Viral Hemorrhagic Fevers

WRAIR- GEIS 'Operational Clinical Infectious Disease' Course
AKA

Blood outside the body is bad II
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
Selected Pathogens
Case Presentation

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

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

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

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

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

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

• He requires emergent bronchoscopy for bleeding

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

• Co-located with Afghan army

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

This is not a case of Ebola...
Case Presentation

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

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

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

• Emergency IND approval for IV ribavirin from the FDA

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

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

• However:
• SEP 14
  – Patient had a asystolic/PEA arrest
  – Declared brain dead
    • At time of death, viral load had declined and antibodies present
    • Cerebral edema on CT
Post Exposure

• Prevention
  – BACK TO THE INITIAL CASE PRESENTATION...
    • 18 HCPs identified as being **HIGH** risk exposures
    • Offered oral ribavirin post-exposure prophylaxis
    • 2 individuals had more significant symptoms to meds

  Both were found to have developed antibodies to the CCHF virus
Crimean-Congo Hemorrhagic Fever
Crimean-Congo Hemorrhagic Fever

• Geographic regions
  – 12th Century: Tajikistan
    • HF syndrome: blood in urine, rectum, gums, vomit
  – 1944-45: First clinical description
    • Soviets (N=200, CFR = 10%) assisting peasants in Crimea
  – 1956: febrile patient in Belgian Congo
  – Common antigenic structure: Crimea & Congo viruses = CCHF
AFRICOM (CCHF Risk)

• Low Risk
  – Algeria, Morocco,

• Intermediate Risk
EUCOM (CCHF Risk)

• High Risk
  – Kosovo, Montenegro, Turkey

• Intermediate Risk
  – Albania, Armenia, Azerbaijan, Belarus, Bosnia/Herzegovina, Bulgaria, Croatia, Georgia, Hungary, Macedonia, Moldova, Romania, Russia, Serbia, Slovenia, Ukraine
Extensive likely geographic distribution
50° North latitude: limit for geographic distribution of genus Hyalomma ticks

CCHF
Figure 5. Number of Crimean-Congo hemorrhagic fever cases and deaths in Turkey between 2002-2008. 

WRAIR
Crimean-Congo Hemorrhagic Fever

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

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

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

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

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

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

- Containment & Prevention
  - Ribavirin
    - High risk contacts can be considered
    - Use oral ribavirin
      - For the CCHF case from Afghanistan, it was recommended that high risk contacts take 600 mg PO twice daily for 14 days
      - Providers only took meds for 7 days in all cases, due to gastrointestinal side effects
Crimean-Congo Hemorrhagic Fever

Treatment

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

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

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

- Individuals with severe disease did better with corticosteroids added
Crimean-Congo Hemorrhagic Fever

• Treatment
  – Ribavirin appears to be beneficial to overall survival in at least moderate to severe disease
  – Earlier the therapy the better (within first 4 days of illness)
  – Corticosteroids in severe illness in addition to ribavirin may be beneficial to survival
Crimean-Congo Hemorrhagic Fever

• Vaccine Development
  – DNA vaccine study in mice not impressive
  – Attenuated vaccinia (poxvirus) virus vector vaccine
    • Expresses the CCHF virus glycoproteins
    • Protected all mice in challenge model

[References]
Hantaviruses
Hemorrhagic Fever with Renal Syndrome (HFRS)

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

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

• Geographic regions
  – “Old World”:
    • Hantaan (Korea, China, Eastern Russia)
    • Dobrava (Balkans)
    • Seoul (Worldwide)
    • Puumala (Scandinavia, W. Russia, W. Europe)
    • Saaremaa (C. Europe, Scandinavia)
  – “New World”: Sin Nombre (U.S.), Andes
AFRICOM (HFRS Risk)

• Intermediate Risk
  – Algeria, Burkina Faso

• Low Risk
  – Benin, CAR, Djibouti, Equatorial Guinea, Gabon, Madagascar, Nigeria, Senegal
EUCOM (HFRS Risk)

• Intermediate Risk
  – Albania, Belarus, Bosnia/Herzegovina, Bulgaria, Croatia, Czech Rep., Estonia, Georgia, Hungary, Kosovo, Latvia, Lithuania, Macedonia, Moldova, Montenegro, Poland, Romania, Russia, Serbia, Slovakia, Slovenia, Ukraine

• Low Risk
  – Armenia, Azerbaijan, Israel, Turkey
Hantaviruses

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

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

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

• Diagnosis
  – Presentation:
    • Hemorrhagic Fever with Renal Syndrome (Old World)
      – Incubation period may be 1-2 weeks
      – Flu-like symptoms (fever, Back/abd pain, chills, nausea, blurred vision, flushing or rash, red eyes,
      – Progresses to shock, MOF, hemorrhagic symptoms possible, acute renal failure
      – Milder presentation: Puumala, Seoul, Saaremaa (CFR 1%)
      – Severe: Hantaan (CFR 5-15%), Dobrava

