Viral Hemorrhagic Fevers

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Disclaimer

- The views expressed in this presentation are those of the speaker and do not reflect the official policy of the Department of Navy, Department of Defense, or U.S. Government

- “Off label” uses of medications will be discussed, and identified as such

Case Presentation

- U.S. Army Active Duty Native American (50%) enlisted male in his early 20s
- Co-located with Afghan army at an Afghan Army base
- Staying in old Afghan army dorms
  - Frequently slept outside
- Patient and roommate both with recent tick bites (pulled off with tweezers) within a week of illness onset
  - A common occurrence with bragging rights

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Pre-Hospital Course

- Presented to the local clinic
  - Fever, headache, fatigue, chills, but no rash
  - Initial Dx: “viral syndrome”
- A couple days later unimproved
  - Referred to the clinic at Kandahar
  - 4 day history of nausea/vomiting
  - Develops lethargy, bloody diarrhea, bleeding gums, shortness of breath requiring intubation
    - Elevated LFTs, thrombocytopenia
  - Treated for presumptive pneumonia
    - Concern about possible septic shock
  - Air evacuated to LRMC
    - Considered less ill than other patient on medevac flight.

Pre-Hospital Course

- En route, began oozing blood from IV sites and old puncture sites
- Arrived at Landstuhl RMC ~5 days after onset of illness (Friday evening)
- Upon arrival, appeared very ill:
  - Oozing blood
  - Blood coming from ET tube
  - Required emergent assistance

Hospital Course

- Emergent bronchoscopy
  - Required suction of significant amounts of blood
  - Urgent transfusions of clotting factors, FFP, cryoprecipitate, and red blood cells
  - Appeared to stabilize
  - Required paralysis on the ventilator.

Differential Diagnosis?

Treatment

- Saturday morning: PCR and IGM + for CCHF
  - Bernard Nocht Institute, Hamburg

- 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 obtained from a European manufacturer
  - Begun ~12 hours after oral treatment (48 hours of hospitalization)

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Hospital Course

- Patient appeared to be improving off pressors
- However:
- Tues/Weds
  - Patient experienced asystolic/PEA arrests
  - Declared brain dead (~ 9-10 days after illness onset/5 days after arrival)
    - At time of death, viral load declined and serology increased

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Outline

- VHFs in general
- Epidemiology
- Clinical aspects
- Diagnosis
- Preventive measures
- Treatment

Definition

- **Viral hemorrhagic fever (VHF):**
  - **Acute, *febrile*, multisystemic illness characterized by malaise, myalgia, prostration, and *bleeding diathesis***
  - **Caused by lipid-enveloped, single-stranded, *RNA viruses***

- Hemorrhagic fever virus (HFV) is a term used to generically identify those agents that cause VHF.

http://www.cdc.gov.mill1.sjlibrary.org/ncidod/dvrd/spb/mnpages/dispages/vhf.htm

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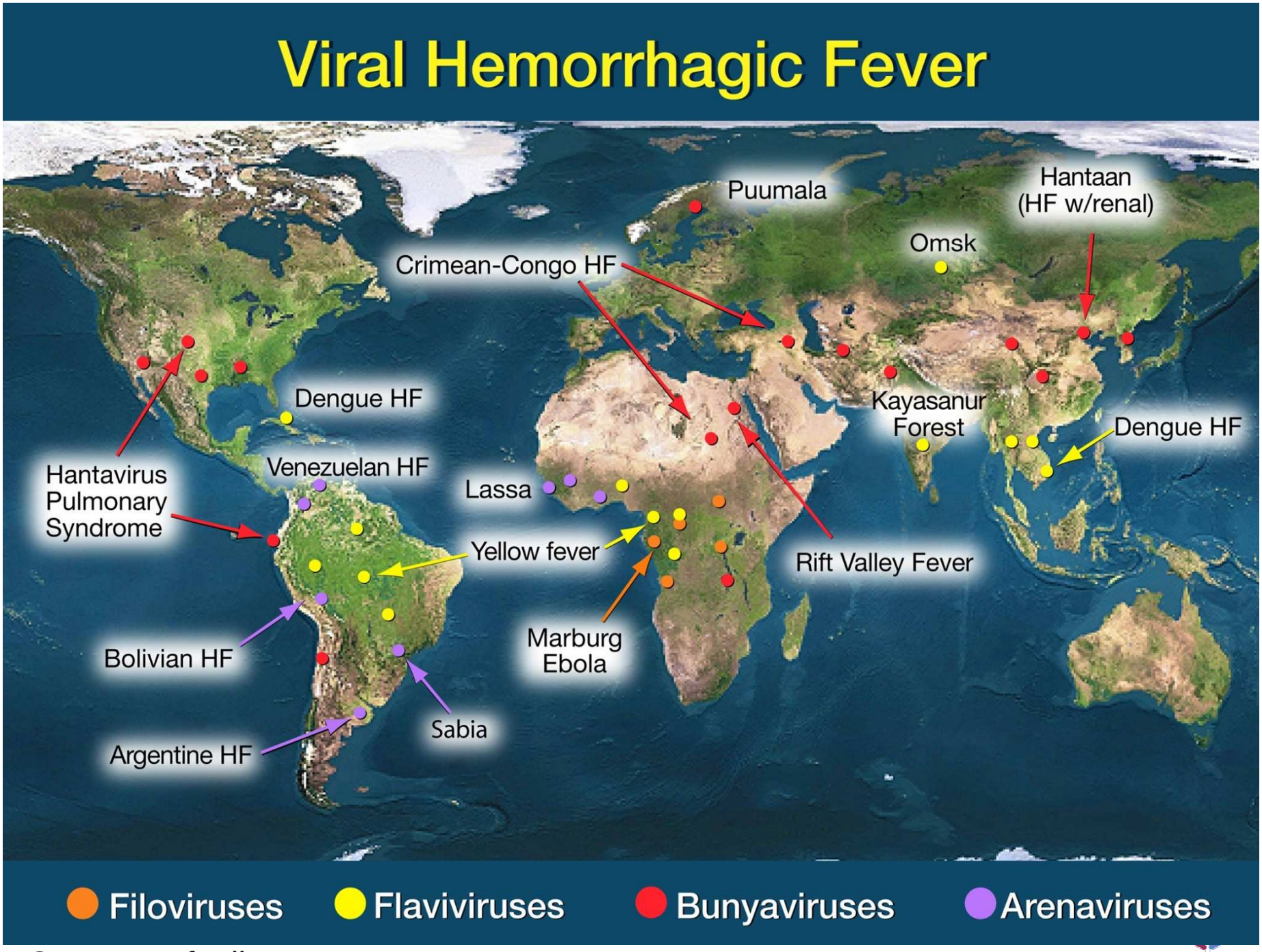
Step 1

