Preparing for and Responding to Bioterrorism
Information for Primary Care Clinicians

Tularemia and Viral Hemorrhagic Fevers

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Acknowledgements

This manual and the accompanying MS PowerPoint® slides were prepared for the purpose of educating primary care clinicians in relevant aspects of bioterrorism preparedness and response. Instructors are encouraged to freely use all or portions of the material for its intended purpose. The following people and organizations provided information and support in the development of this curriculum.

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“Preparing for and Responding to Bioterrorism: Information for Primary Care Clinicians” is intended to provide primary care clinicians with a basic understanding of bioterrorism preparedness and response, how the clinician fits into the overall process, and the clinical presentation and management of diseases produced by agents most likely to be used in a biological attack. The course was designed by the Northwest Center for Public Health Practice in Seattle, Washington, and Public Health – Seattle & King County.

The course incorporates information from a variety of sources, including the Centers for Disease Control and Prevention, the United States Army Medical Research Institute in Infectious Disease (USAMRIID), the Working Group on Civilian Biodefense, Public Health – Seattle & King County, and the Washington State Department of Health, among others (a complete list of references is given at the end of the manual). The course is not copyrighted and may be used freely for the education of primary care clinicians.

Course materials will be updated on an as-needed basis with new information (e.g., research study results, consensus statements) as it becomes available. For the most current version of the curriculum, please refer to: http://nwcphp.org/bttrain/.
How to Use This Manual

This manual provides the instructor with additional useful information related to the accompanying MS PowerPoint® slides. The manual and slides are divided into four major sections: Introduction to Bioterrorism, Bioterrorism Preparedness and Response, Diseases of Bioterrorist Potential, and Psychological Aftermath of Crisis. Learning objectives precede each section, and a list of resources is given at the end of each section. Four slide sets comprise the section on the diseases of bioterrorist potential: Anthrax, Smallpox, Plague and Botulism, and Tularemia and Viral Hemorrhagic Fevers. Each disease slide set contains the same introductory material on the critical agents at the beginning, and the same list of resources at the end. Instructors who want to skip this introductory material can use the navigation pages provided in the Plague and Botulism and Tularemia and Viral Hemorrhagic Fever modules (click the section to which you want to go), or the custom show option in the Anthrax and Smallpox modules (go to “Custom Shows” under the “Slide Show” option on the MS PowerPoint® toolbar; select “Anthrax/Smallpox, skip intro”).

Links to Web sites of interest are included in the lower right-hand corner of some slides and can be accessed by clicking the link while in the “Slide Show” view. Blocks of material in the manual are summarized in the “Key Point” sections to assist the instructor in deciding what material to include in a particular presentation. A Summary of Key Points is indicated in bold, at the beginning of each section.

The slide set can be presented in its entirety, in subsections, or as an overview, depending on the level of detail included. The entire course was intended to be presented in a six- to seven-hour block of time, divided into one- to three-hour blocks according to instructor/audience preference. For instructors who want to present a less detailed, “overview” course, suggestions for more abbreviated presentations are incorporated into the modules. These latter options are built into the slide set and can be accessed by going to “Custom Shows” (under the “Slide Show” option on the MS PowerPoint® task bar).
The photo shows, from left to right, gram stains of *Bacillus anthracis* (anthrax), *Yersinia pestis* (plague), and *Francisella tularensis* (tularemia). The source for the first two photos is CDC, and for the gram stain of *F. tularensis*, the Armed Forces Institute of Pathology.
Learning Objectives (Slide 4)

The learning objectives for this session are:

1. Be familiar with the agents most likely to be used in a biological weapons attack and the most likely mode of dissemination
2. Know the clinical presentation(s) of the Category A agents and features that may distinguish them from more common diseases
3. Be familiar with diagnosis, treatment recommendations, infection control, and preventive therapy for management of infection with or exposure to Category A agents
Section 1: Biological Agents of Highest Concern (Slides 6-10)

CDC has designated critical agents with potential for use as biological weapons and grouped them according to level of concern (Rotz et al., Emerging Infect Dis 2002; 8(2):225-230). Several factors determine the classification of these agents, including previous use or development as a biological weapon, ease of dissemination, ability to cause significant mortality or morbidity, and infectious nature.

