Clinical Aspects of Critical Biological Agents

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Agent Selection Considerations

- Catastrophic public health consequences
  - Mass casualties which overwhelm medical systems
  - High morbidity or mortality
  - Contagious

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Agent Selection Considerations (continued)

- Require comprehensive public health preparedness
  - stockpile therapeutics
  - enhanced surveillance or diagnostics
  - response planning
- Heightened public perception

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Biological Agents of Highest Concern

- Variola major (Smallpox)
- *Bacillus anthracis* (Anthrax)
- *Yersinia pestis* (Plague)
- *Francisella tularensis* (Tularemia)
- Botulinum toxin (Botulism)
- Filoviruses and Arenaviruses (Viral hemorrhagic fevers)

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Important

Report ALL suspected or confirmed illness due to these agents to health authorities immediately

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Why These Agents?

- Can cause disease via aerosol route
- Organisms fairly stable in aerosol
- Susceptible civilian populations
- High morbidity and mortality

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Why These Agents?
(continued)

- Some with person-to-person transmission (smallpox, plague, VHF)
- Difficult to diagnose and/or treat
- Previous development for Biological Warfare

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Covert vs. Overt Event

	Covert	Overt
Recognition	early	delayed
Response	early	delayed
Treatment	early	delayed
Responders	Traditional "First Responders"	Health Care Workers

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Anthrax: Overview

- Primarily disease of herbivores
- Natural transmission to humans by contact with infected animals or contaminated animal products

CDC: Gram stain of *B. anthracis*

Anthrax: Overview
(continued)

- Soil reservoir
- Woolsorter's disease (inhalation anthrax)
- <u>No</u> person-to-person transmission of inhalational anthrax

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Anthrax: Cutaneous

- Most common form (95%)
- Inoculation of spores <u>under</u> skin
- Incubation: hours to 7 days
- Small papule ? ulcer surrounded by vesicles (24-28h)
- Painless eschar with edema
- Death 20% untreated; rare if treated

USAMRICD: Eschar with surrounding edema

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Anthrax: Gastrointestinal

- Ingestion of contaminated meat
- Incubation: hours or up to 7 days
- Fever, acute gastroenteritis, vomiting, bloody diarrhea

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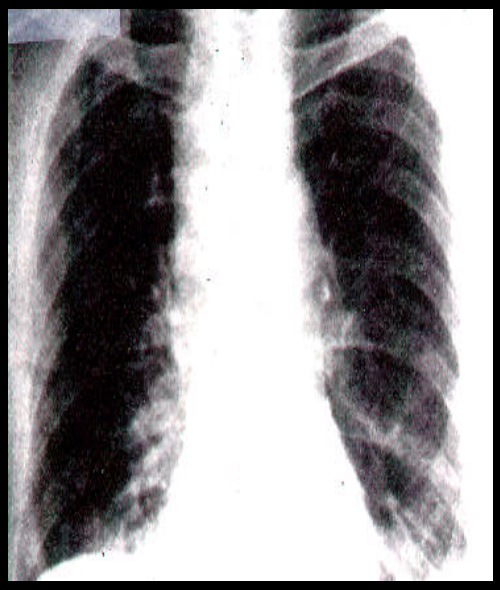
Anthrax: Gastrointestinal (continued)

- Intestinal eschar similar to cutaneous anthrax lesion
  - hemorrhagic
- Progression to generalized toxemia
- Mortality rate 50 -100% despite treatment

CDC: Intestinal lesion of GI anthrax

Anthrax: Inhalational

- Inhalation of spores
- Incubation: 1 to 43 days
- Initial symptoms (2-5 d)
  - fever, cough, myalgia, malaise



CDC: CXR with widened mediastinum of inhalational anthrax

Anthrax: Inhalational
(continued)

- Terminal symptoms (1-2d)
  - High fever, dyspnea, cyanosis
  - hemorrhagic mediastinitis/pleural effusion
  - Rapid progression to shock/death
- Mortality rate ~100% despite aggressive Rx

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Inhalational Anthrax: Differential Diagnoses

- Community acquired pneumonia (CAP)
  - If infiltrate (rare) or pleural effusion present
- Pneumonic Tularemia or Plague
  - If pleural effusion present

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Inhalational Anthrax: Differential Diagnoses
(continued)