Know What's There and How You Can Get It



Courtesy of Mike Bray, NIAID

Overview of Epidemiology of HFVs

Disease (virus)	Distribution	Natural Host/ Vector	Other Sources	Incubation (days)
Filoviruses				
Ebola HF	Africa, Philippines (ER)	Bats?	Nosocomial, etc.	2-21
Marburg HF	Africa	Bats?	Nosocomial, etc.	5-10
Arenaviruses				
Lassa fever	Africa	Rodent	Nosocomial, etc.	5-16
Argentine HF (*Junin*)	South America	Rodent	Nosocomial	7-14
Bolivian HF (*Machupo*)	South America	Rodent	Nosocomial	9-15
Venezuelan HF (*Guanarito*)	South America	Rodent	Nosocomial	7-14
Brazilian HF (*Sabia*)	South America	Rodent	Nosocomial	7-14
Bunyaviruses				
CCHF	Europe, Asia, Africa	Tick	Animal slaughter	3-12
Rift Valley fever	Africa	Mosquito	Animal slaughter	2-6
HFRS/HPS (*Bunyaviridae*)	World-wide	Rodent		9-35
Flaviviruses				
Omsk HF	Soviet Union	Tick		2-9
Kyasanur forest disease	India	Tick		2-9
Dengue HF	Asia, Americas, Africa	Mosquito	Nosocomial	3-15
Yellow fever	Africa, tropical America	Mosquito		3-6

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How are VHFs Spread?

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

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

3 – Contact with human/animal blood/body fluids or tissues

- Nosocomial/lab transmission

4 - Artificially generated aerosols

- Biowarfare/bioterrorism/lab

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VHF Human-to-human transmission

- Only dengue and yellow fever virus have adapted to efficient human-to-human transmission (only via mosquitoes).
  - For other HF viruses, humans are “dead-end” hosts.
- Typical story for nosocomial transmission:
  1. Uncertain how first human/NHP is infected
  2. Patient enters the health care facility
  3. VHF is not recognized or infection control procedures are not followed.
  4. Unrecognized nosocomial spread from blood/body fluid contact
     1. Health care personnel among the victims
     2. Victims carry infection to the community
  5. Close family members and those doing burial rites facilitate further spread
- Blood/body fluid contact
- No proven human to human respiratory transmission (but aerosolized viruses are infectious). Historical concerns with filoviruses, but if it exists, it is a rare phenomenon.

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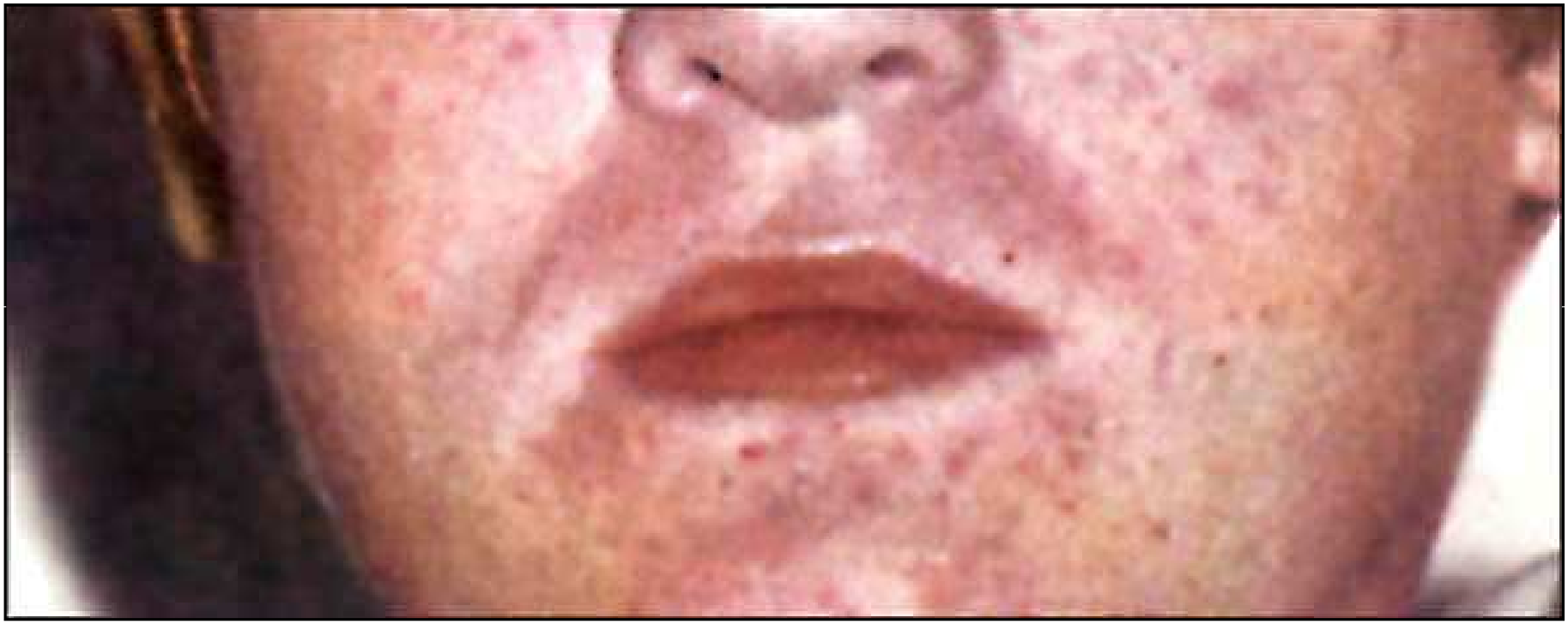
Step 2