Category A agents, designated as agents of highest concern, will be the focus of this session; they are listed in slide 7. Category A agents include variola major (smallpox), *Bacillus anthracis* (anthrax), *Yersinia pestis* (plague), *Francisella tularensis* (tularemia), *Clostridium botulinum* toxin (botulism), and the filoviruses and arenaviruses (hemorrhagic fever viruses).

Category B agents are of the next highest level of concern and are listed in slides 8 and 9. These agents are moderately easy to disseminate and produce lower mortality and moderate morbidity.
A subset of the Category B agents includes food- and water-borne agents. These agents more commonly produce disease outbreaks from a non-deliberate source and may also be employed in a biological attack.

The final category of agents – **Category C** – includes emerging pathogens with potential for mass dissemination based on availability, ease of production and dissemination, and potential for high morbidity and mortality. They are listed in slide 10.

**The Laboratory Response Network**

CDC has established a multi-level Laboratory Response Network (LRN) for bioterrorism. Labs are identified by increasing levels of proficiency to respond to bioterrorism, from Level A to Level D; these categories take into consideration the biosafety level capacity of the labs, as well as other resource and capacity issues.

- **Level A** – Most clinical labs are Level A and include public health and hospital labs with a certified biological safety cabinet as a minimum.
- **Level B** – State and local public health labs with BSL-2 facilities that incorporate BSL-3 practices
- **Level C** – BSL-3 facilities with the capability to perform nucleic acid amplification, molecular typing, toxicity testing (Washington Public Health Laboratories, for example)
- **Level D** – Possess BSL-3 and BSL-4 biocontainment facilities and include CDC and USAMRIID labs. Level B/C labs can register for the LRN and then have password-protected access to information over the Web.
Tularemia (Slides 12-35)

Summary of Key Points:
(Listed in slides 34-35)
1. In naturally occurring tularemia, infection virtually always occurs in a rural setting. Infection in an urban setting with no known risk factors or contact with infected animals suggests a possible deliberate source.
2. The most likely presentations of tularemia in a BT attack are pneumonic and typhoidal disease, as opposed to cutaneous disease in naturally occurring cases.
3. Tularemia is not transmitted person to person.
4. Tularemia can be treated and prevented with antibiotics.

Key Points, Slides 12-22
1. Tularemia is a vector-borne illness that occurs naturally in the United States following the bite of an infected arthropod or deer fly, direct exposure to contaminated animal tissues and fluids, or ingestion of contaminated food, water, or soil.
2. Tularemia is usually a mild cutaneous disease, but pneumonic and typhoidal forms can be more severe.
3. All forms of tularemia begin with a non-specific, febrile, flu-like illness.
4. Aerosol exposure may produce profound constitutional debility in the absence of marked respiratory involvement.
5. Some cases may be rapidly progressive and fatal.
Francisella tularensis, a small gram negative cocco-bacillus and the causative agent of tularemia, exists as two major subspecies called biovars. *F. tularensis* biovar tularensis (type A) is a virulent strain responsible for most infections in North America. *F. tularensis* palaearctica (type B) causes milder disease and is prevalent in Europe and Asia.

The disease occurs naturally in the south-central and western states of the U.S. and northern and central Europe. In these areas, *F. tularensis* is found in a wide variety of animal hosts (particularly small mammals) and natural habitats including water, soil, and vegetation. Infection is acquired through the bite of an infected tick, mosquito, or deer fly; through contact with infected animal tissues or secretions (e.g., field dressing small game); ingestion of contaminated food, water, or soil; and inhalation of infected aerosols. Hunters, trappers, farmers, and butchers are at increased risk for tularemia where the disease is endemic. Microbiology laboratory staff can be infected through exposure to culture plates via the aerosol route.
F. tularensis has a low infectious dose and is more easily obtainable than some of the other agents (e.g., variola major, Y. pestis). Tularemia is not transmitted person to person and, in its naturally occurring state, is rarely fatal. Pneumonic tularemia has a higher case fatality rate than other forms of tularemia, but is a less severe illness than that caused by either Y. pestis or B. anthracis.