- Hantavirus pulmonary syndrome (HPS)
- Bacterial/Fungal/TB mediastinitis
- Fulminate mediastinal tumors
- Dissecting aortic aneurysm
  - Widened mediastinum but usually <u>no</u> fever

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Anthrax: Treatment

- **Antibiotics**
  - **Penicillin or Doxycycline (FDA approved), or Ciprofloxacin** (animal and in vitro studies)
- **Supportive care**
- **Standard precautions, no quarantine needed**

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Anthrax: Treatment
(continued)

- Duration of treatment dependent on form of anthrax and/or vaccine use
- Early treatment improves prognosis
- Antibiotic susceptibility testing to help guide therapy

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Anthrax: Post-Exposure Treatment

- Start oral antibiotics as soon as possible after exposure
  - Ciprofloxacin or Doxycycline or Amoxicillin/Penicillin (if known PCN sensitive)

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Post-Exposure Treatment (continued)

- Antibiotics for 60 days without vaccine
- Antibiotics for 30 days with 3 doses of vaccine (animal studies)
- Long-term antibiotics necessary because of spore persistence in lung/lymph node tissue

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Anthrax: Vaccine

+ Current U.S. vaccine (FDA Licensed)
  - FDA approved for persons 18-65 year of age
  - Active component is Protective Antigen (PA) from attenuated non-encapsulated strain
  - Protective against cutaneous (human data) and possibly inhalational anthrax (animal data)

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Anthrax: Vaccine
(continued)

+ Current U.S. vaccine (FDA Licensed) - continued
  - FDA approved for 6 dose regimen over 18 months
  - 3 dose regimen (0, 2, and 4 weeks) may be effective for post-exposure treatment (animal studies)
  - Limited availability

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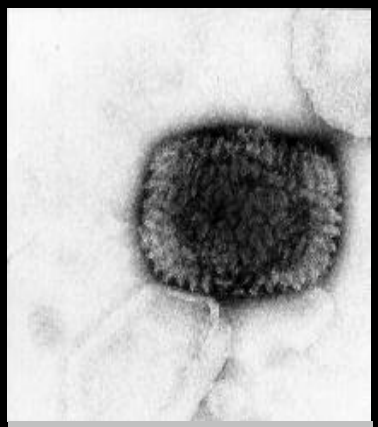
Smallpox: Overview

- 1980 - Global eradication
- Humans were only known reservoir
- Person-to-person transmission (aerosol/contact)
- Up to 30% mortality in unvaccinated



CDC: Electron micrograph of Variola major

Smallpox: Clinical Features

- Prodrome (incubation 7-17 days)
  - Acute onset fever, malaise, headache, backache, vomiting
  - Transient erythematous rash

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Smallpox: Clinical Features
(continued)

+ Exanthem (Rash)
  - Begins on face, hands, forearms spreads to lower extremities then trunk over ~ 7 days
  - Synchronous progression: macules ? vesicles ? pustules ? scabs
  - Lesions on palms /soles

USAMRICD: ater stage facial lesions of smallpox

Smallpox: Complications

- Encephalitis[1]
  - 1 in 2,000 cases Variola minor
  - 1 in 500 cases Variola major
- Keratitis, corneal ulceration[2]
  - Blindness in 1% of cases

[1] Marsden, JP. Bulletin of Hygiene. 1948; 23: 735-46

[2] Hughes, K. Geneva, Switzerland: 1978. WHO/SE78.101

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Smallpox: Complications (continued)

+ Infection in pregnancy[3]
  - High perinatal fatality
  - Congenital infection

[3] Marsden, JP, Greenfield CRM. Arch Dis Child. 1934;9:309-14.