Know What They Can Do

VHF: Spectrum of Clinical Presentations

- Variety of presentations
- Prodrome
  - High fever, Headache, Malaise, Arthralgias, Myalgias
  - Nausea, Abdominal pain, Nonbloody diarrhea
- Early signs
  - Fever, Tachycardia, Tachypnea, Conjunctivitis, Pharyngitis
  - Flushing, Skin Rash
- Late
  - ↓ BP, Hemorrhagic diathesis, Petechiae, Mucous membrane
  - Conj. hemorrhage, Hematuria, Hematemesis, Melena
- Major Manifestations
  - DIC, Circulatory Shock, CNS dysfunction

Marburg Infection Human



Maculopapular rash

Photo credit: Martini GA, Knauff HG, Schmidt HA, et. al. *Ger Med Mon*. 1968:13:457-470.

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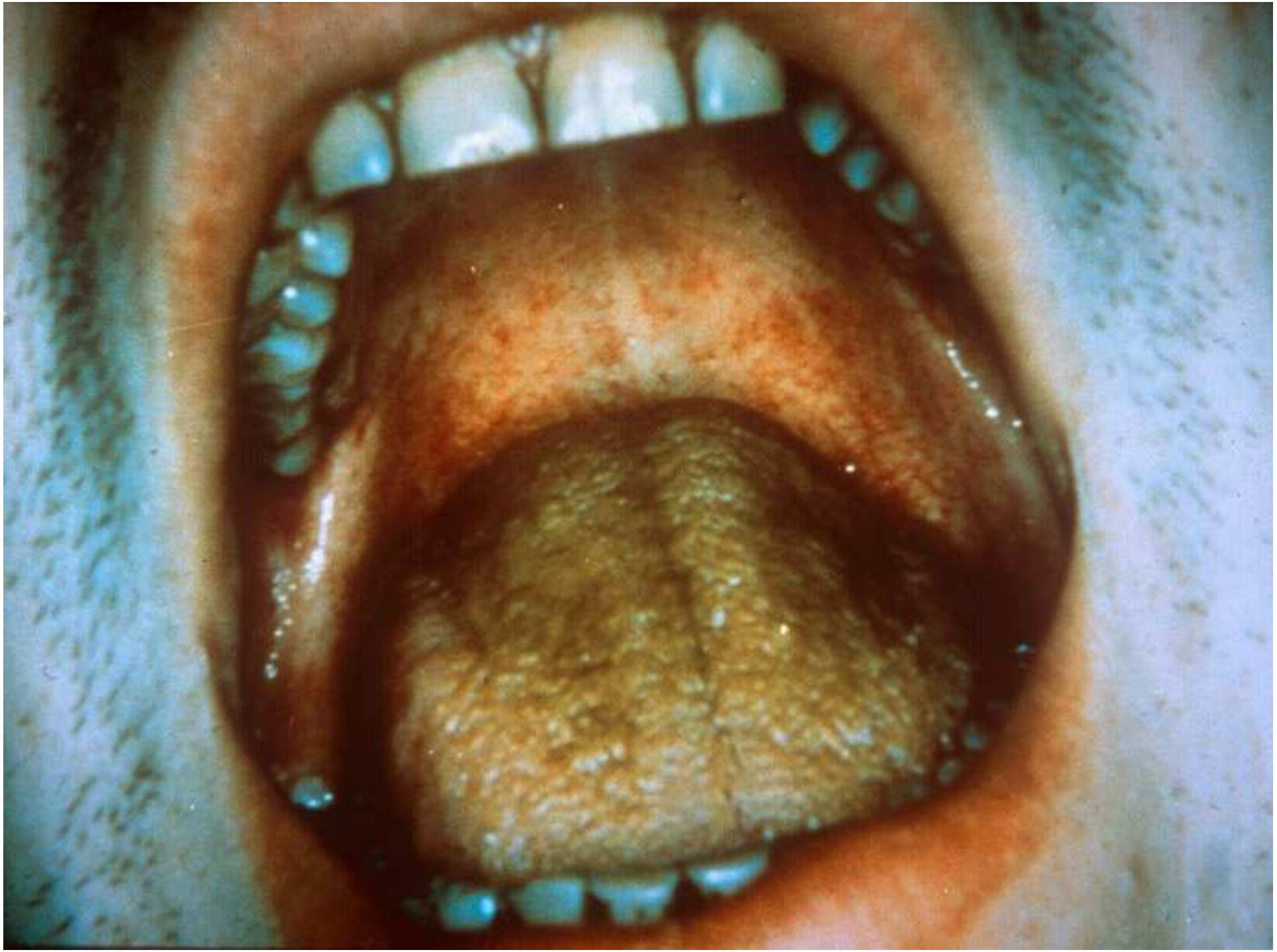
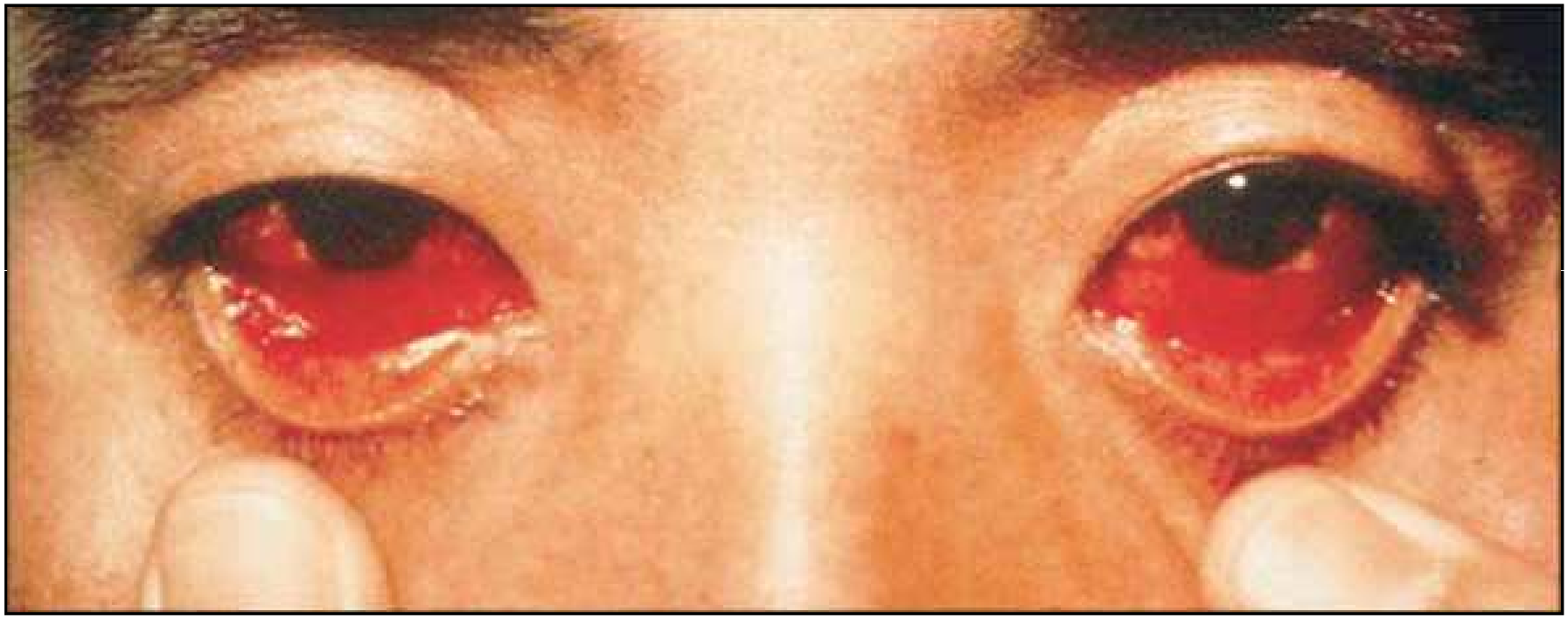