Epidemiologic clues are helpful in determining whether a case of tularemia has a deliberate source. Naturally occurring cases are typically infected in an outdoor or rural setting where the disease is endemic, usually in the summer. Cases occurring in winter are usually hunters exposed to infected animal carcasses. Infection in an urban setting (without known environmental exposure or other risk factor) and clusters of cases should immediately alert one to a potentially deliberate source.
*Francisella tularensis* can infect humans through the skin, mucous membranes, GI tract, and lungs. The organism multiplies intracellularly within macrophages and spreads from the inoculation site to regional lymph nodes, then disseminates via the blood stream to target organs throughout the body. An intense inflammatory cell response with suppuration, necrosis, and granuloma formation occurs in infected tissues. Hemorrhagic inflammation of the airways, bronchopneumonia, pleuritis with effusion, and hilar lymphadenopathy have been described in humans after inhalational exposure.

**Clinical Features and Forms (Slides 17-23)**

The clinical forms of tularemia depend on the route of exposure. Naturally occurring cases usually result from direct contact, and thus ulceroglandular tularemia is the most likely naturally occurring form of disease. As is the case with most of the critical agents, a biological attack using *F. tularensis* is most likely to occur via an aerosol release. Hence the most likely BT presentation is pneumonic tularemia. The next most likely BT presentation is typhoidal tularemia. Oropharyngeal tularemia occurs after ingestion of the organism.
The general clinical features of tularemia are listed in slide 19. Symptoms and laboratory signs are non-specific. Besides pneumonic tularemia, pneumonia can also occur with other forms of tularemia, most commonly typhoidal. Aerosol exposure to tularemia can produce profound constitutional symptoms in the absence of prominent respiratory signs, in addition to rapidly progressive pneumonia and septicemia in a smaller number of cases. Slide 20 describes the clinical presentation of ulceroglandular tularemia.
Slide 21 shows two stages of the typical ulceroglandular tularemia lesion (papule and ulcer) and a photo of a thumb with a tularemia skin ulcer.

Slide 22 describes the clinical presentation of pneumonic tularemia. Pneumonic tularemia may be severe, but is not as rapidly progressive as pneumonic plague or anthrax. Radiographic signs are often minimal early in disease. The earliest radiographic findings in inhalational tularemia may be peribronchial infiltrates, progressing to bronchopneumonia in one or more lobes and often accompanied by pleural effusions and hilar lymphadenopathy.

Slide 23 shows infiltrates in the lower left lung, tenting of the diaphragm (probably caused by pleural effusion), and enlargement of the left hilum, in a patient with pneumonic tularemia.
Key Points, Slides 24-25

1. The differential diagnosis of pneumonic tularemia includes other causes of community-acquired pneumonia.
2. Radiographic signs are often minimal early in disease.
3. Laboratory testing is important in establishing the diagnosis – be sure to alert the laboratory that tularemia is suspected to avoid infection of laboratory staff.

When to Think (BT) Tularemia?

Slide 24 lists epidemiological and patient history clues suggesting a possible BT attack with \textit{F. tularensis}. The presence of these clues may suggest an intentional infection and an unusual etiologic agent as a potential source of disease. Seasonal and geographical factors (i.e., Is it the right time of year for tularemia? Has the patient been in a state where tularemia is prevalent, and location where natural infection might have occurred?) are important in determining the nature of infection (i.e., natural vs. deliberate) in a person with tularemia. A thorough social, travel, and occupational history is critical.
Differential Diagnosis

The differential diagnosis of pneumonic tularemia is listed in slide 25 and includes other causes of community-acquired pneumonia. Brucellosis (commonly known as “undulating fever”) is often characterized by an intermittent or irregular fever of variable duration. In Q Fever, a rickettsial infection caused by *Coxiella burnetti*, pneumonitis may be present on chest x-ray, but cough and physical findings in the lungs are usually not prominent. Abnormal liver function tests are common. Histoplasmosis, a fungal infection, is caused by inhalation of contaminated soil. The acute benign respiratory form of disease varies from a mild respiratory illness to short-term incapacitation with constitutional symptoms and a nonproductive cough. Hantavirus pulmonary syndrome has a more fulminant course than pneumonic tularemia; it progresses rapidly to severe respiratory failure and shock. An elevated hematocrit, a marked shift to the left with immature and precursor white blood cells on peripheral smear, thrombocytopenia, and hypoalbuminemia are often present.