• Hantavirus Pulmonary Syndrome (New World)
  – Early = nonspecific, flu-like symptoms
  – Late = severe shortness of breath and cough secondary to pulmonary edema

  – Lab diagnosis similar to other VHF's mentioned
Hantaviruses

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

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

• Containment & Prevention
  – Rodent control and maintain adequate food storage
  – No need for VHF isolation procedures
  – Vaccines are being developed
    • Recently completed a phase 1 study at WRAIR
      – Phase 2a study started in July 2014
Lassa
Lassa

- **Geographic regions**
  - *Arenavirus* first described in Nigeria in 1969 with distribution primarily in West Africa
  
  - Outbreaks have occurred in:
    - Central African Republic
    - Guinea
    - Liberia
    - Nigeria
    - Sierra Leone (1987)
      - 10-16% of all adult medical admissions
      - 30% of adult deaths
      - 25% of all maternal deaths

  - Serological evidence found in Democratic Republic of the Congo, Mali, and Senegal
AFRICOM (Lassa Risk)

- **High Risk**
  - Guinea, Liberia, Nigeria, Sierra Leone
- **Intermediate Risk**
  - Benin, Burkina Faso, Cameroon, Cote D’Ivoire, Gabon, The Gambia, Ghana, Guinea-Bissau, Mali, Senegal, Togo
- **Low Risk**
  - CAR, Niger, Sudan, S. Sudan, Uganda
Lassa

- Exposure Risks
  - Reservoir: *Mastomys* rodents
    - Rodent-to-human:
      - Inhalation of aerosolized virus from rodent urine and feces
      - Ingestion of food or materials contaminated by infected excreta
      - Catching and preparing *Mastomys* as a food source
  
  - Human-to-human:
    - Direct contact with blood, tissues, secretions or excretions
    - Needle stick or cut
    - Inhalation of aerosolized virus suspected

- Mortality Rates: 15-20% of hospitalized
Lassa

• Exposure Risks
  – Nosocomial Outbreaks
    • Dry season (JAN to APR)
    • All age groups and both sexes
  – Pregnant women and fetus at high risk
    • 80% fetal death
  – The Kenema Government Hospital
    • January to April 2004
    • 95 pediatric cases admitted
    • 50% of all cases aged under 15 years
      – CFR was 30–50% in children <5
      – CFR was 71% in children <1

(FAQ, Weekly Epi Record, MAR 2005)

Dr. Conteh attempted femoral venipuncture and sustained a needlestick.

Aniru Conteh
1942–2004

Photo by F. Jacquiez
Lassa

• Diagnosis
  – Clinical diagnosis is tough
    • May present with nonspecific symptoms
      – Sore throat, swollen face and neck
    • Hemorrhagic manifestations may not be evident
    • Neurologic symptoms *(hearing loss*, tremors, encephalitis*)

  – ELISA (antibody or antigen)
  – Viral culture (wouldn’t do this unless you have BSL-4)
  – Immunohistochemical staining of tissue
  – RT-PCR
<table>
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<tr>
<th>Stage</th>
<th>Symptoms</th>
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| 1 (days 1-3) | General weakness and malaise.  
|         | High fever, >39°C, constant with peaks of 40-41°C                         |
| 2 (days 4-7) | Sore throat (with white exudative patches) very common  
|         | Headache; back, chest, side, or abdominal pain                            |
|         | Conjunctivitis                                                           |
|         | Nausea and vomiting                                                      |
|         | Diarrhoea                                                                |
|         | Productive cough                                                         |
|         | Proteinuria                                                               |
|         | Low blood pressure (systolic <100 mm Hg)                                  |
|         | Anaemia                                                                   |
| 3 (after 7 days) | Oedema of the face and neck  
|         | Convulsions                                                               |
|         | Mucosal bleeding (mouth, nose, eyes)                                      |
|         | Internal bleeding                                                        |
|         | Encephalopathy with confusion or disorientation                           |
| 4 (after 14 days) | Coma                                                             |
|         | Death                                                                    |
Lassa

• Containment & Prevention
  – Rodent control (food storage is key)
  – Use of VHF barrier precautions can limit or eliminate healthcare worker risks
  – Isolation of patients as discussed
  – Excreted in the urine for 3 – 9 weeks
  – Lassa vaccine
    • USAMRIID had a vaccine based on a live viral platform that protected monkeys against a lethal challenge of Lassa
    • Monkeys did not have symptoms, BUT were found to have circulating virus