Bolivian Hemorrhagic Fever
(Machupo virus – New World Arenavirus)



Conjunctival injection & subconjunctival hemorrhage

Ref: Current Science/Current Medicine (Peters CJ, Zaki SR, Rollin PE). Viral hemorrhagic fevers. In: Fekety R, vol ed. Atlas of Infectious Diseases, p10.1-10.26, Volume VIII, 1997.

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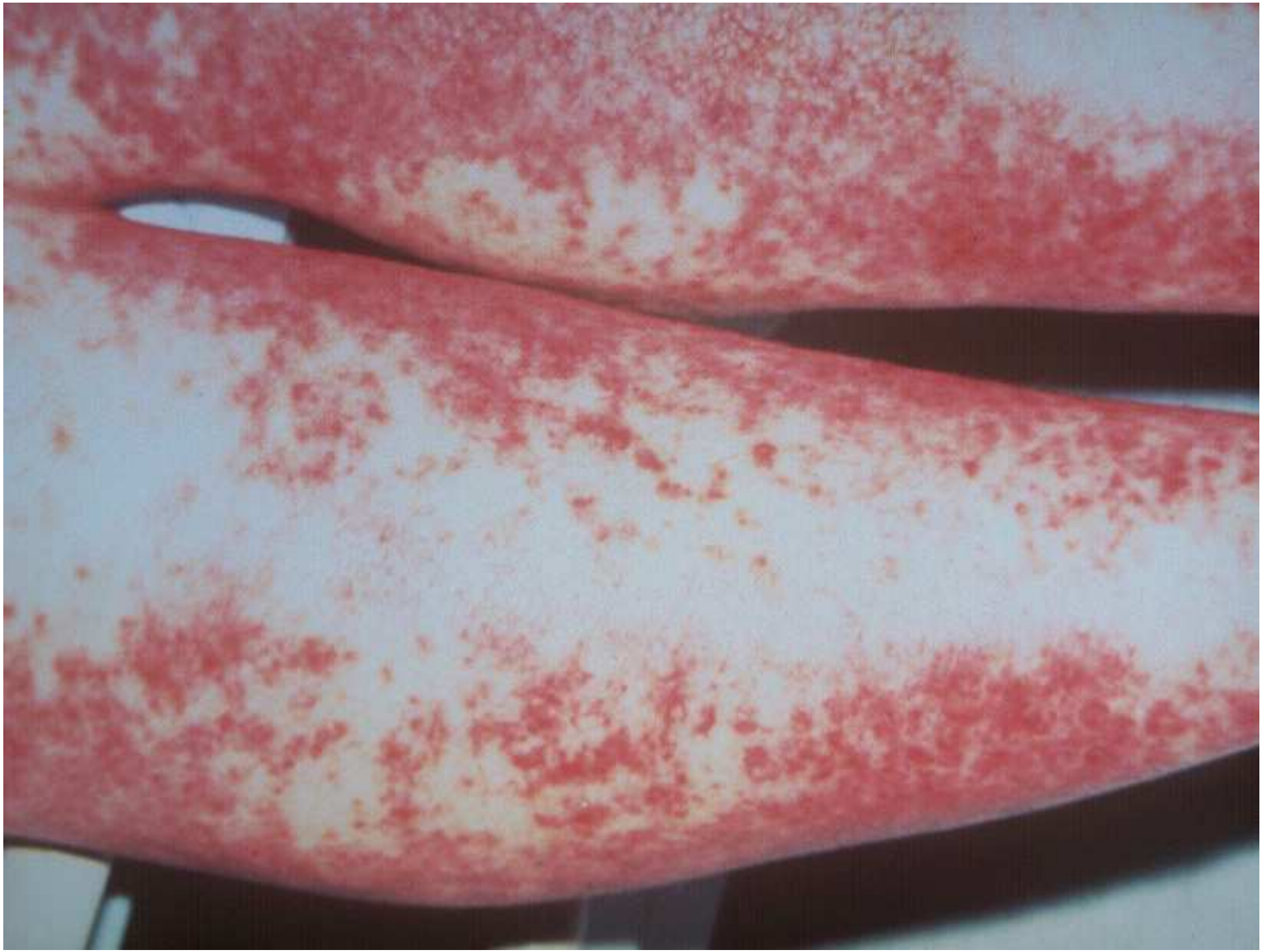