A dry to slightly productive cough is typical of pneumonic tularemia whereas hemoptysis is suggestive of pneumonic plague. The course of illness is more gradual in tularemia, as opposed to fulminant in pneumonic plague.
The cough and constitutional symptoms of inhalational anthrax may be similar to that of pneumonic tularemia, but the course of illness tends to be more aggressive.

The “atypical pneumonias” are the most difficult to differentiate from pneumonic tularemia. In this case, history supportive of an atypical pneumonia or exposure to *F. tularensis*, or epidemiologic clues suggesting a deliberate source, will help to direct the clinical evaluation. Sore throat may be found in both mycoplasma and tularemia pneumonia cases.

**Laboratory Diagnosis**

Slides 26-27 lists laboratory tests for diagnosis of tularemia. Because of the risk of infection to laboratory staff and the need for special culture media, the laboratory must be alerted when tularemia is present or suspected. Immunohistochemical and direct fluorescent antibody stains and culture of respiratory secretions should be obtained to identify *F. tularensis*. Blood cultures should also be obtained, but are less commonly positive in pneumonic disease. Light microscopy shows small pleomorphic, weakly staining organisms. Growth in culture may be visible as early as 24-48 hours after inoculation, but may be delayed if antibiotics were administered prior to specimen collection. Serum antibody levels usually are not at diagnostic levels until 10 or more days after infection, and thus are not useful for clinical purposes; they may be useful for epidemiological or forensic purposes. These tests are available at most state public health laboratories and some clinical laboratories.
Treatment, Prophylaxis and Infection Control: Slides 28-32

Key Points
1. Gentamicin and streptomycin are recommended antibiotics for BT-associated tularemia in a contained casualty setting.
2. Doxycycline and ciprofloxacin are recommended antibiotics for BT-related tularemia in a mass casualty setting, or for prophylaxis.
3. Only standard precautions are necessary, due to lack of person-to-person transmission.
Treatment and Prophylaxis

Slides 29-31 list the recommendations of the Working Group on Civilian Biodefense for prophylaxis and treatment of tularemia in mass casualty and contained casualty situations. Persons for whom the time of exposure to tularemia is known and who are in the incubation period should be treated with 14 days of oral doxycycline or ciprofloxacin. Persons for whom the exposure time is uncertain can be observed and treated if fever or symptoms of infection develop within 14 days of presumed exposure. Note that these recommendations from the Working Group on Civilian Biodefense (June 2001) assume a deliberate source of infection, with likely antibiotic resistant forms of the bacteria. In the event of a BT attack of tularemia, clinicians should be alert to current recommendations made by CDC for patient management (http://www.bt.cdc.gov). Isolation is not recommended for tularemia patients because of the lack of person-to-person transmission.
Infection Control

Slide 32 summarizes necessary infection control precautions when caring for patients with tularemia. Because of the risk of infection to laboratory staff and the need for special culture media, the laboratory must be alerted when tularemia is present or suspected.
Summary of Key Points

- In naturally occurring tularemia, infection virtually always occurs in a rural setting. Infection in an urban setting with no known risk factors or contact with infected animals suggests a possible deliberate source.
- Tularemia is not transmitted person to person.

Case Studies and Reports

Slide 35 contains links to case studies and reports on tularemia. Note that these are not BT-related cases.
Viral Hemorrhagic Fevers (VHFs) (Slides 36-61)

Summary of Key Points: (Listed in slides 59-60)
1. A thorough travel and exposure history is key to distinguishing naturally occurring from intentional viral hemorrhagic fever cases.
2. Viral hemorrhagic fevers can be transmitted via exposure to blood and bodily fluids.
3. Contact and airborne precautions are recommended for health care workers when caring for infected patients.
4. Diagnostic laboratory testing for the viral hemorrhagic fevers must be done in a bio-safety level 4 lab (i.e., CDC); contact the local or state health department before specimen collection in suspected cases.