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Smallpox vs. Chickenpox

	Variola	Varicella
Incubation	7-17 days	14-21 days
Prodrome	2- 4 days	minimal/none
Distribution	centrifugal	centripetal
Progression	synchronous	asynchronous
Scab formation	10-14 d p rash	4-7 d p rash
Scab separation	14-28 d p rash	<14 d p rash

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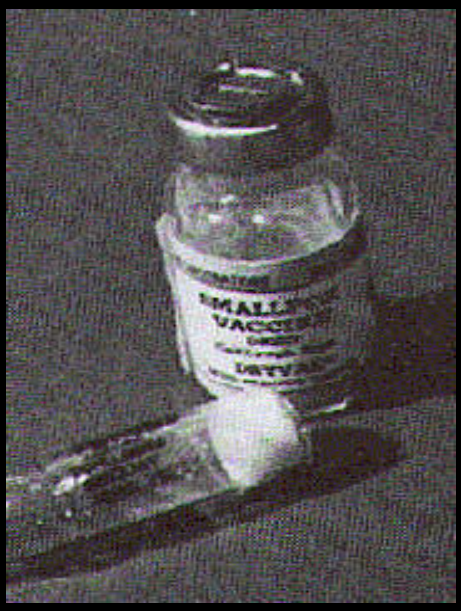
Smallpox: Current Vaccine

- Made from live Vaccinia virus
- Intradermal inoculation with bifurcated needle (scarification)
  - Pustular lesion/induration surrounding central scab/ulcer 6-8 days after vaccination



WHO: Smallpox vaccine vials

Smallpox: Current Vaccine (continued)

- Low grade fever, axillary lymphadenopathy
- Scar (permanent) demonstrates successful vaccination
- Immunity <u>not</u> life-long

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Smallpox: Vaccination Complications

+ Most common
  - Inadvertent inoculation (skin, eye)
+ Less Common
  - Generalized vaccinia (242/million) †
  - Post-vaccination encephalitis (2.9/million)*

* Lane, et al., NEJM, 1969;281:1201

† Lane, et al., J Infect Dis., 1970; 122:303

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Smallpox: Vaccination Complications (continued)

- Less common (continued)
  - Fetal vaccinia
  - Eczema vaccinatum (38/million) †
  - Vaccinia necrosum (0.9/million) †
- Primary vaccination - 1 death/million*
- Revaccination - 0.1 deaths/million*

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Smallpox: Vaccination Complications

WHO: Inadvertent inoculation below eye

WHO: Eczema vaccinatum

WHO: Vaccinia necrosum

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Smallpox: Vaccinia Immune Globulin (VIG)

- Used for treatment of adverse reactions (AR)
  - Approximately 25AR's/100,000 vaccinations*
  - AR rate possibly increased in present day due to higher immunocompromised population

*Stöm J., Zetterberg B., ed. (1966) Smallpox outbreak and vaccination problems in Stockholm, Sweden, 1963.
Acta Medica Scandinavica, supplementum, 464:1-171

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Vaccine (continued)

+ Post-exposure prophylaxis
  - Pregnant patients (VIG + Vaccinia vaccine)
  - Eczema (VIG + Vaccina vaccine)
  - Immunocompromised patients, No consensus (VIG alone vs. VIG + Vaccinia vaccine?)
+ Current supplies limited

Ström J., Zetterberg B., ed. (1966) Smallpox outbreak and vaccination problems in Stockholm, Sweden, 1963 .Acta Medica Scandinavica, supplementum, 464:1-171

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Smallpox: Medical Management

- Strict respiratory/contact isolation of patient
  - Patient infectious until all scabs have separated
- Notify public health authorities <u>immediately</u> for suspected case
- Identify contacts within 17 days of the onset of case's symptoms

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Smallpox: Management of Contacts

- Immediate vaccination (or boosting) of ALL potential contacts including health care workers
  - Vaccination within 4 days of exposure may prevent or lessen disease
  - 17 day observation for fever or rash

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Smallpox: Management of Contacts (cont)

- Passive immunization (VIG)
  - Potential use for contacts at high risk for vaccine complications (pregnancy, dermatoses, immunosuppression)

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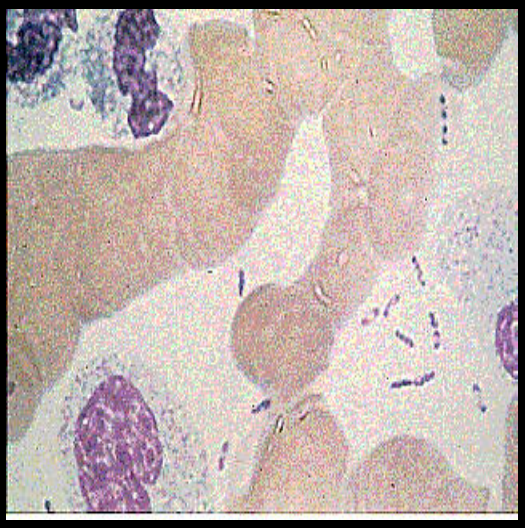
Plague: Overview

