

Viral Hemorrhagic Fever

Jim Powers DO, FACEP

November 12, 2009

What is Viral Hemorrhagic Fever (VHF)?

- Clinical multi-system illness associated with **fever & a bleeding diathesis**.
- Clinical syndromes with overlapping features_(a)
 - Initial **nonspecific prodrome**
 - Fever
 - Malaise
 - Headache
 - Myalgia
 - Progresses to more severe symptoms & death
 - **Hemorrhage**
 - **Increased vascular permeability**
 - **Shock**
 - **Multiorgan failure**
- Caused by members of 4 distinct families of RNA viruses.
 - **Filioviridae**
 - **Arenaviridae**
 - **Bunyviridae**
 - **Flaviviridae**
- Many cause rapidly progressive illness & high mortality rates _(t)

Letters in parenthesis correspond to references at end of the presentation

Viral Hemorrhagic Fever (VHF)

- Viruses capable of causing Viral Hemorrhagic Fever (VHF) are known collectively as Hemorrhagic Fever Viruses (HFVs)

Epidemiology of HFV Transmission

Epidemiology of HFV Disease Transmission

■ HFVs are **zoonoses**

- Animal hosts or arthropod vectors

■ Natural infection of humans

1. **Bite of infected arthropod**
2. **Aerosol from infected rodent excreta**
3. **Direct contact with infected animals / carcasses or fomites** ^(c)
 - All human Ebola outbreaks in Gabon & DRC from 2001-2003 resulted from handling infected wild animal carcasses (10 gorillas, 3 chimpanzees, 1 duiker) ^(b)

■ Incubation period

- Generally **2-21 days** ^(c)

■ Human to Human & Nosocomial Transmission

- Possible for most HFVs ^(c)
- Most person-to-person spread 2^o direct contact with infected blood & body fluids
 - Mucous membrane contact, aerosolized, semen, vomit, sweat,

Epidemiology of HFV Disease Transmission

- **Percutaneously acquired infections common**

- **Airborne transmission appears to be likely**

- **Ebola (filovirus)**

- Multiple studies in nonhuman primates have documented the aerosol spread of Ebola virus ^(b)
 - Droplet spread suspected as a mode of dx transmission among infected humans – although human to human aerosol transmission appears to be rare ^(b)

- **Lassa virus (arenavirus)**

- Documented to be spread by aerosol transmission in nonhuman primates in lab studies ^(b)
 - 1969 outbreak in Nigeria, an index patient transmitted Lassa to 16 other pts in same hospital ward – thought to be due to droplet aerosol spread ^(b)

- **Junin (arenavirus)**

- Acquired by aerosolization of infected rodent excreta ^(b)
 - Lab workers working with these agents have become infected through inhalation of aerosols ^(b)

- **Yellow Fever (flavivirus)**

- Lab related aerosol transmission has also been described ^(b)

Mortality in HFV Infections

■ Case-fatality varies

■ Organism

■ Filoviruses

- High as 90% for Ebola
- Varies with Ebola subtype _(b)

■ Flavivirus

- As low as 0.5% for Omsk HF

■ Arenavirus – 15-30%

■ Mode of exposure

- Percutaneous exposure
universally fatal in Ebola outbreak
1976 _(b)

■ Viral Load

- Higher viral loads = \wedge mortality

■ Death usually preceded by:

- Hemorrhagic diathesis
- Shock
- Multi-organ failure
- Time to death varies

Microbiology of the HFVs

■ Microbiology

- All small **single-stranded RNA viruses** with lipid envelopes _(c)
- All cause disease during period of viremia
- **Low infectious dose**
 - 1-10 organisms _(z)

■ Potential for Bioweapons?

- Most replicate in cell culture to concentrations sufficient to produce **small terrorist weapon** _(c)
- Except Dengue, all HFVs typically **stable & highly infectious as fine particle aerosols** _(c)
- Most have **high M+M** _(c)

Pathogenesis of the HFVs

- Target organ in VHF is **vascular bed** ^(c)
 - 1^o effect - **microvascular damage & vascular permeability**
- Virus replicates intracellularly - infected cells release large # of new viral particles
- Acute disease - **viremia & cytokine activation** ^(b)
- Systemic Inflammatory Response
 - Cytokines, chemokines, proinflammatory mediators ^(w)
 - Endothelial dysfunction, \wedge vascular permeability, vasodilation, shock
- **Hemorrhagic Complications** ^(b)
 - Platelet dysfunction & thrombocytopenia
 - \vee levels of coagulation factors
 - Marrow injury
 - **Death rarely due to hemorrhage** ^(c)
- **Shock & multisystem organ failure**

Clinical Manifestations of HFVs

■ General Points

- Wide variety of clinical manifestations
 - Not all patients develop classic VHF syndrome
- Symptoms related to increased vascular permeability
- Significant overlap of symptoms – may be hard to differentiate among diseases based on clinical grounds
 - Also clinically similar to # of other diseases
- Incubation period 2-21 days

Early Clinical Manifestations of HFVs

■ Non-specific prodrome (<1week)

- High fever
- Headache
- Malaise
- Arthralgias/myalgias
- Nausea
- Abdominal pain
- Non-bloody diarrhea

■ Early signs

- Fever
- Hypotension
- Cutaneous flushing or skin rash
- Conjunctivitis or pharyngitis
- Relative bradycardia
- +/- Tourniquet Test
 - Inflate BP cuff to midpoint between systolic & diastolic BP; keep inflated for 4-5 minutes
 - > 20 petechiae / in.² is +

Late Clinical Manifestations of HFVs

■ Hemorrhagic complications

- Petechiae/purpura
- Mucous membrane / conjunctival hemorrhage
- Generalized bleeding
- Hematuria
- Hematemesis
- Melena, blood in stool (occult, overt)
- DIC
- Shock
- Jaundice

■ CNS Dysfunction

- Delirium / Coma, seizures
- Imparts poor prognosis

■ Renal Failure

- Prominent in Hanta

■ Pulmonary Involvement

- Pneumonia/ hemorrhagic pulmonary edema

Differential Diagnosis

■ Infectious (b)

- Influenza
- Viral hepatitis
- Staphylococcal or gram – sepsis
- Meningococemia
- Salmonellosis and shigellosis
- Leptospirosis
- **Malaria***
- Rickettsial disease
- Measles
- Smallpox – hemorrhagic
- Toxic Shock
- Septicemic Plague
- Trypanosomiasis

■ Non-infectious (b)