Causative Agents, Epidemiology, and Pathology (Slides 37-43)

Key Points
1. The viral hemorrhagic fevers (VHFs) are a group of illnesses caused by four families of viruses: arenaviruses, filoviruses, flaviviruses, and bunyaviruses.
2. The VHFs differ by geographic occurrence, vector or reservoir, and prognosis, but have certain pathogenic and clinical similarities.
Overview

VHFs are zoonotic diseases; rodents and arthropods are the main reservoirs for infection. The illness course, geographic occurrence, and animal and arthropod reservoirs differ among the VHF agents, but the target organ (vascular bed) and initial presentation (febrile illness with coagulation abnormalities) is similar. Mortality rates vary by agent, from 0.5% reported for Omsk hemorrhagic fever to 53-92% reported in outbreaks of Ebola hemorrhagic fever. Only the arenaviruses and filoviruses are considered Category A agents.

Slide 38 shows an electron micrograph of the Ebola Zaire virus (Dr. F.A. Murphy, then CDC, now UC Davis; top), and extracellular virus particles budding from the surface of a Vero E6 tissue culture cell infected with an arenavirus (Cynthia Goldsmith, MS, Infectious Disease Pathology Activity, DVRD, NCID, CDC; bottom).
Transmission

Under natural circumstances, humans are infected after contact with the natural host. This may occur through the bite of an infected arthropod, through inhaling aerosol-ized rodent excreta, or through contact with infected animal carcasses. Most cases have resulted from direct contact with blood, secretions, or tissues of infected patients or nonhuman primates. These epidemiological features should be thoroughly reviewed in cases of suspected VHF (i.e., a compatible clinical illness occurring within 21 days of spending time in a VHF-endemic region).

Several VHF agents are transmissible from person to person, primarily through direct percutaneous exposure to blood and bodily fluids. Percutaneous exposure results in a high risk of infection. For filoviruses and arenaviruses, rare instances of airborne person-to-person transmission may occur, but this mode of transmission has not been convincingly established or ruled out. Laboratory workers are at risk for Rift Valley fever from inhalation of infectious aerosols during specimen processing. Rift Valley fever may also infect domestic animals after a biological attack, with potential establishment of the disease in the environment.

Person-to-person transmission has not been described for Rift Valley fever and the flaviviruses (Yellow fever, Omsk hemorrhagic fever, or Kyasanur Forest disease). In general, standard infection control precautions including blood and bodily fluid precautions have been effective at interrupting transmission during outbreaks.
Slides 40 & 41 summarize the natural geographic occurrence, reservoir or vector, and transmission of the viral hemorrhagic fever viruses.
Pathogenesis

All VHF can produce thrombocytopenia, and some also cause platelet dysfunction. Coagulopathy may result from hepatic dysfunction or DIC and is most prominent in Rift Valley fever and yellow fever. Infection with filoviruses, Rift Valley fever virus, and yellow fever virus causes destruction of infected cells.

Filoviruses may cause a hemorrhagic diathesis and tissue necrosis through direct damage to vascular endothelial cells and platelets with impairment of the microcirculation, as well as through immunological and inflammatory mediators. DIC is characteristic of filovirus infections.

Arenaviridae, on the other hand, appear to mediate hemorrhage via the stimulation of inflammatory mediators by macrophages, thrombocytopenia, and the inhibition of platelet aggregation. DIC is not a major pathophysiologic mechanism in arenavirus infections.
Clinical Presentation (Slides 44-51)

Key Points

1. Not all infected persons develop a classic hemorrhagic fever syndrome, and specific signs and symptoms vary according to the specific type of VHF.

2. Initial signs and symptoms reflect vascular damage and increased capillary permeability and may include marked fever, fatigue, dizziness, muscle aches, weakness, and exhaustion. Severe cases may show bleeding manifestations ranging from petechiae to spontaneous bleeding.

3. The differential diagnosis of viral hemorrhagic fevers includes other causes of febrile illness, vasculitis, and DIC.

4. All suspected cases of VHF should be immediately reported to public health authorities and the hospital infection control or epidemiology team.