- Natural vector - rodent flea
- Mammalian hosts
  - rats, squirrels, chipmunks, rabbits, and carnivores
- Enzootic or Epizootic



CDC: Wayson's Stain of *Y. pestis* showing bipolar staining

Plague: Overview (cont)

- About 10-15 total cases/year in U.S.
  - Mainly SW states
  - Bubonic most common form
  - Only 1-2 cases/yr. of pneumonic form

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Plague: Clinical Forms Bubonic

- Bubonic
  - Inguinal, axillary, or cervical lymph nodes most common
  - 80% can become bacteremic
  - 60% mortality if untreated

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Plague: Bubonic

- Incubation: 2-6 days
- Sudden onset headache, malaise, myalgia, fever, tender lymph nodes
- Regional lymphadenitis (Buboes)
- Cutaneous findings
  - possible papule, vesicle, or pustule at inoculation site
  - Purpuric lesions - late

USAMRICD: Inguinal/femoral buboes

Plague: Pneumonic

+ Pneumonic
  - From aerosol or septicemic spread to lungs
  - Person-to-person transmission by respiratory droplet
  - 100% mortality untreated

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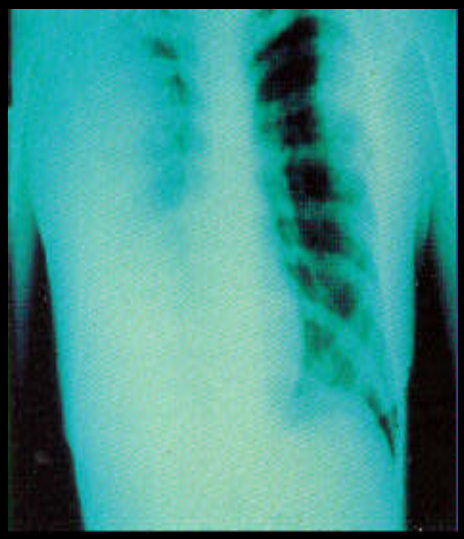
Plague: Pneumonic (cont)

- Incubation: 1-3 days
- Sudden onset headache, malaise, fever, myalgia, cough
- Pneumonia progresses rapidly to dyspnea, cyanosis, hemoptysis
- Death from respiratory collapse/sepsis



USAMRICD: Pneumonic infiltrate of pneumonic plague

Plague: Septicemic

- Primary or secondary
  - Secondary from bubonic or pneumonic forms
  - 100% mortality if untreated
- Severe endotoxemia
- Systemic inflammatory response syndrome
- Shock, Disseminated intravascular coagulopathy (DIC)
- Adult Respiratory Distress Syndrome (ARDS)

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Plague: Differential Diagnosis

+ **Bubonic**
  - Staph/streptococcal adenitis
  - Glandular tularemia
  - Cat scratch disease

+ **Pneumonic**
  - Other bioterrorism threats
    - Anthrax
    - Tularemia
    - Melioidosis
  - Other pneumonias (CAP, influenza, HPS)
  - Hemorrhagic leptospirosis

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Differential Diagnosis (cont)

+ Septicemic
  - Other gram-negative sepsis
  - Meningococcemia
  - Rocky Mountain Spotted Fever (RMSF)
  - Thrombotic Thrombocytopenic Purpura (TTP)

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Plague: Medical Management

- Antibiotic therapy
  - Gentamicin or Streptomycin
  - Tetracyclines
  - Sulfonamides
  - Chloramphenicol (meningitis/pleuritis)

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Plague: Medical Management

- Supportive therapy
- Isolation with droplet precautions for pneumonic plague until sputum cultures negative
- Antibiotic resistant strains have been documented

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Plague: Prophylaxis

- Bubonic contacts
  - If common exposure, consider oral Doxycycline, Tetracycline, or TMP/SMX for 7 days
  - Other close contacts, fever watch for 7 days (treat if febrile)

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Plague: Prophylaxis
(continued)