- DIC
- ITP
- TTP / HUS
- Acute leukemia
- Vasculitis
- Collagen-vascular diseases

Arenavirus

Lassa Fever

New World Arena Viruses

Arenavirus: Old + New World AV

- Arenaviruses - **rodent borne** HFVs
 - Mainly rats & mice
- Severe VHF in Africa & S. America
 - One in North America
- **Incubation 3-19 days**
- 2 Types: Old World & New World
 - **Old World** – Africa & Europe
 - **Lassa Fever**
 - Lymphocytic Choriomeningitis (LCM)
 - **New World** - Americas
 - South American HFVs
 - Junin (Argentine HF)
 - Machupo (Bolivian HF)
 - **Whitewater Arroyo (North America)**

Arenaviruses

- Natural transmission occurs through:
 - **Inhaled aerosols** of rodent urine/feces
 - Ingestion of food or water contaminated with rodent excreta
 - Direct contact of rodent excreta with abraded skin / mucous membranes
 - Contact with contaminated fomites
 - Contact with rodent blood
- Person to person transmission does occur
 - Direct contact with blood, urine, pharyngeal secretions & other fluids
 - **Airborne transmission possible**
 - Sexual transmission likely
 - Lassa fever detected in semen up to 3 months after acute infection
- Mortality 15-25%

Case #1 (b)

- 2004 – New Jersey
- 38 y/o businessman presents to an ED in NJ with a fever to 103.6, sore throat, chills, diarrhea and back pain
- His condition deteriorated rapidly during hospitalization, requiring intubation
- History revealed several recent trips to Liberia & Sierra Leone in West Africa
- DDX: Yellow Fever, Lassa fever, Typhoid Fever, malaria
- Pt died despite aggressive supportive tx
- Postmortem exam confirmed diagnosis of **Lassa fever** by serum antigen detection, viral culture and RT-PCR assay

Lassa Fever

■ West Africa

- Mild subclinical infections common, asymptomatic in up to 80% _{(z)(WHO)}
- 10-15% of adult hospital admissions _(c)
- Infects 100,000-300,000, killing 5,000-10,000 _(c)
- Another 30,000 deaf _(c)

■ Mortality overall 1-2% _(s)

- More severe in pregnancy (16% mortality) & children _(c)
 - Fetal loss up to 80% in 3rd trimester (WHO)

- Periodically imported to Europe, US, Japan, & Canada from travelers _(c)

- Most infections traceable to contact w/ carrier rat, *Mastomys natalensis* _(c)

- Rodent excreta (inhaled or contact)

■ Person-person transmission occurs

- Percutaneous injury
 - Contact w/ body fluids
 - Mucosal splashes from infected fluids

Whitewater Arroyo Virus

- 3 cases of fatal Arenavirus identified in CA 1999-2000 (j)
 - All female, aged 14, 32, 52 years
 - All began as **non-specific febrile** symptoms
 - All developed ARDS & lymphopenia
 - 2 developed hemorrhagic manifestations & liver failure
 - Nucleotide sequence identical showing Whitewater Arroyo virus
- Host - white throated wood rat (Neotoma spp)

Bunyviruses:

Rift Valley Fever

Hantavirus

Crimean Congo HF

Bunyviruses

- Viral hosts: **arthropod vectors & rodents** ^(c)
 - Mosquitoes – Rift Valley Fever
 - Ticks – Crimean Congo Fever
 - Rodents – Hanta Virus

- All can be acquired by: ^(c)
 - Exposure to infected animals or their carcasses
 - Contact with **blood & bodily secretions of infected persons**
 - By **aerosol**

Rift Valley Fever

- Mosquito-borne disease primarily affecting sheep & goats
- Most human infections are **unapparent**
 - Self limited febrile illness _(s)
 - 1% develops typical VHF _(s)
- Short incubation: 3-6 days _(a)
- Mortality 1% _(a)
- Humans acquire infection by:
 - Bite of infected mosquito
 - Contact with infected animal tissues
 - Aerosolization of virus from infected animal carcasses
 - Ingestion of contaminated raw animal milk
- No reported cases of person-to-person transmission

Rift Valley Fever

■ Outbreaks Common

- Kenya 1997-1998 (w)
 - 89,000 infected; 473 deaths
- Saudi Arabia (Aug. – Nov. 2000)_(f)
 - 516 infected / 87 dead (17%)
- Kenya 2006-2007 (w)
 - 404 cases; 118 deaths (29% fatality)

■ Theory - potential use as a **biological weapon**

- Susceptible domestic livestock could be infected
- Livestock develop high levels of viremia & infect susceptible mosquito vectors _(y)
- Several mosquitoes in U.S. (Aedes, Anopheles, Culex) have capacity to act as vectors