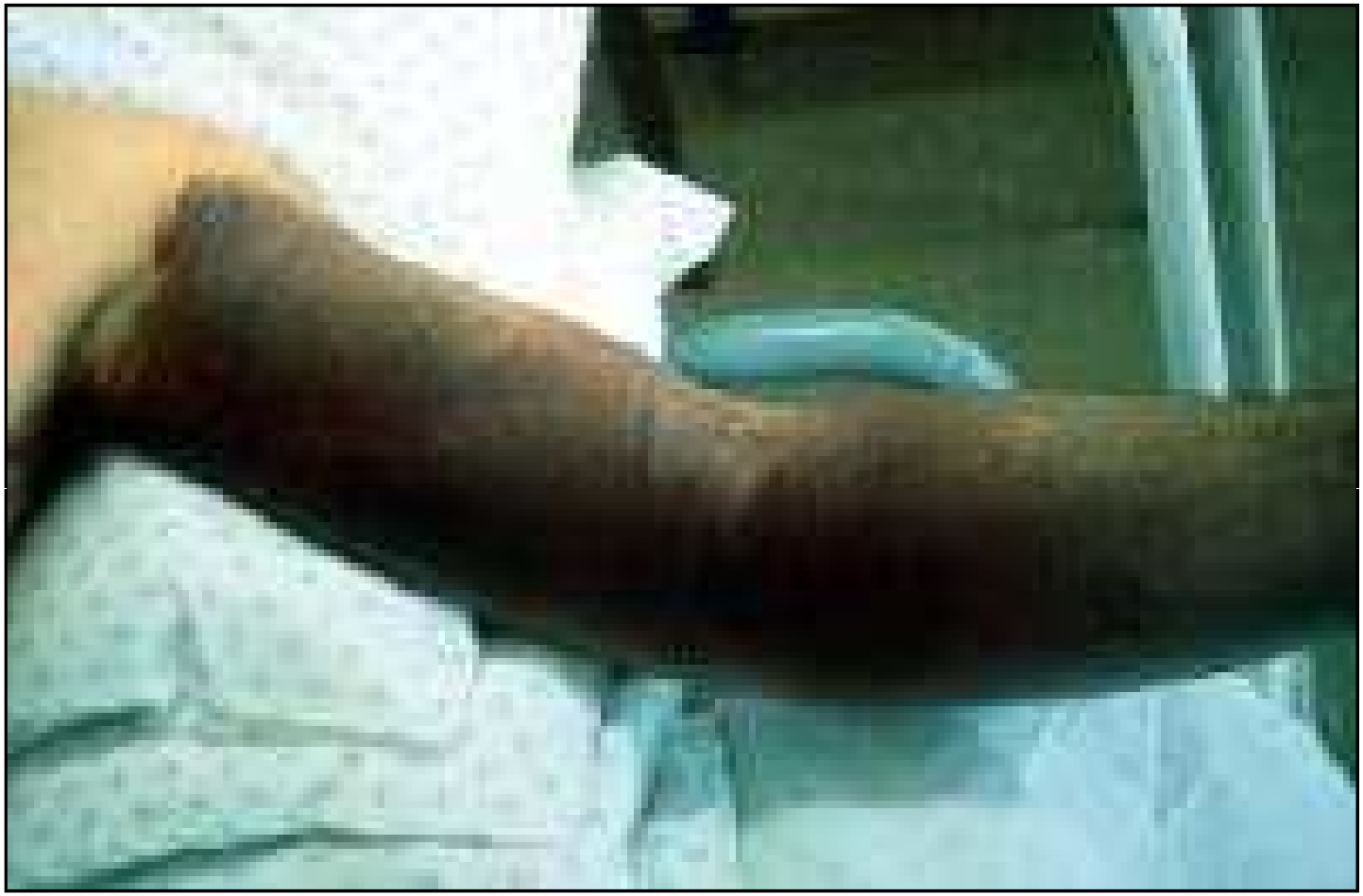
Argentine Hemorrhagic Fever
(Junin virus – New World Arenavirus)

Gingival hemorrhage



CCHF

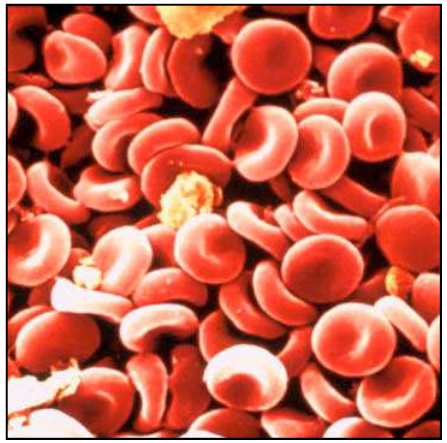


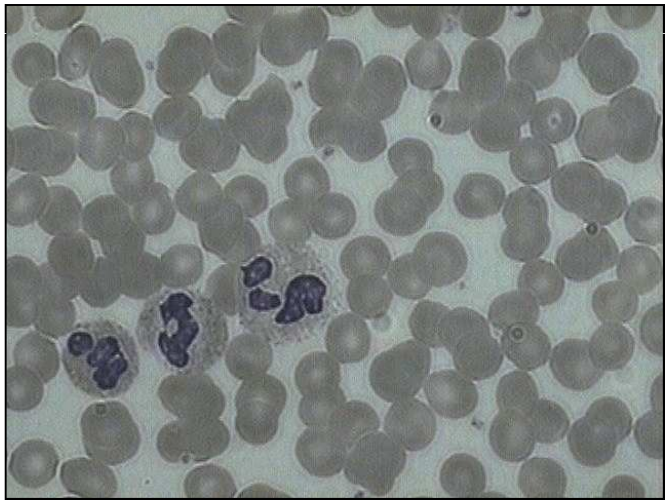
Left arm. Ecchymosis, diffuse, severe.
(1 week after clinical onset)

Photo credit: Robert Swaneopoel, PhD, DTVM, MRCVS, National Institute of Virology, Sandringham, South Africa.