5. Infection control measures for protection of health care workers should be implemented for suspected VHF cases.
The different VHF agents produce a spectrum of symptoms and clinical manifestations, complicating diagnosis. The incubation period for the viral hemorrhagic fevers ranges from 2-21 days, depending on the agent, and is followed by a prodromal illness lasting less than a week. Initial symptoms (slide 45) may include high fever, headache, malaise, arthralgias, myalgias, weakness, exhaustion, dizziness, nausea, abdominal pain, and non-bloody diarrhea. Illness onset is typically abrupt for the filoviruses, flaviviruses, and Rift Valley fever and more insidious with the arenaviruses.

Clinical signs (slide 46) reflect vascular damage and increased capillary permeability with hemodynamic signs (hypotension) and can ultimately lead to shock. Conjunctivitis and pharyngitis may occur. Most diseases show a cutaneous flushing or skin rash. A positive tourniquet/capillary fragility test may be present and is indicative of thrombocytopenia.

**Tourniquet Test**
A circle 2.5 cm in diameter, the upper edge of which is 4 cm below the crease of the elbow, is drawn on the inner aspect of the forearm. Pressure midway between the systolic and diastolic blood pressure is applied above the elbow for 15 minutes, and a count of petechiae within the circle is made: 10, normal; 10 to 20, marginal zone; over 20, abnormal (Stedman's Medical Dictionary).
Differentiating Features

A few clinical features predominate in some viral hemorrhagic fevers but not in others, and are useful in distinguishing between agents.

Hemorrhagic and neurological manifestations are prominent features of the South American hemorrhagic fevers, but not with Lassa fever.

Lassa fever patients may have severe peripheral edema, and hearing loss is a common sequelae of the disease.

Hepatic involvement is common in hemorrhagic fevers, and liver enzymes may be elevated, but overt manifestations such as jaundice are seen only in a small percentage of patients with yellow fever, Rift Valley fever, Congo-Crimean hemorrhagic fever, and Marburg and Ebola hemorrhagic fevers.

Dengue hemorrhagic fever is an uncommon complication of infection with the Dengue virus, thought to result from an immune reaction following sequential infections with different dengue viral serotypes.

A macular rash is a distinguishing feature of hemorrhagic fevers caused by the filoviruses (Ebola - maculopapular; Marburg – scarlatiniform). Disseminated intravascular coagulation (DIC) is usual with Ebola and Marburg, as well as Congo-Crimean hemorrhagic fever.

Renal failure is a prominent feature of hemorrhagic fever with renal syndrome (HFRS; caused by Hantaan virus), whereas it usually only occurs as a secondary manifestation to cardiovascular compromise in other hemorrhagic fevers. Pulmonary involvement is a central feature of the Hantavirus Pulmonary Syndrome.
Clinical Identification of Suspected Viral Hemorrhagic Fever (Slides 47-48)

The World Health Organization has developed surveillance criteria to assist in early identification of naturally occurring outbreaks of viral hemorrhagic fevers. A modified version of the WHO criteria, shown in slide 47, can be used to identify early VHF cases arising from a biological attack (Borio et al., 2002). Once the particular agent has been identified, public health officials will develop more specific case definitions.

Viral hemorrhagic fevers are not endemic to the United States, and thus, it is important to establish whether there is a potential natural explanation for the infection by asking about travel, insect bites, and exposure to animals or ill persons. All suspected cases of VHF should be immediately reported to local or state public health authorities and the hospital infection control or epidemiology team.
Differential Diagnosis (Slide 49)

The differential diagnosis of viral hemorrhagic fever includes other febrile viral and bacterial illnesses, with or without DIC, and vasculitis. Recovery and convalescence may be prolonged and complicated by persistent weakness, fatigue, and other symptoms.

Malaria presents very similarly to viral hemorrhagic fevers. The cyclical pattern of fever, chills and sweats followed by a fever-free interval every one to three days will help to distinguish Plasmodium vivax, malariae, and ovale from the viral hemorrhagic fevers. Infection with Plasmodium falciparum, presenting with a more varied clinical picture and complicated course, may be more difficult to distinguish clinically from viral hemorrhagic fevers.