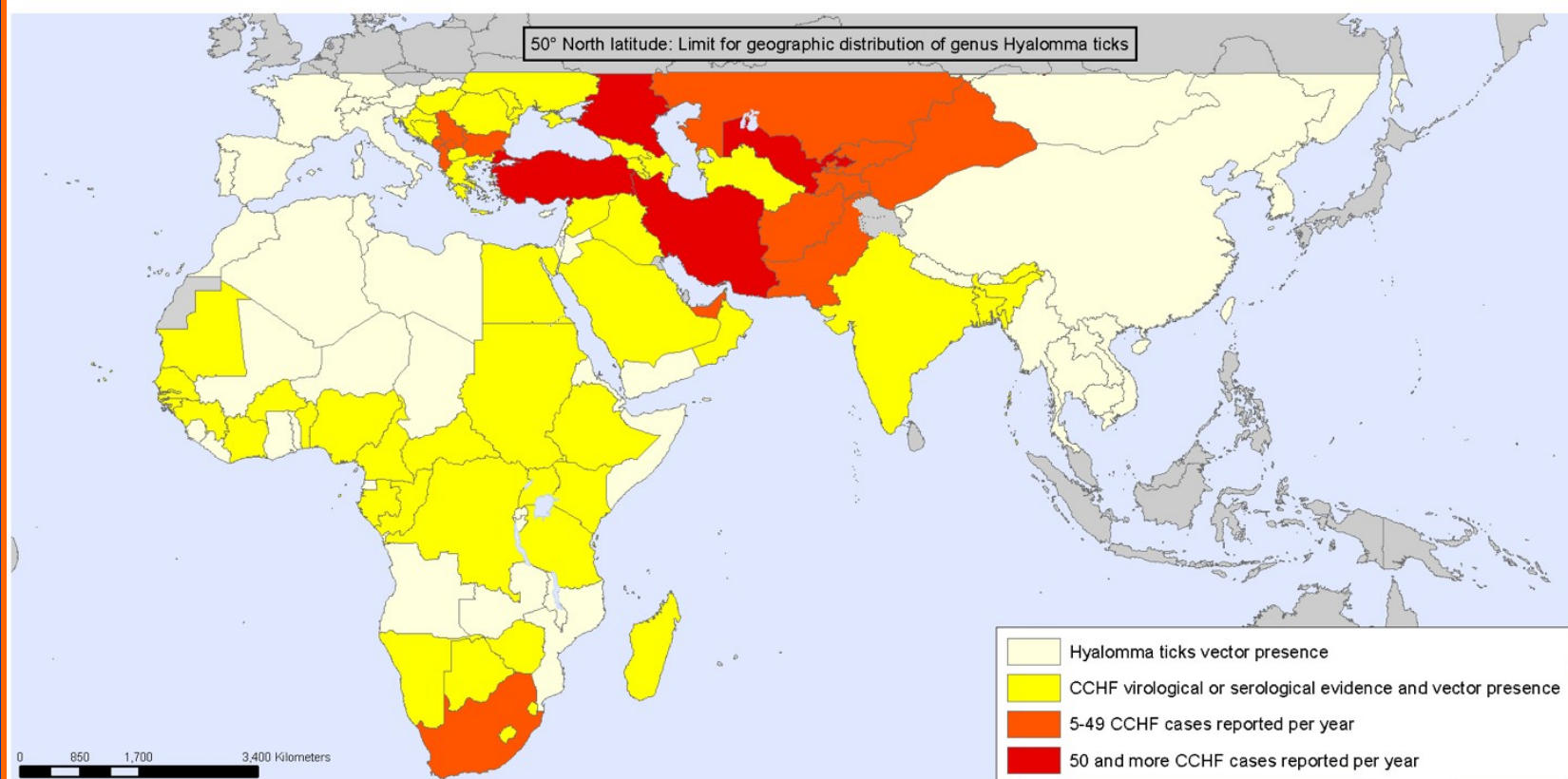
Crimean Congo Hemorrhagic Fever

■ Transmission

- Bite of at least 29 species of **ticks** _(c)
- Contact with blood or tissue from infected persons or livestock _(w)
- **Blood of infected pt highly infectious** _(c)
- **Spreads easily by aerosol**
- Endemic in Africa, Europe & Asia _(c)
- Causes sporadic but **severe disease**
- Usually produces **profound DIC** _(c)
- **Copious hemorrhage** – one of most hemorrhagic VHFs _(c)
- 75% have hemorrhagic symptoms _(a)
- **Incubation 2-12 days** _(a)
- **Mortality 15-50%** _(a)

Geographic Distribution of CCHF

Geographic distribution of Crimean-Congo Haemorrhagic Fever



The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.

Data Source: World Health Organization
Map Production: Public Health Information
and Geographic Information Systems (GIS)
World Health Organization



© WHO 2008. All rights reserved

2 Cases _(p)

■ July 2004

■ Patient A

- Wildlife sciences graduate student – 32 y/o
- To ED with fever, cough, sore chest for 1 day
- Temp 102.7, Sats 96%
- CBC - lymphopenia
- CXR - faint right sided pneumonia
- Admitted for IVF and abx
- Became hypoxic, requiring intubation & MV
- Repeat CXR –B/L pulmonary edema
- Next day hypotensive, required pressors
- Died on 3rd day
- DDX: pneumococcal sepsis, tularemia, HPS
- Serum specimens + for IgG & IgM for **hantavirus** – confirmed by CDC
- **Hantavirus** RNA detected by RT-PCR
- Further hx – had **spent previous month trapping & handling mice**

2 Cases (p)

■ July 2004

■ Patient B

- Pt **12 miles from pt A** - spent weekend at log cabin with family
- 2 days later - fatigue, ha, mild fever
- Next day temp 102.9 & hematuria
- Saw pcp & started on abx for possible UTI
- 2 days later HA worse - went to ED
- Hypoxic; CXR - pneumonia & CHF
- Airlifted to referral hospital with hypotension & bradycardia
- ICU admission with pressors & abx
- Initial ddx – viral myocarditis, atypical pneumonia, opportunistic infection
- Intubated next day & had onset of thrombocytopenia, DIC, & renal failure requiring dialysis
- Began to improve after 5 days and recovered slowly over next month
- Serum + for IgG & IgM against Hanta virus; confirmed by CDC
- Hanta RNA detected by RT-PCR
- Additional hx – **found cabin reeking of rodent urine & found 2 live mice in trashcan**
 - Pt killed mice, disposed of remains and cleaned trashcan w/o gloves
 - Trapped 6 additional mice

Epidemiology of Hanta Virus

- First recognized in US in May 1993 in New Mexico
 - 4 Corners region epidemic in 1993
- Through March 26, 2007 **465 cases** of hantavirus pulmonary syndrome reported in 31 states in U.S.
 - Prominent cardio-pulmonary compromise
 - Resembles ARDS clinically
 - Can cause frank hemorrhage
- **38% of cases have resulted in death**
- Incubation 2-3 weeks _(s)

Epidemiology of Hanta Virus

■ Transmission of Hanta Virus

- No arthropod vector
- Exposure to **infected rodent**
- Rodent saliva/droppings dry up, **"aerosolized"** & breathed in
- No person-to-person transmission in the U.S.

Clinical Features of Hanta Virus

■ Common Findings_(p)

- Prodrome of fever, myalgias, cough, & nausea/vomiting
- Rapid progression to **pulmonary edema** & nonischemic cardiogenic shock
- Thrombocytopenia & hemoconcentration
- **ARDS on CXR**

■ Physical Exam Findings

- Tachypnea
- Tachycardia
- Hypotension
- Crackles/rales on lung exam

Flaviviruses

Yellow Fever

Dengue Fever

Omsk HF

Kyasanur Forest Disease

Epidemiology of Flaviviruses

- Mode of transmission
 - Yellow Fever - mosquito
 - Dengue Fever - mosquito
 - Omsk HF/Kyasanur FD: Tick bite
- **No reported cases of person-to-person transmission**
- Potential as a biological weapon
 - Similar to RVF

Dengue Fever

- Described as “breakbone fever” by Benjamin Rush in 1789 _(c)
- Endemic throughout Americas, Asia & Africa _(c)
- Vector - *Aedes aegypti* mosquito
- Most prevalent mosquito-borne viral dx _(v)
- Incubation 3-14 days _(r)
- Greatest morbidity & mortality of any of the arthropod-borne viruses _(c)