- Pneumonic contacts (respiratory/droplet exposure)
  - Consider oral Doxycycline, Tetracycline, or TMP/SMX
  - Continue for 7 days after last exposure
- Vaccine no longer manufactured in U.S.
  - Not protective against pneumonic plague

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Tularemia: Overview

- Disease of Northern Hemisphere
- In U.S., most cases associated with rabbits/hares (winter) and ticks (summer)
- About 200 cases/year in U.S.
  - most in South central and Western states
  - majority of cases in summer (tick exposure)

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Tularemia: Overview (cont)

- Low infectious dose
  - 1 to 10 organisms by aerosol or intradermal route
- No person-to-person transmission

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Tularemia: Clinical Forms

- Ulceroglandular
  - Ulcer with regional adenopathy
- Glandular
  - Regional adenopathy without skin lesion
- Oculoglandular
  - Painful purulent conjunctivitis with adenopathy

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Tularemia: Clinical Forms (cont'd)

- Typhoidal
  - Septicemia, no adenopathy
  - Possible presentation for BT
- Pneumonic (primary or secondary)
  - Possible presentation for BT

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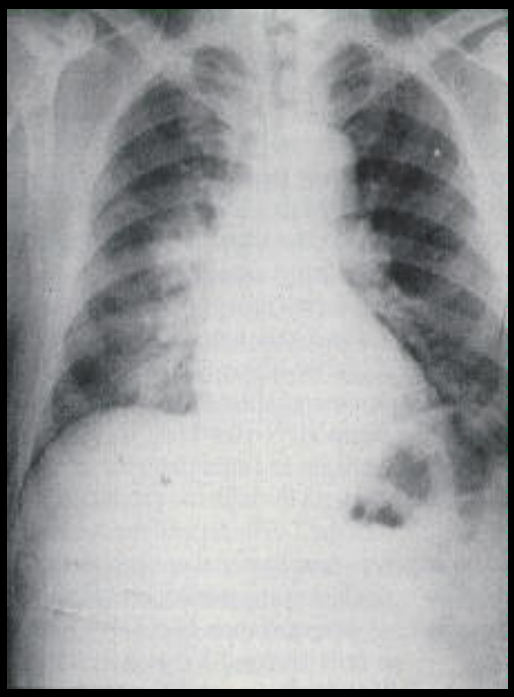
Tularemia: Pneumonic

- Incubation: 3 to 5 days (range 1-21 days)
- Abrupt onset fever, chills, headaches, myalgia, non-productive cough
- Segmental/lobar infiltrates, hilar adenopathy, effusions
- Mortality 30% if untreated; < 10% if treated



USAMRICD: Pneumonic infiltrates of pneumonic tularemia

Pneumonic Tularemia: Differential Diagnoses

- Community acquired pneumonia (CAP)
  - Atypical CAP (Legionella, Mycoplasma)
  - Streptococcal pneumonia, Influenza, H. influenza

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Pneumonic Tularemia: Differential Diagnoses

+ Other Zoonoses
  - Brucellosis
  - Q Fever
  - Pneumonic plague
  - Histoplasmosis
  - Inhalational Anthrax
  - Hantavirus Pulmonary Syndrome (HPS)

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Tularemia: Treatment/Prophylaxis

- Treatment
  - Streptomycin or Gentamicin
  - Tetracyclines
- Prophylaxis
  - Fever watch for 7 days (preferable)
  - Doxycycline or Tetracycline for 14 days if febrile

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Tularemia - vaccine

+ Vaccine investigational
  - Not available for general use
  - Role in treatment of disease or post-exposure prophylaxis unknown

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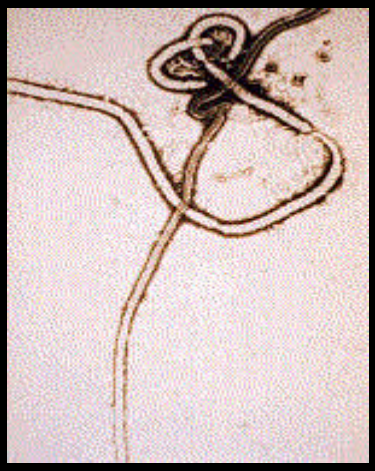
Viral Hemorrhagic Fevers (VHF): Overview

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



CDC: Electron micrograph of Ebola virus

Viral Hemorrhagic Fevers (VHF): Overview (cont'd)

- Natural vectors - virus dependent
  - rodents, mosquitoes, ticks
- <u>No</u> natural occurrence in U.S.