*Salmonella typhi* and *Salmonella paratyphi*, the causative agents of typhoid fever, colonize only humans (i.e., there is no animal reservoir or vector); infection usually occurs via ingestion of food or water contaminated with human excreta.

Meningococcal infections peak in late winter and early spring, and occur more commonly in children than in adults.

Leptospirosis is a bacterial zoonotic disease that presents with headache, chills, myalgia, and conjunctival suffusion; the fever may be diphasic.
Laboratory Diagnosis (Slides 50-51)

The initial diagnosis of VHF should be based on clinical criteria and judgment. Laboratory findings include leukopenia, thrombocytopenia, anemia or hemoconcentration, and elevated liver function tests. Coagulation abnormalities may be present.

Thrombocytopenia is usually present, except in the case of Lassa Fever. Leukopenia is also typically present, except in some cases of Lassa Fever (in which leukocytosis occurs), Hantavirus syndromes or severe cases of Congo-Crimean hemorrhagic fever. Aspartate transaminase (AST) levels correlate with Lassa fever severity. Urinalysis may reveal proteinuria and hematuria, and patients may develop oliguria and azotemia. A progressive hemorrhagic diathesis may evolve, with petechiae, hemorrhage from mucous membranes and conjunctiva, hematuria, hematemesis, and melena followed by DIC and circulatory shock. CNS involvement with delirium, seizures, or coma may be present and is a poor prognostic sign.
Public health professionals should be contacted to facilitate confirmatory laboratory testing for VHF cases. The most useful laboratory confirmatory tests in the acute phase of illness are antigen detection with enzyme-linked immunosorbent assay (ELISA) and reverse transcriptase polymerase chain reaction (RT-PCR). Viral isolation can only be performed at a level D laboratory (either CDC or USAMRIID). There are plans to decentralize the process required for the laboratory confirmation of these viruses by equipping selected U.S. public health laboratories in the Laboratory Response Network with standard diagnostic reagents. IgM antibodies or four-fold rise in titer between in acute and convalescent sera are also diagnostic. Because antibodies do not usually appear until the second week of illness, at the onset of recovery, serology is of limited value in individual case management.
Key Points, Slides 52-56

1. Treatment of viral hemorrhagic fevers is primarily supportive.
2. Ribavirin therapy may be beneficial for patients with VHF secondary to arenaviridae or bunyaviridae.
3. There is no licensed vaccine or prophylaxis for arenaviridae or filoviridae.

Medical Management (Slides 52-54)

All suspected cases (based on the criteria in slide 47) of a viral hemorrhagic fever should be immediately reported to the local or state health department, and to your practice or facility’s infection control and laboratory personnel. Treatment of viral hemorrhagic fevers is primarily supportive. Argentine HF responds to therapy with two or more units of convalescent plasma given within eight days of disease onset. The use of convalescent plasma is investigational, and would most likely not be feasible during a biological attack, due to logistical difficulties and low supply.
Ribavirin has some in vitro and in vivo activity against arenaviridae and bunyaviridae and is available for compassionate use under an investigational new drug (IND) application. The Civilian Working Group for Biodefense recommends that ribavirin therapy be initiated for all suspected cases of VHF (Borio et al., 2002). If subsequent tests lead to a filovirus, flavivirus (ribavirin is ineffective against these viruses), or non-VHF diagnosis, ribavirin should be discontinued at that time.

Slide 54 outlines recommendations by the Civilian Working Group for Biodefense, for ribavirin therapy in patients with clinically evident VHF of unknown etiology, or secondary to arenaviruses or bunyaviruses. The use of ribavirin for VHF is not approved by the FDA and should be administered under an IND protocol. Ribavirin has been shown to be teratogenic in several animal species and, therefore, is classified as a pregnancy category X drug.