Dengue Fever

- > 100 countries have endemic dengue transmission _(c)
 - 25 cases in Tx in 2005 _(r)
 - 122 cases in HI in 2001-2002 _(r)
- GeoSentinel Surveillance Network – 2006 analysis of 17,000 ill travelers _(v)
 - Dengue - 10.4% of post-travel systemic febrile illness; 2nd only to?
 - Most frequently identified cause of systemic febrile illness in travelers returning from:
 - Southeast Asia (32%)
 - Caribbean (24%)
 - South Central Asia (14%)
 - South America (14%)
 - Central America – only slightly less common than malaria (12%)

Dengue Fever

- Four Dengue Virus Serotypes (DENV 1,2,3,4)

- All can cause severe & fatal infection
- Each provides specific lifetime immunity

- DHF/DSS - pts previously exposed to heterologous dengue serotypes (c)

- 2^o immunopathological mechanism triggered by sequential infections with different dengue viral serotypes

- Complicated pathogenesis – partially attributable to Ab-dependent enhancement (r) (c)

Manifestations of DHF

■ 4 Manifestations of disease_(r)

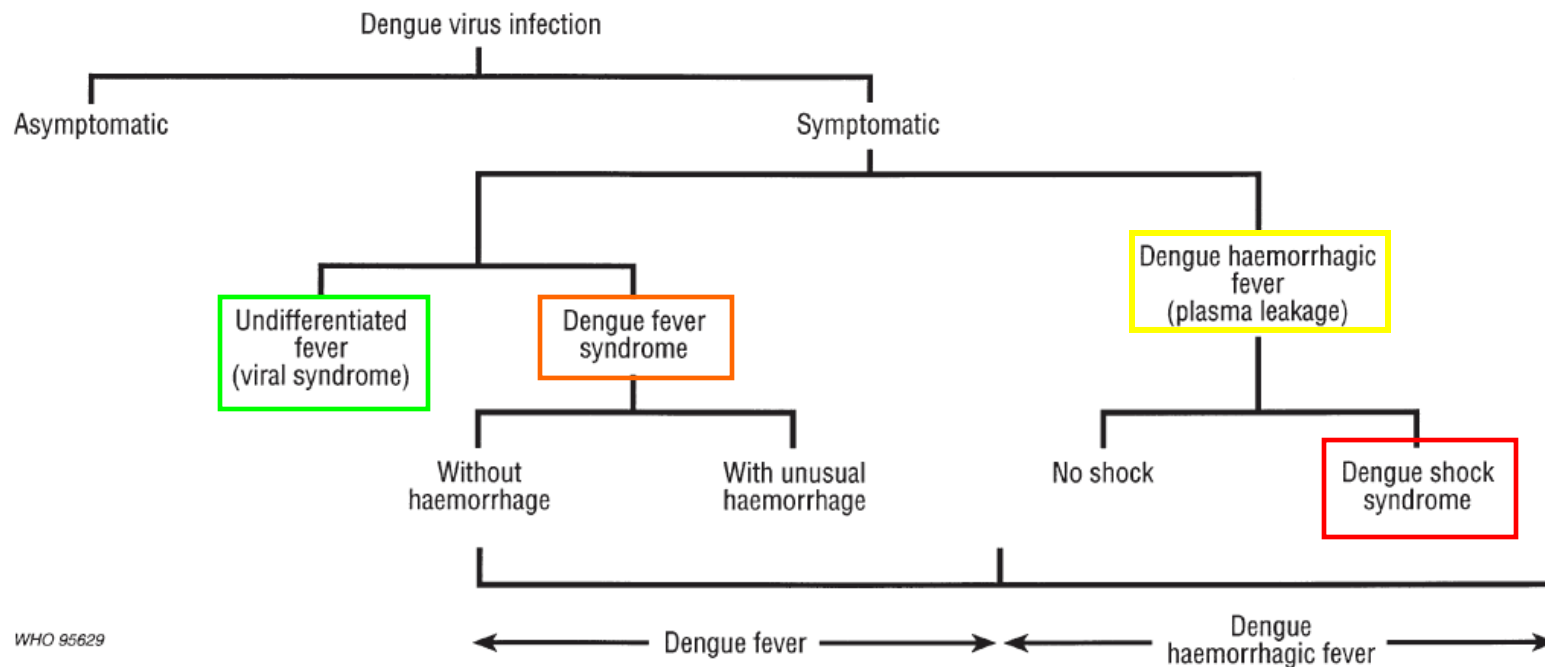
- Undifferentiated fever
- Classic Dengue Fever
- Dengue Hemorrhagic Fever
- Dengue Shock Syndrome

■ Hemorrhagic Manifestations – $\approx 1/3$.

Often mild, can be severe _(r)

- Skin: petechiae (45%), purpura, ecchymoses
- Gingival bleeding (8%) / Nasal bleeding (13%)
- GI: hematemesis, melena, hematochezia
- Hematuria (28%); \wedge menstrual flow

Manifestations of dengue virus infection



Dengue Fever

- Classic Dengue Fever_(r,v)
 - Acute febrile illness
 - Severe HA often described as retro-ocular;
 - Myalgias & arthralgias – often severe (breakbone fever);
 - Nausea & vomiting > 50%; diarrhea (30%)
 - Rash (50%) - appearance variable — maculopapular, petechial, or erythematous.
 - +/- Hemorrhagic manifestations

Dengue Hemorrhagic Fever

■ Dengue Hemorrhagic Fever_(r)

- Most serious form of dengue infection
- WHO estimates **500,000 cases /year**
- Mortality $\approx 10\%$ _(s); high as 50% _(a)

■ WHO Diagnostic Criteria – **4 features (must have all 4)**

1. **Fever** - lasting 2-7 days
2. **Hemorrhagic manifestations**
 - Petichia, purpura, ecchymosis, + tourniquet test, mucosal bleeding
3. **Low platelet count** ($\leq 100,000 \text{ mm}^3$)
4. Evidence of “**leaky capillaries:**” **
 - \wedge hematocrit ($\geq 20\%$ over baseline)
 - pleural effusion, ascities etc.