VHF: Spectrum of Laboratory Abnormalities

- Leukopenia
  - Lassa with leukocytosis
- Anemia
- Hemoconcentration
- Thrombocytopenia
- Elevated liver enzymes
- Coagulation abnormalities





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VHF: Spectrum of Laboratory Abnormalities

- Coagulation abnormalities
  - Prolonged bleeding time
  - Prothrombin time
  - Activated PTT
  - ↑ fibrin degradation
  - ↓ fibrinogen
- Urinalysis
  - Proteinuria
  - Hematuria
  - Oliguria
  - Azotemia

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Potential distinguishing features

- Jaundice/icterus
  - YF,RVF, CCHF, filoviruses (rare)
- Renal failure
  - Hantaan/hantaviruses, YF
- Encephalopathy
  - Filoviruses, YF, S. Am HF, Omsk, Kyasanur
- Rash
  - Dengue, filoviruses, Lassa

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The “Deadly” VHFs

VIRUS	Mortality Rate
Ebola Zaire	75-90%
Marburg	25-90%
Lassa	15-20% of hospitalized
CCHF	3-30%
Rift Valley fever	50% of patients with hemorrhagic form

Step 3

Know What Else to Consider and how to Diagnose

Geographic Considerations in the Differential Diagnosis

Distribution of RVF

Distribution of CCHF

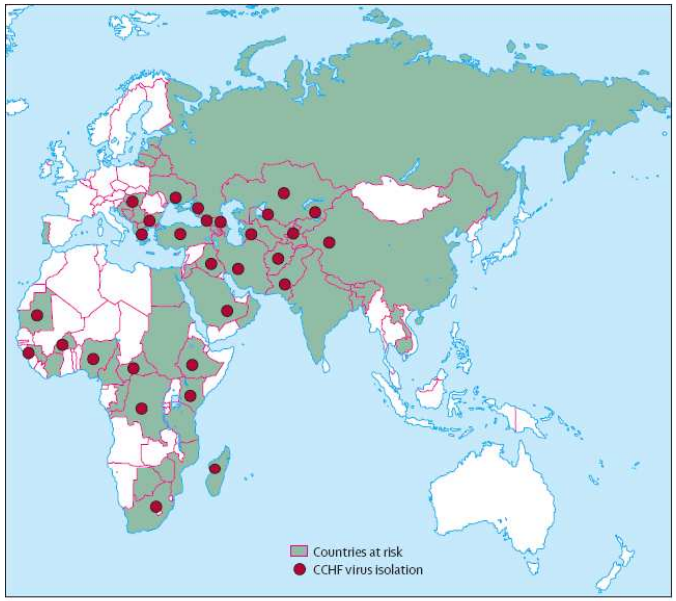
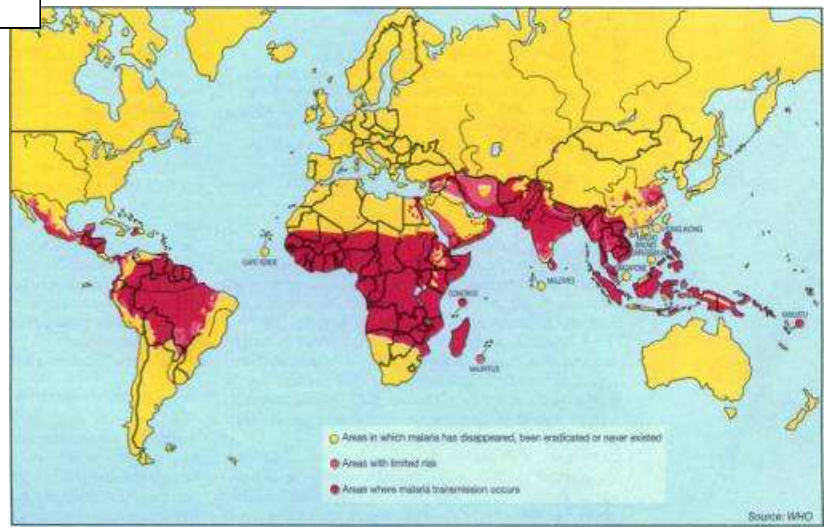


Figure 1: Worldwide distribution of CCHF virus

Distribution of Malaria



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Differential Diagnosis of VHF

Clinical presentation: Febrile, hemorrhage/purpura, thrombocytopenia, CNS signs, elevated , leukopenia, thrombocytopenia, DIC, multisystemic / multi-organ failure

- **Protozoal**
  - Malaria
- **Bacterial**
  - Typhoid fever
  - Rocky Mountain Spotted Fever (*Rickettsia rickettsii*) & other rickettsioses
  - Leptospirosis
  - Meningococci
  - Q fever (*Coxiella burnetti*)
  - Plague
- **Viral**
  - Influenza
  - Viral meningitis / encephalitis (e.g. henipaviruses)
  - HIV / co-infection
  - Hemorrhagic smallpox
- **Other**
  - Vasculitis, thrombotic thrombocytopenic purpura (TTP), hemolytic-uremic syndrome (HUS), heat stroke

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Diagnosis
Laboratory Confirmation

- Gold Standard - Virus isolation from blood, serum or tissue biopsy
  - BSL-4 Lab
- Electron microscopy
- Reverse transcription - polymerase chain reaction (RT-PCR)
  - Increasingly important tool

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Diagnosis
Laboratory Confirmation

- Rapid ELISA techniques most easily employed
  - Antigen capture detection
  - IgM (test of choice for Hantaviridae, yellow fever, & Dengue) or IgG antibody capture
- Serology on paired sera
- Immunohistochemistry (IHC) & in situ hybridization (ISH) of infected tissues
  - Formalin-fixed tissue
  - CDC has developed a skin biopsy procedure for detection of EBOV using IHC

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Step 4

Know How To Protect Yourself and Others

Prevention / Control

- YELLOW FEVER
  - Licensed 17D vaccine, highly efficacious
  - Recent 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

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Prevention / Control – None Licensed

- RIFT VALLEY FEVER
  - Formalin-inactivated
    - safe but requires 3 shots, intermittent booster
    - limited supply
  - Live, attenuated MP-12
    - Phase II testing
- Ebola
  - Adenovirus vectored +/- DNA prime
  - VEE replicons
  - VSV vectored
  - Virus-like particles (VLP)
- Marburg
  - Recent NHP study at RIID: 100% survival following challenge w/ lethal dose of MBGV and then post-exposure treatment w/ recombinant VSV-GP Marburg vaccine

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CDC Recommendations prevention of nosocomial transmission

- Standard Precautions in initial assessments
- Private room upon initial hospitalization
  - Barrier precautions – including face shields, surgical masks, eye protection within 3 feet of patient
  - 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

MMWR 1988;37(S-3):1-16. MMWR 1995;44(25):475-79.