Lassa

• Treatment
  – Supportive Care
  – Ribavirin
    • If used early (within 6 days) may significantly reduce mortality (76% to 9%)
      – If you wait to start ribavirin after 6 days, rate goes up to 47%
    • WHO recommends use (CDC also promotes its use)
    • DoD use via the open label study (see CCHF info above)

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

- Marburg Virus (RNA Filovirus)
- Risk is year round; affects humans and NHP; sporadic outbreaks
- Reservoir
  - Bats (African Fruit Bat)
  - Unidentified animals (primates)
- Transmission
  - Mines, caves (bat feces/aerosols)
  - Consumption of infected animal
  - Human to human (health care facilities*: blood/bf, nosocomial without PPE)
Marburg (Clinical)

- Incubation period 3-9 days
- Acute onset fever, chills, HA, myalgias, truncal MP rash (5th day), N/V/CP/sore throat/AP/diarrhea
- Progressing to jaundice, pancreatitis, weight loss, delirium, shock, liver failure, hemorrhage, MOF
- CFR 25-90%
- Diagnosis
  - Clinical suspicion (isolate, PPE, notify PH)
  - Antigen-capture ELISA, PCR, IgM-capture ELISA (few days)
  - Viral Isolation (BSL-4)
  - IgG-capture ELISA (confirmatory)
  - Dead: IHC, isolation, PCR
- Treatment: supportive
AFRICOM (Marburg Risk)

- Low Risk
  - Angola, CAR, DRC, Kenya, S. Africa, Sudan, S. Sudan, Uganda
Rift Valley Fever (RVF)

- Acute febrile viral disease of domesticated animals
- Caused by Rift Valley Fever Virus (RVFV, Bunyavirus)
- Transmission
  - Mosquitoes (several species, Aedes)
  - Contact with infected animals (slaughter, birth)
  - Aerosol in lab
  - No human to human
- Risk Factors
  - Rural, outdoor exposures, animal contact, during outbreaks
- Prevention
  - Decrease vector, animal contacts
  - Vaccine: animals yes, humans no
AFRICOM (RVF Risk)

• High Risk:
  – Kenya, Somalia, Sudan, Tanzania

• Intermediate Risk
  – Benin, Botswana, Burkina Faso, Cameroon, CAR, Chad, Cote D’Ivoire, Ethiopia, The Gambia, Guinea, Guinea-Bissau, Madagascar, Malawi, Mali, Mauritania, Mozambique, Namibia, Niger, Nigeria, Senegal, Sierra Leone, S. Africa, S. Sudan, Togo, Uganda, Zambia, Zimbabwe

• Low Risk
  – Angola, Burundi, DRC, Djibouti, Eritrea, Gabon, Ghana, Lesotho, Liberia, Rwanda, Swaziland
Signs/Symptoms/Diagnosis

• IP 2-6 days
• Asx or mild febrile illness with liver abn, weakness, back pain, dizziness...recover 2-7 days
• Severe disease (8-10%):
  – Eye: 1-3 weeks out, blurred/decreased vision, resolve (10-12 weeks), macular: 50% vision loss (1-10% of patients)
  – Encephalitis: 1-4 weeks out, HA, coma, seizures
  – Hemorrhagic Fever (<1%, 50%CFR), 2-4 days out, jaundice, bleeding; death 3-6 days after
• Diagnosis
  – Early Phase: viral culture, antigen-detection ELISA, PCR
  – Later: Antibody testing (ELISA)
• Treatment: supportive
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

EID 2009; 15(10): 1598-1602
Emerging Threats

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

Overview of VHF

• 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 VHF, 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 VHF are working their way into human clinical trials.
Additional Resources

Ebola (Ebola Virus Disease)

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<tr>
<th>Ebola (Ebola Virus Disease)</th>
<th>CDC &gt; Ebola (Ebola Virus Disease) &gt; Healthcare Workers &gt; Safety Training Course: Healthcare Workers Going to West Africa</th>
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<tr>
<td>About Ebola</td>
<td><strong>Detailed information on CDC's Safety Training Course for Healthcare Workers Going to West Africa in Response to the 2014 Ebola Outbreak</strong></td>
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<tr>
<td>2014 West Africa Outbreak</td>
<td><strong>CDC's Safety Training Course for Healthcare Workers Going West Africa in Response to the 2014 Ebola Outbreak</strong> 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.</td>
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<tr>
<td>2014 Democratic Republic of the Congo Outbreak</td>
<td><strong>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.</strong></td>
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<tr>
<td>Outbreak List</td>
<td><strong>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.</strong></td>
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<tr>
<td>Signs and Symptoms</td>
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<td>Case Definition for Ebola Virus Disease (EVD)</td>
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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
United States Army Medical Research Institute of Infectious Diseases (USAMRIID)
Questions?