Leaky capillaries, NOT hemorrhage
differentiates Dengue Fever from DHF

Dengue Fever

■ Dengue Shock Syndrome (DSS)

- 4 criteria for DHF AND
- Evidence of circulatory failure or shock:
 - Rapid, weak pulse, narrow pulse pressure (≤ 20 mm Hg)
 - Hypotension for age
 - Cold, clammy skin, AMS

■ Bottom Line Principles

- **Consider Dengue in any traveler presenting within 14 days of return to:**
 - SE or Central Asia,
 - Caribbean,
 - South America
 - Central America
- Capillary leakage signifies presence of Dengue Hemorrhagic Fever

Epidemiology of Yellow Fever

- Historic texts dating back 400 years
 - Endemic as far north as Philadelphia in 19th century _(s)
- 1880 Panama Canal
 - 52,816 of 86,800 men contracted YF
 - 5,627 died _(a)
- Endemic in tropical areas of Africa & 9 countries in South America
- Small # of **imported cases** each year
- Transmission – bite of infected **mosquito**
- Est. **200,000 cases, 30,000 deaths / yr**
 - ^ # of people affected over past 2 decades

Yellow Fever

- Incubation **short** - 3-6 days _(a)
- Mortality of 5-10% _(a); 20-50% in epidemics, hospitalized pts _(z)
- **Initial symptoms**
 - Fever, chills, severe HA, back pain, muscle aches, nausea, fatigue
- May have short period of symptom remission
- **Toxic phase** - fever returns with initial symptoms **PLUS**
 - Coagulopathy & hemorrhage - hematemesis (**black vomit**)
 - **Jaundice**
 - Hypotension, shock, metabolic acidosis, arrhythmias
 - Confusion, seizures, and coma can occur
- **Faget's sign** – relative bradycardia with fever _(a,z)
- **Vaccine is available**
 - Immunity in 1 week in 95% of people
 - Protection for 30-35 yrs

Filoviruses

Ebola and Marburg

Filoviruses

■ Filoviruses: Ebola & Marburg

- Cause severe HF that resembles fulminant septic shock_(w)

■ Mortality Rate

- Ebola: 50-90%
- Marburg: 25-30%

■ Incubation – usually 5-7 days

- 2-21 days for Ebola
- 3-10 days for Marburg

- 9.6 days (mean) from symptom onset to death

■ Filovirus Presentation

- Similar to other HFVs - abrupt onset of fever, chills & general malaise, HA, muscle aches, pharyngitis, N/V/D

■ Hemorrhage – may be severe

- Most commonly conjunctival hemorrhages, easy bruising, failure of IV sites to clot

■ Rash

- Nonpruritic maculopapular rash on upper body during first week of illness
- Should ^ suspicion of filoviral infection_(w)

Filovirus – Natural Transmission

■ Natural Reservoir Unclear

- Rodents, bats, plant virus?
- Bats support replication & circulation of high titers of Ebola virus w/o showing overt illness _(c)
- 20% fruit bats collected in Gabon & DRC had Ebola-Zaire virus-specific IgG in serum _(x)
 - Marburg IgG found in serum of fruit bats in same region _(w)
- 2 outbreaks of Marburg HF in DRC & Uganda involved men exposed to bats while working in abandoned gold mines _(x)

Filoviruses - Transmission

■ Transmission

- Major - direct contact with body fluid of infected pts
 - Large # of Ebola viral particles found in human skin & sweat gland lumens
- Lab Studies
 - Animal studies - infection via many routes – ingestion, inhalation, breaks in skin, droplets to mouth or eyes _(x)
 - Aerosolized filoviruses highly infectious for laboratory animals

■ Nosocomial Transmission

- Several cases due to needle sticks – very high mortality
- 1995 Kikwit _(x)
 - Pt hospitalized for abd pain – underwent laparotomy
 - Entire surgical team became infected – thought likely 2° unprotected respiratory exposure to aerosolized blood _(x)
 - These persons hospitalized and spread dx to staff, patients and family members
- Uganda 2001-2002 _(b)
 - 14 (64%) of 22 healthcare workers involved in care of Ebola pts were infected despite isolation wards _(b)

Filoviruses: Transmission

■ Airborne transmission possible

- Small-droplet airborne nuclei
- Shown in animal studies, outbreaks in lab primates; could not be ruled out in 2 human outbreaks

■ Spread to HCW by aerosols generated during medical procedures _(x)

■ Ebola reston outbreak 1989

- Hundreds of infections in monkeys; high mortality
- Aerosol transmission
- No human illness although 4 caretakers seroconverted _(c)

■ Sexual transmission likely

- Ebola in seminal fluid of convalescing patients to 101 days after disease onset

Filoviruses: Transmission

■ Other Modes of Transmission

- Ritual contact with bodies of deceased patients
- Contact with infected gorillas or chimpanzees through hunting _(x)
- Accidental infection in BSL-4 facility
- Use as biological weapons
- NO evidence carried by mosquitoes, biting arthropods _(x)

■ Bottom Line Principles

- While aerosolized spread to humans documented, epidemiologic studies show that rarely, if ever, spread from person to person via respiratory route
- **Transmission not likely prior to S+S**
- Must maintain strict universal precautions

Marburg

- First outbreak of filovirus VHF - Marburg in 1967 in Germany & Yugoslavia ^(c)
 - Lab workers exposed to blood & tissues of African green monkeys imported from Uganda
 - Secondary transmission to medical personnel and family
 - Mortality 23%

Marburg

■ Transmission

- Direct contact with body fluids
 - **Droplet precautions recommended** _(w)
 - Appears **easily transmissible** _(w)
- Death from septic shock with massive hemorrhage & multiorgan failure _(w)

■ Outbreaks

- Northern Angola March 2004-2005 _(w)
 - 374 cases, 329 deaths (CFR 88%)
_(WHO)
- DRC 1998 _(w)
 - 154 infections; 128 deaths (CFR 83%)
- **Imported Cases in travelers**
 - U.S. – 2008: travel to Uganda
 - Netherlands: 2008 – travel to Uganda

Ebola

- First identified in 2 near simultaneous outbreaks in Sudan & Zaire (now Congo) in 1976
 - Sudan: June-Nov. 1976: 284 cases / 117 deaths (41%)
 - Zaire: Sept.-Oct. 1976: 318 cases / 280 deaths (88%)
- Use of unsterilized needles/syringes led to many nosocomial infections (c)
- Since 1976 there have been several small – midsize outbreaks (c)

Ebola HF Outbreaks

- Outbreaks of ZEBOV in Gabon & DRC 2001-2003 with loss of **large #s of ape population** _(c)
 - Likely role in transmission to humans
- Selected outbreaks _(q)
- Oct 2007 DRC
 - Ebola-Zaire strain
 - 249 cases; 183 deaths (78%)
- Jan 2008 Uganda
 - 149 cases with 37 deaths (25%)
 - Appears to be **new strain**
- Nov 2008 Philippines
 - **First known Ebola (Reston) infection in pigs**
 - 6 workers seroconverted but did not become ill