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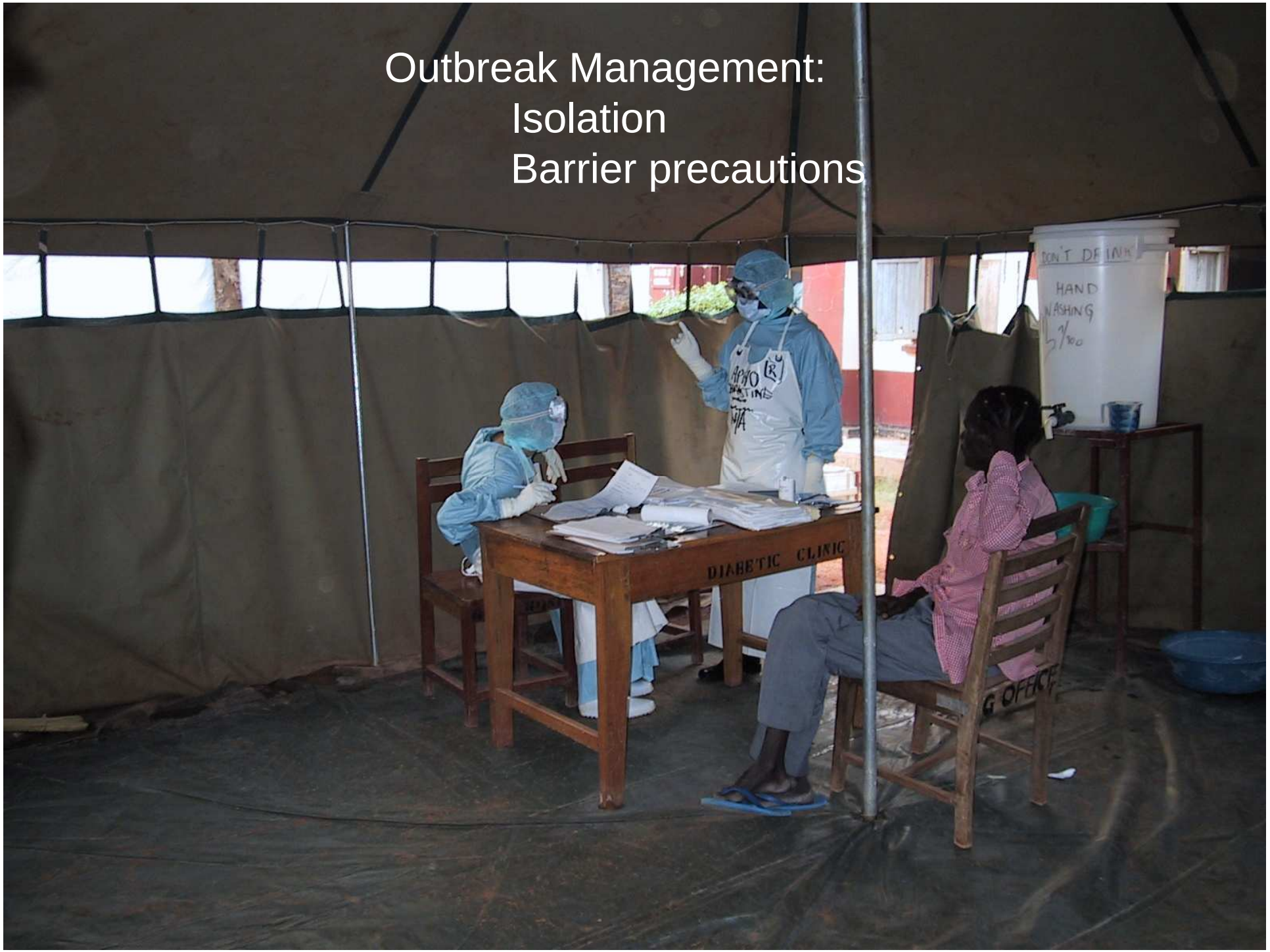
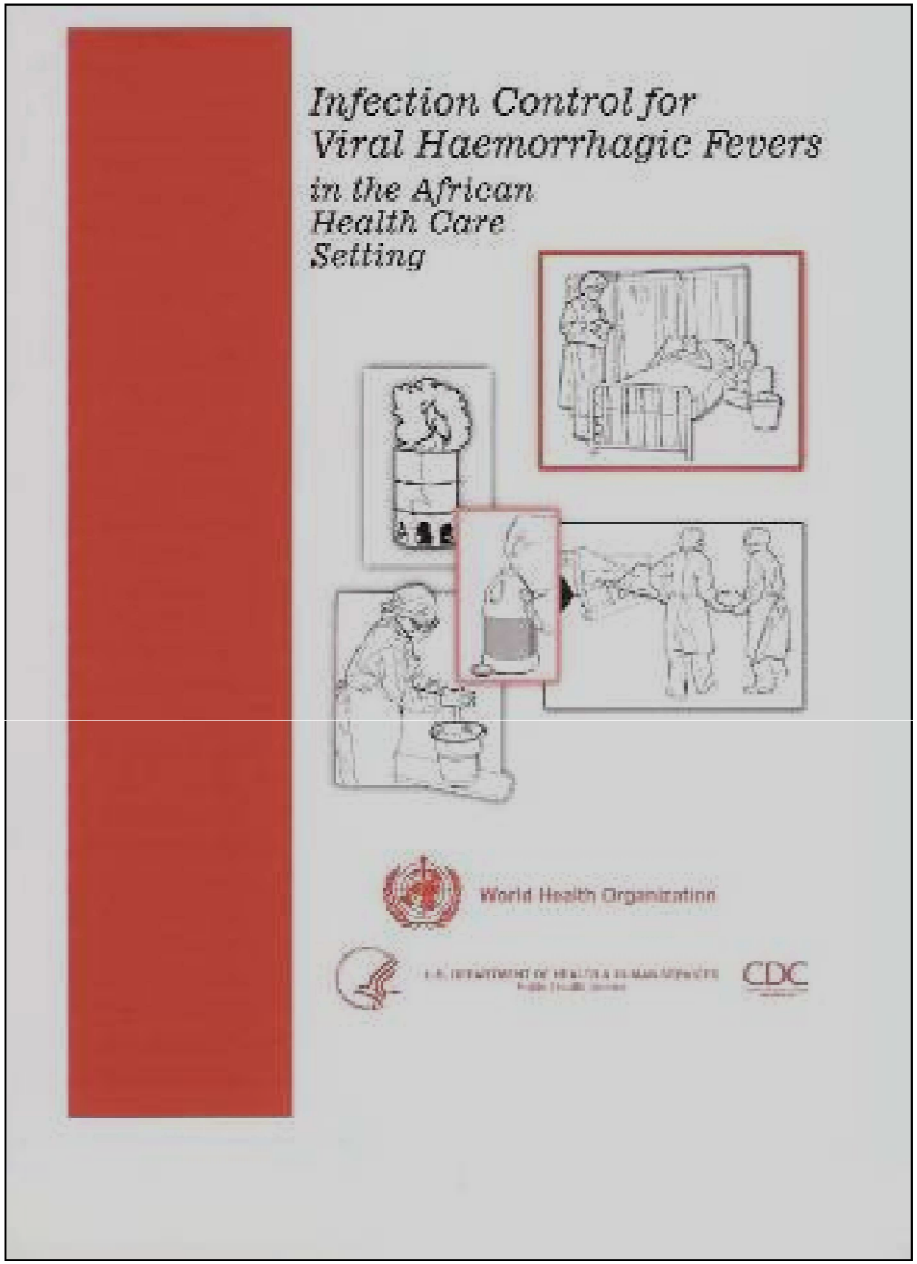
Outbreak Management:
Isolation
Barrier precautions



