through cytokines without much cytopathologic effect (Hanta, Lassa)
- Others are cytotoxic without significant inflammation (Ebola, Marburg, YF, RVF)
- Ebola pathogenesis:
  - Lymphatic spread > killing of T cells and NK cells > unchecked viral replication > cytokine storm > coagulation system activation > DIC > hemorrhage > shock > death
Viral Hemorrhagic Fevers

- Clinical features vary by agent but all are associated with febrile prodrome and bleeding diathesis

- Prodrome last up to 1 week
  - High fever, HA, malaise, N/V, abdominal pain, diarrhea
  - Hypotension, bradycardia, cutaneous flushing, rash

- Sign of bleeding diathesis
  - Petechiae, mucus membrane/conjunctival hemorrhages, hematuria, melana, DIC, shock
  - Some have severe liver dysfunction

- Mortality ranges <1% to >90%
Viral Hemorrhagic Fevers (VHF): Overview

- Caused by several different viruses families
  - Filoviruses (Ebola, Marburg)
  - Arenaviruses (Lassa, Junin, Machupo, Sabia, Guanarito)
  - Bunyaviruses
  - Flaviviruses

- Natural vectors - virus dependent
  - rodents, mosquitoes, ticks

- No natural occurrence in U.S.
## Specimen Collection: Viral hemorrhagic fever

<table>
<thead>
<tr>
<th>Site</th>
<th>Specimen</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ebola, Marburg, Argentine, Junin, Bolivian hemorrhagic fevers and Lassa fever</td>
<td>Serum</td>
<td>Collect 10 – 12 ml of serum</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Do not collect or ship any specimens without consultation from MDCH or CDC</td>
</tr>
</tbody>
</table>
CLINICAL LABORATORY PROCEDURES

▸ Strict barrier precautions
  – Gloves, gown, mask, shoe covers, and protective eyewear and faceshield
  – Consider a respirator with a HEPA filter
  – Handle specimens in a biosafety cabinet when possible

▸ Spills/splashes
  – Immediately cover with disinfectant and allow to soak for 30 minutes
  – Wipe with absorbent towel soaked in disinfectant

▸ Waste disposal
  – Same as for patient isolation practices

<table>
<thead>
<tr>
<th>Disease</th>
<th>Incubation period</th>
<th>Duration of illness</th>
<th>Case fatality rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhalational anthrax</td>
<td>1-6 days</td>
<td>3-5 days</td>
<td>Untreated, 100%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Treated, 45%</td>
</tr>
<tr>
<td>Botulism</td>
<td>6hrs-10days</td>
<td>24-72 hrs</td>
<td>Outbreak-associated, first patient, 25%</td>
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<td></td>
<td></td>
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<td>Subsequent patients, 4%</td>
</tr>
<tr>
<td>Tularemia</td>
<td>1-21 days</td>
<td>2 weeks</td>
<td>Untreated, 33%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Treated &lt;4%</td>
</tr>
<tr>
<td>Pneumonic plague</td>
<td>2-3 days</td>
<td>1-6 days</td>
<td>Untreated, 40%-70%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Treated, 5%</td>
</tr>
<tr>
<td>Smallpox</td>
<td>7-17 days</td>
<td>4 weeks</td>
<td>Overall, 20%-50%</td>
</tr>
<tr>
<td>Viral hemorrhagic fevers</td>
<td>4-21 days</td>
<td>7-16 days</td>
<td>Overall, 53%-88%</td>
</tr>
</tbody>
</table>
Marburg Virus Hemorrhagic Fever

- Angola, October 2004 - April 5th, 2005
  - Total of 163 cases, 150 fatal
  - 75% of reported cases in children aged <5 years
  - Healthcare workers
  - Predominant symptoms: fever, hemorrhage, maculopapular rash, vomiting, cough, diarrhea, and jaundice
Wizard of Id

I'd like to see the doctor.

What's wrong?

Whisper.

Whisper.

Have a seat, but don't touch the magazines.
Ebola Patient (Intensive Care)
VHF viruses and immunity

- RNA viruses
- High mutation potential
- Evade and block interferons
- Induce macrophages to secrete cytokines
- Infected monocytes initiate DIC
- The immune system has trouble clearing the virus
VHF: Clinical Information

- Usual patient history
  - Foreign travel to endemic or epidemic area
  - Rural environments
  - Nosocomial exposure
  - Contact with arthropod or rodent reservoir
  - Domestic animal blood exposure

- Incubation
  - Typical 5 to 10 days
  - Range 2 to 16 days