Ebola

■ 5 major subtypes

- Zaire – mortality 90%
- Sudan – mortality 40-50%
- Reston (1989)– monkeys only, no human infections
- Ivory Coast (1994) – chimpanzees; 1 nonfatal human infection _(c)
- Bundibugyo – Uganda 2007

■ Reston Outbreak_(c)

- 1989 Reston, Virginia
- Quarantined cynomolgus monkeys imported from Philippine Islands
- **Aerosol transmission** causing hundreds of infections & high mortality
- No human illness (4 seroconversions)
- Similar infections in facilities in US & Europe in 1992 & 1996 _(c)

Diagnosis of VHF & HFVs

Criteria for ID of Index Case of VHF (WHO)

(y)

THESE

- Fever ≥ 101 of < 3 weeks duration
- Severe illness
- No predisposing factors for hemorrhagic manifestations
- **AND** no established alternative diagnosis

AND at least 2 of these

- Hemorrhagic or purple rash
- Epistaxis
- Hematemesis or hemoptysis
- Blood in stool
- Other hemorrhage

Diagnosis should be based initially on clinical criteria and judgment

Pattern Recognition in VHF

■ Basic Facts

- Diagnosis of VHF a major challenge
 - Variable clinical presentation
 - Share S+S with many other diseases
- 2 mechanisms of infection – **natural + bioterrorism**
- Dx requires a **high index of suspicion**
- Use **historical features** & **clinical features** to develop pattern recognition

Bioterrorist event

- Will **lack historical risk factors** for natural occurring cases
- Large # of febrile pts with nonspecific constitutional symptoms
- **VHF detected in US patient w/out risk factors = bioterrorist event**

■ Historical Features – within 21 days

1. Pts from or **travel to endemic areas**
 - Even if nonspecific S+S_(b)
 - Comprehensive **travel history** critical_(c)
2. History of **tick, mosquito bites**_(y)
3. Hx of **contact w/ mice or their excreta**
4. History of **contact with patient with above risk factors** & VHF symptoms
5. Contact with **sick animals or carcasses** in endemic areas

■ Clinical Features

1. Fever
2. Rash
3. Abnormal bleeding

Lab Evaluation & Confirmation of HFVs

Lab Abnormalities in HFV Infection

■ Lab Abnormalities — nonspecific

- Leukopenia
- Anemia
- Hemoconcentration
- Thrombocytopenia
- Elevated LFTs
- Azotemia

■ Coagulation abnormalities

- Prolonged bleeding time, PT, PTT
- Increased FDP
- Decreased Fibrinogen
- DIC

■ U/A

- Hematuria, proteinuria, oliguria

Methods of Laboratory Diagnosis

■ General Info

- Most patients have **readily detectable viremia** at presentation (except hantavirus) _(c)
- Labs not currently equipped to make a rapid diagnosis of HFVs _(b)
- Clinical specimens should be sent to **CDC or USAMRIID**
- CDC requires 1 working day for preliminary diagnosis
- Packaging protocols for biological agents may be found at www.bt.cdc.gov/Agent/VHF/VHF.asp

Methods of Laboratory Diagnosis

- Specific methods of diagnosis of VHF agents
 - **Antigen detection by ELISA & RT-PCR*** _(c,z)
 - RT-PCR successfully used in real time dx of VHF agents; now most commonly used assay for ID of suspected cases of VHF _(c)
 - IgM antibody detection by ELISA
 - Viral Isolation
 - Culture ID usually requires 3-10 days
 - Must be done in **BSL-4 lab**
 - Aided by electron microscopy and immunohistochemical stains _(c)
- Diagnosis should be based initially on clinical criteria and judgment!

Treatment of VHF

Treatment of VHF

■ Mainstay of treatment is supportive

- Fluid & electrolyte balance
- Supplemental O₂, MV
- Circulatory & BP support
 - Early vasopressors
- Blood products
 - Platelets
 - Clotting factor concentrates, FFP
- Pain control
- Secondary infections common - aggressive tx with abx _(a)

■ Interventions to be avoided

- Aspirin & NSAIDs
- IM injections
- Anticoagulant therapies
- Steroids are of no benefit

■ Minimize invasive procedures; √ risk of iatrogenic transmission

■ Must maintain **strict barrier controls**

- Patients should be isolated

Drug Treatment of HFVs

- Currently NO antiviral drugs approved by the FDA for treatment of HFVs (b) (c)(y)
- **Ribavirin** only drug shown to have some efficacy in treatment of HFVs
- **Ribavirin**
 - Non-immunosuppressive nucleoside analog with broad antiviral properties (c)
 - Activity against
 - Arenaviruses
 - Bunyviruses
 - **NO ACTIVITY** against
 - Filoviruses
 - Flaviviruses
 - Available for compassionate use under an IND protocol (b) for tx of VHF caused by **arenaviruses & bunyviruses** (c)

Ribavirin Treatment of HFVs

■ Ribavirin – Important points

- Pregnancy category X - generally contraindicated in pregnancy
- Oral, IV Ribavirin NOT approved by the FDA for children
- IV Ribavirin limited availability in US
- Not FDA approved for HFVs; use for this purpose should be as an IND
- NOT indicated for the treatment of VHF due to Filovirus or Flavivirus
- Initially exact HFV may not be known - consider starting ribavirin & stop if filovirus/flavivirus identified_(s)

Passive Immunization in Treatment of VHF

■ Passive Immunization

- Studies & case reports evaluating convalescent plasma as therapy (or prophylaxis) yielded mixed results.
- In 1995 Kikwit outbreak, 8 Ebola pts received whole blood transfusions from Ebola survivors _(b)
 - 7 survived; no clear evidence linking their survival directly to this tx
- Use of immune plasma has proved effective in tx of some arenaviruses (Junin and Machupo) _(b)

Post-Exposure Prophylaxis and Management

Post-Exposure Prophylaxis & Management

- PEP hampered by absence of effective vaccines & antiviral medications
- Percutaneous or mucocutaneous exposures
 - Immediately wash affected skin with soap and water ; flush eyes
- The Working Group on Civilian Biodefense Recommendations
 - Prophylactic antiviral therapy (including Ribavirin) NOT recommended for persons exposed to HFVs in the absence of clinical illness_{(z)(y)}
- High Risk Exposures & Close Contacts
 - Place under medical surveillance
 - Record temps. 2x/day. Report any temp. $\geq 101^{\circ}\text{F}$
 - Report any S/S of VHF
 - Initiate Ribavirin if S/S of VHF develop (arenavirus or bunyvirus only)
- Convalescing pts should refrain from sexual activity for 3 months following recovery