- 

www.cdc.gov/ncidod/dvrd/spb/mnpages/vhfmanual.htm

Standard Precautions for All Patients

- Identify a minimum level of Standard Precautions
- Establish routine handwashing
- Establish safe handling and disposal of used needles and syringes
- 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

Use VHF Isolation Precautions

- Isolate the patient
- Wear protective clothing:
  - Scrub suit, gown, apron, two pairs of gloves, mask, headcover, eyewear, rubber boots
- Clean/disinfect spills, waste, and reusable safety equipment, soiled linens, and laundry safely
- Use safe disposal methods for non-reusable supplies and infectious waste
- Counsel staff about the risk of VHF transmission
- Provide information to families and the community about VHF prevention and care of patients

Step 5

Know What To Do for Yourself or Others

Medical Management

- Consider the Differential Diagnosis!
  - R/O malaria, etc! Treat presumptively!

- Supportive Care
  - Careful management of fluid and electrolytes
  - Close attention to hemodynamics
  - Vasopressors and cardiotonic drugs (some cases do not respond to i.v. fluids)
  - Hemodialysis or hemofiltration as needed
- Cautious sedation and analgesia
- Follow coagulation studies – replace as needed
- Avoid aspirin, NSAIDs, anticoagulant therapies, or IM injections

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Medical Management
Antiviral Therapy

- Ribavirin
  - Investigational drug, compassionate use
  - Contraindicated in pregnancy
  - Arenaviridae (Lassa, AHF, BHF)
  - Bunyaviridae (HFRS, RVF, CCHF)
  - NO UTILITY FOR FILOVIRUSES OR FLAVIVIRUSES

- Immune (convalescent) plasma
  - Arenaviridae (AHF & BHF; ?Lassa)
  - Passive immunoprophylaxis post-exposure?
  - Experimental studies in animals have not proven efficacy against filovirus infection
  - NOT READILY AVAILABLE

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Medical Management For Arenavirus & Bunyavirus

- Ribavirin Treatment
  - 30 mg/kg IV single loading dose
  - 16 mg/kg IV q 6 hr for 4 days
  - 8 mg/kg IV q 8hr for 6 days

- Prophylaxis
  - 500 mg PO q 6 hr for 7 days

Note: Parenteral and oral Ribavirin are investigational and available only through human use protocols

Borio L, *et al*. *JAMA* 287(18):2391-2405, 2002
McCormick JB *et. al. N Eng J Med* 314(1):20-26, 1986
Jahrling PB *et al. J Infect Dis* 141:580-589, 1980

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Final Thoughts

- Maintain an index of suspicion
- BYOP (Bring your own PPE):
  - Masks, gowns, gloves, goggles, caps
- Have an exit strategy
- Don’t let let anyone use a non-sterile needle on you
- Rodent/bat control
- Get WHO guidelines

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Questions

1) Which of the following diseases should be considered in the differential diagnosis of a viral hemorrhagic fever:

a) malaria

b) smallpox

c) typhoid fever

d) leptospirosis

e) all of the above

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Questions

2) What is the primary mechanism of human to human transmission that has occurred in outbreaks of viral hemorrhagic fevers?

a) inhaled small droplet nuclei (respiratory aerosols)

b) percutaneous or mucus membrane contact with blood or body fluids of a victim

c) contact with urine

d) sharing the same household

e) inhaled large droplets

Questions

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Questions

3) What is the most important aspect for preventing spread of viral hemorrhagic fevers in an outbreak?

a) isolating patients in a negative pressure room

b) caregivers use basic barrier methods (gloves, masks, gowns, goggles)

c) place the patient in a separate facility a minimum of 20 foot distance from the primary care area

d) rapid treatment with an effective antiviral medication

e) vaccination of all close contacts

Questions

3) What is the most important aspect for preventing spread of viral hemorrhagic fevers in an outbreak?

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Gunung Gede peak in clouds at sunset, Puncak, West Java, Indonesia