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VHF: Patient History

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

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VHF: Clinical Presentation

- Incubation
  - Typical 5 -10 days
  - Range 2 -16 days
- Symptoms
  - Fever, headache, malaise, dizziness
  - Myalgias
  - Nausea/vomiting

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VHF: Clinical Presentation
(continued)

+ Initial signs
  - Flushing, conjunctival injection
  - Periorbital edema
  - Positive tourniquet test (petechiae form below tourniquet or inflated blood pressure cuff)
  - Hypotension

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VHF: Clinical Presentation

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

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VHF: Clinical Presentation
(continued)

- Usually improving or moribund within a week (exceptions: HFRS, arenaviruses)
- Bleeding, CNS involvement, marked SGOT elevation indicate poor prognosis
- Mortality: virus dependent (10 to 90%)

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VHF: Differential Diagnosis

- Bacterial
  - Typhoid fever, meningococcemia, rickettsioses, leptospirosis
- Protozoa
  - Falciparum malaria
- Other
  - Vasculitis, TTP, Hemolytic Uremic Syndrome (HUS), heat stroke

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VHF: Treatment

- Supportive care
- Cautious sedation and analgesia
- Correct coagulopathies as needed
- No antiplatelet drugs or IM injections
- Ribavirin possibly effective for:
  - Arenaviruses
  - Bunyaviridae (CCHF, Hantaan, RVF)

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VHF: Patient Isolation

+ Single room with adjoining anteroom (if available)
  - Handwashing facility with decontamination solution
+ Negative air pressure

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VHF: Patient Isolation (continued)

- Strict barrier precautions including protective eyewear/faceshield
  - Needed for Filoviruses and Arenaviruses
- Disposable equipment /sharps in rigid containers with disinfectant then autoclave or incinerate
- All body fluids disinfected

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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 (dose, route of administration, and duration of treatment unclear)

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VHF: Contact Management
(continued)

+ High-Risk contacts
  - Mucous membrane, penetrating injury with exposure to body fluids or tissue
  - Consider post-exposure prophylaxis

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Botulism: Overview

- Caused by toxin from *Clostridium botulinum*
  - toxin types A, B, E, most commonly associated with human disease
  - most potent lethal substance known to man (lethal dose 1ng/kg)

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Botulism: Overview
(continued)

- *C. botulinum* spores found in soil worldwide
- Approximately 100 reported cases/year in the U.S.
  - infant most common (72%)
  - Food-borne not common
- No person-to-person transmission

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Botulism: Clinical Forms

- Foodborne
  - toxin produced anaerobically in improperly processed or canned,
  - low-acid foods contaminated by spores
- Wound
  - toxin produced by organisms contaminating wound

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Botulism: Clinical Forms (continued)

- Infant
  - toxin produced by organisms in intestinal tract
- Inhalation botulism
  - No natural occurrence, developed as BW weapon

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Botulism: Clinical Presentation

- Incubation: 18 to 36 hours (dose dependent)
- Afebrile, alert, oriented; normal sensory exam
  - Early nausea, vomiting, diarrhea
- Cranial Nerve symptoms
  - Ptosis, blurry/double vision, difficulty swallowing/talking, decreased salivation

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Botulism: Clinical Presentation
(continued)

+ Motor symptoms (progressive)
  – Bilateral descending flaccid paralysis --> respiratory paralysis

+ Death 60% if untreated; <5% if treated

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Botulism: Differential Diagnoses

+ Neuromuscular disorders
  - Stroke syndrome
  - Myasthenia gravis
  - Guillain-Barre syndrome (Miller-Fisher variant)
  - Tick paralysis
  - Atropine poisoning
  - Paralytic shellfish/puffer fish poisoning
+ Diagnosis based on clinical presentation with subsequent laboratory confirmation

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Botulism: Treatment/Prophylaxis

- Ventilatory assistance and supportive care
- Botulinum antitoxin
  - Trivalent equine product against types A,B, and E available from CDC
  - Most effective if given early
- Antibiotics for wound botulism
  - Penicillin
- Recovery may be prolonged with supportive care necessary
- Vaccine investigational
  - not available

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