Vaccination for HFVs

Vaccination for HFVs

■ Yellow Fever Vaccine (flavivirus)

- Live attenuated vaccine
- Highly effective prior to exposure
- Limited supply
- **NOT useful in post-exposure setting**

■ Filoviruses

- Ebola DNA plasmid vaccine recently completed NIH-sponsored Phase I human trials & is in active follow-up phase; no data is yet available ^{(b)(z)}
- Use of adenovirus & vesicular stomatitis virus to express VHF viral glycoprotein has been successful in primates ^(c)

■ Arenaviruses

- Live attenuated virus vaccine against Argentine HF (Junin) is effective ^{(b)(a)(z)}
 - Not available in large quantities ^(y)
 - May protect against Bolivian HF ^(b)

■ Bunyviruses

- 5 commercially available hantavirus vaccines being produced in China ^(c)
- RVF vaccine available as IND ^(z); requires annual boosters ^(s)
 - Not widely available ^(y)

■ Many experimental vaccines being studied

- Research into vaccines against Lassa Virus & other New World arenaviruses ongoing at CDC

Infection Control & HFVs

Infection Control and HFVs

- Infection-control Guidelines_(b)
 - Report suspected cases immediately
 - Infection control officer, local & state public health officials and CDC
 - Isolation of all suspected cases
 - Strict hand washing
 - Double gloving
 - Use of impermeable gowns
 - N-95 masks or powered air-purifying respirators
 - Negative pressure isolation with 6-12 air exchanges / hour
 - Leg & shoe covering
 - Face shields & goggles
- All contacts of pts dx with VHF including hospital personnel & lab workers should be placed under medical surveillance for signs of VHF infection for 21 days _(b)

Infection Control and Lab Testing

- All HFVs are highly infectious in lab setting
- May be transmitted to lab personnel by small particle aerosols
- Notify lab immediately if VHF suspected
- All specimens should be:
 - Clearly identified
 - Double bagged
 - Hand carried to lab
- Do NOT transport specimens in pneumatic tube

Postmortem Practices in VHF

- Contact with cadavers implicated in Ebola transmission
- Recommendations in a VHF outbreak
 - Prompt burial or cremation
 - Minimal handling of corpses
 - NO embalming
 - Surgery or post-mortem exams only when absolutely necessary

Environmental Decontamination for HFVs

- VHF barrier precautions for all custodial staff
- Double bag all linens and wash in bleach
- Disinfect surfaces with 1:100 bleach solution
- HFVs are not environmentally stable

HFVs as Bioweapons

What is the Real Threat?

Criteria For Biological Agents At Risk For Weaponization

- High M+M ✓
- Potential for person-person transmission ✓
- Low infective dose ✓
- Highly infectious by aerosol dissemination +/- ✓
- Vaccine unavailable or limited supply ✓
- Potential to cause public & health care worker anxiety, fear ✓
- Availability of pathogen or toxin +/- ✓
- Feasibility of large scale production +/- ✓
- Environmental stability
- Prior research & development as weapon ✓

HFVs As Biological Weapons

- Biologic agents are considered WMDs - use may result in large-scale M&M
 - 2000 - CDC classified HFVs Category A Bioweapon agents
 - High mortality, greatest potential for major impact on public health. Based on:
 - Potential to cause widespread illness & death
 - Ease of dissemination (esp. by **aerosol**)
 - Potential for major public health impact
 - Required special action to achieve public health preparedness
- Most HFVs replicate in cell culture to concentrations sufficient to produce a small terrorist weapon _(c)
 - Exceptions – CCH & Hantaviruses _(z)
 - All these HFVs typically **stable & highly infectious as fine particle aerosols** _(c)
 - Exception – Dengue _(a,z)

HFVs as Bioweapons

■ General Facts

- HFVs have been weaponized by former Soviet Union, Russia, & the U.S. ^(d)
- Former Soviet Union & Russia produced large quantities of **Marburg, Ebola, Lassa, & New World Arenaviruses** until 1992 ^(c,d)
- Evidence **Yellow Fever** has been weaponized by North Korea ^(d,z)
- Japanese studied the use of **Hantavirus** as a weapon ^(c)
- Studies show that only a **few virions of Marburg & Ebola administered by aerosol can produce lethal infection** in monkeys ^(c,d)
- **Yellow Fever & Rift Valley Fever** developed as weapons by US biological weapons program prior to its termination in 1969 ^(c)
- Japanese terrorist cult Aum Shinrikyo unsuccessfully attempted to obtain Ebola virus as part of effort to create biological weapons ^{(b) (c)}

Quotes from “Biohazard”

- “In 1997, (a team from the Russian Academy of Sciences) reported in the Russian publication *Questions of Virology* that they had successfully inserted a gene for Ebola into the genome of vaccinia (virus related to small pox).”
- “One of our goals had been to study the feasibility of a smallpox-Ebola weapon.”
- “I have no way of knowing whether a combined Ebola-smallpox agent has been created, but it is clear that the technology to produce such a weapon now exists.”

Quotes from “Biohazard”

- “A strain of Marburg arrived in the Soviet Union a decade after it was first isolated. It wasn’t clear from the records whether we obtained it from the United States or directly from Germany, but it was immediately added to our growing collection of viral warfare agents. We were already investigating a number of microorganisms that weaken blood vessels and cause hemorrhagic fevers, such as Junin from Argentina and Machupo from Bolivia. Marburg quickly proved to have great potential.”

Quotes from “Biohazard”

- “At the end of 1989, a cryptogram from Sandakchiev arrived in my office with the terse announcement that **Marburg Variant U had been successfully weaponized (aerosolized)**. He was asking for permission to test it.”
- “After testing the weapon in explosive chambers, we applied it to the monkeys. Every one of the twelve monkeys contracted the virus. They were all dead within three weeks. **In early 1990, Marburg Variant U was ready for approval by the Ministry of Defense.**”

Bottom Line:

It is likely that the technology exists

There are likely weaponized HFVs

There are people who would like to acquire them

Future Research and Recommendations by the Working Group

Recommendations for Future Preparedness

- Develop **rapid diagnostic methods** for the HFVs
- Augment **supply of Ribavirin**
- Pursue **new antiviral therapy** for HFVs
- Continue **vaccine development** for HFVs
- Pursue **passive immunization strategies** with recombinant human monoclonal antibodies

Conclusions

- HFVs are **naturally occurring diseases**
- HFVs can have a **high M+M**
- Most **easily transmitted from human to human**
 - Strict universal precautions
 - Respiratory protection with any aerosol generating procedures
- Several have been or have the **potential to be weaponized**
- Protect yourself when travelling – DEET containing insect repellent, clothing, netting, daily tick checks
- Maintain a high index of suspicion for HFVs
 - Anyone with travel to endemic area
 - Anyone with fever, a rash and abnormal bleeding

Questions?

Thanks so much!

jpowers@vcom.vt.edu

References

- a. Ciotto, GR et al. *Disaster Medicine*. 3rd Edition. 2006.
- b. Pigott, DC. Hemorrhagic Fever Viruses. *Crit Care Clin* 21 (2005). 765 – 783.
- c. Marty, AM et al. Viral Hemorrhagic Fevers. *Clin Lab Med*. 26 (2006) pp345-386.
- d. Borio L, Inglesby T, Peters CJ, et al, for the Working Group on Civilian Biodefense. Hemorrhagic Fever Viruses as Biological Weapons. *JAMA*. 2002;287:2391-2404.
- e. Notice to Readers Update: Management of Patients with Suspected Viral Hemorrhagic Fever—United States. *MMWR Morb Mortal Wkly Rep*. 1995;44(25):475-479.
- f. Update: Outbreak of Rift Valley Fever – Saudi Arabia, August – November 2000. *MMWR Morb Mortal Wkly Rep*. 2000;49(43):982-985.
- g. Outbreak of Ebola Hemorrhagic Fever – Uganda August 2000-January 2001. *MMWR Morb Mortal Wkly Rep*. 2001;50(05):73-77.
- h. Update: Filovirus Infections Among Persons with Occupational Exposure to Nonhuman Primates. *MMWR Morb Mortal Wkly Rep*. 1990;39(16):266,273.
- i. Update: Filovirus Infection Associated with Contact with Nonhuman Primates or Their Tissues. *MMWR Morb Mortal Wkly Rep*. 1990;39(24):404-405.
- j. Fatal Illnesses Associated With a New World Arenavirus-California, 1999-2000. *MMWR Morb Mortal Wkly Rep*. 2000;49(31):709-711.
- k. Ebola-Reston Virus Infection Among Quarantined Nonhuman Primates – Texas, 1996. *MMWR Morb Mortal Wkly Rep*. 1996;45(15):314-316.
- l. Miranda ME, Ksiazek TG, et al. Epidemiology of Ebola (Subtype Reston) Virus in the Philippines, 1996. *The Journal of Infectious Diseases*. 1999;179:S115-119.
- m. Peters CJ, Zaki SR. Role of the endothelium in viral hemorrhagic fevers. *Critical Care Medicine*. 2002;30:S268-273.
- n. Peters CJ, LeDuc JW. An Introduction to Ebola: The Virus and the Disease. *The Journal of Infectious Diseases*. 1999;179(Suppl 1):ix-xvi.
- o. Fulhorst, CF et al. Geographic Distribution and Genetic Diversity of Whitewater Arroyo Virus in the Southwestern United States. *Emerging Infectious Diseases*. <http://www.cdc.gov/ncidod/eid/vol7no3/fulhorst.htm>
- p. From the CDC. Two Cases of Hantavirus Pulmonary Syndrome – Randolph County, West Virginia, July 2004. *MMWR*. 2004;53: 1086-1089.

References

- q. Ebola Hemorrhagic Fever. Known Cases and Outbreaks of Ebola Hemorrhagic Fever, in Chronological Order. www.cdc.gov
- r. Dengue: Clinical and Public Health Aspects. <http://www.cdc.gov/ncidod/dvbid/dengue/slideset/set1/iii/slide03.htm>
- s. Cleri, DJ et al. Viral Hemorrhagic Fevers: Current Status of Endemic Disease and Strategies for Control. *Infect Dis Clin N Am*. 20 (2006). Pp359-393.
- t. Moran, GJ et al. Biological Terrorism. *Infect Dis Clin N Am* 22 (2008). 145-187.
- u. Mardani, M. Keshtkar-Jahromi, M. Crimean Congo Hemorrhagic Fever. *Archives of Iranian Medicine*, Volume 10, Number 2, 2007: 204 – 214.
- v. Rothman, AL. Clinical presentation and diagnosis of dengue virus infections. *UpToDate*. www.uptodate.com. Last updated January 13, 2009.
- w. Murdoch, D. Diseases potentially acquired by travel to sub-Saharan Africa. *UpToDate*. www.uptodate.com. Last updated September 8, 2008.
- x. Bray, M. Epidemiology, pathogenesis, and clinical manifestations of Ebola and Marburg hemorrhagic fever. *UpToDate*. www.uptodate.com. Last updated December 2, 2008.
- y. Kman, NE. Nelson, RN. Infectious Agents of Bioterrorism: A Review for Emergency Physicians. *Emergency Medicine Clinics of North America*. 26 (2008). Pp 517-547.
- z. Infectious Diseases Society of America. Viral Hemorrhagic Fever (VHF): Current, comprehensive information on pathogenesis, microbiology, epidemiology, diagnosis, treatment, and prophylaxis. <http://www.cidrap.umn.edu/idsa/bt/vhf/biofacts/vhffactsheet.html>
- aa. Mims, C. Playfair, J. Roitt, I. Wakelin, D. Williams, R. Medical Microbiology. 2nd Edition. Mosby 1998.

References

■ Web Sites

- Center for Biologic Counterterrorism and Emerging Diseases: www.bepast.com
- Institute for Molecular Virology: www.bocklabs.wisc.edu
- Center for Disease Control: www.cdc.gov
- CDC Special Pathogens Branch for Viral Hemorrhagic Fevers: www.cdc.gov/ncidod/dvrd/spb/mnpages/dispages/vhf.htm
- Center For Civilian Biodefense Strategies: www.hopkins-biodefense.org/pages/agents/agentvhf.html
- World Health Organization (WHO): www.who.int
- Infectious Diseases Society of America: www.idsociety.org
- Infectious Diseases Society of America. Viral Hemorrhagic Fever www.idsociety.org/bt/biotemplate.cfm?template=vhf_summary.htm
- eMedicine - CBRNE – Viral Hemorrhagic Fevers. <http://emedicine.com/emerg/topic887.htm>