The associated mortality of VHF tends to be greater in pregnancy, however. Therefore, the Working Group believes the benefits of ribavirin therapy appear to outweigh the fetal risks in the context of VHF of unknown etiology or secondary to arenaviridae or bunyaviridae. Proper doses of ribavirin have not been established for children, however, the doses listed in slide 54 have been used to treat children with adenovirus pneumonia and hepatitis C and were well tolerated.
Management of Exposed Persons (Slides 55-56)

Following a biological attack, all potentially exposed persons, as well as high-risk and other close contacts should be monitored for symptoms and fever, for 21 days beyond the exposure or last contact with an ill patient. High-risk contacts are those who have had mucous membrane contact with a patient (such as during kissing or sexual intercourse) or have had a percutaneous injury involving contact with the patient's secretions, excretions, or blood. Close contacts are those who live with, shake hands with, hug, process laboratory specimens from, or care for a patient with clinical evidence of VHF prior to initiation of appropriate precautions. Prophylaxis consists mainly of washing exposed body surfaces with soap and irrigating mucous membranes with water or saline.
Some VHF viruses may continue to be present in body fluids for long periods following recovery. Patients recovering from an arenavirus or filovirus infection should therefore refrain from sexual activity for three months after clinical recovery. Yellow fever is the only VHF with a licensed vaccine. Yellow fever antibodies take longer than the three- to six-day incubation period to appear, and thus this vaccine would not be useful for prophylaxis during a biological attack. There is limited experimental evidence that postexposure prophylaxis with ribavirin will delay onset of disease from arenaviruses, but not prevent it. The Department of Defense has a compassionate use protocol for prophylactic administration of oral ribavirin to high-risk contacts of Congo-Crimean hemorrhagic fever patients, and CDC guidelines recommend ribavirin to high-risk contacts of Lassa fever patients. The latter recommendations will be undergoing review shortly, and may be revised. The Civilian Working Group for Biodefense does not recommend the administration of ribavirin to exposed individuals in the absence of signs or symptoms.
Infection Control (Slides 57-58)

Photo: Zairian and CDC clinicians care for a patient with Ebola VHF in the Kikwit General Hospital in Zaire, 1995. Source: CDC Public Health Image Library

Infection control precautions are outlined in slides 57-58. VHF\textsc{s} are transmitted via contact with blood and bodily fluids. Hantavirus\textsc{s} are an exception: infectious virus is not present in blood or excreta at the time of clinical presentation. Health care workers should wash their hands thoroughly prior to donning, and after removing, personal protective equipment (PPE). Hands should be cleaned prior to the removal of facial protective equipment and after the removal of all PPE. Care should be taken to avoid touching mucous membranes during patient care and before washing hands. PPE should be changed between patients. An adjoining anteroom is useful as a site for changing into and removal of protective clothing, supply storage and decontamination of specimen containers.

Airborne precautions require that the patient be placed in a room with negative air pressure, 6 to 12 air changes per hour, air exhausted directly to the outdoors or passed through a high-efficiency particulate air (HEPA) filter before recirculation, and doors kept closed.
In mass casualty and other situations in which the use of negative air pressure rooms may not be feasible, all other infection control precautions (as outlined in slides 51-52) should be followed. Available evidence suggests that in the great preponderance of historical cases, these measures were sufficient to prevent transmission of disease to health care workers, family members, and other patients. The decision to use an N-95 mask versus a powered air purifying respirator (PAPR) should be made after considering the benefits and risks of each option in the specific situation. Disadvantages of the N-95 masks include the difficulty in ensuring a reliable face-mask seal with each use and impossibility of effective use by bearded individuals. PAPRs, on the other hand, are more expensive, bulky, impair voice communication, and may increase the risk of needle-stick injuries. Dedicated medical equipment (e.g., stethoscopes) should be used for VHF patients, to decrease the risk of transferring infection to other patients. Point-of-care analyzers are small, portable devices that can be used at the bedside for routine laboratory tests; they should be used if available, to minimize exposure of laboratory personnel to infectious specimens. If point-of-care analyzers are unavailable, specimens should be double-bagged, hand-carried to the laboratory, and pre-treated with Triton X-100, as this may decrease viral titers. Pretreatment with Triton X-100 does not significantly alter serum electrolytes, urea nitrogen, creatinine, and glucose or liver function test results. Embalming of deceased VHF patients should not be done. Autopsies should be performed only by specially trained persons using VHF-specific barrier precautions, HEPA-filtered respirators (N-95 masks or PAPRs) and negative-pressure rooms.
Summary of Key Points

Viral Hemorrhagic Fevers
Summary of Key Points

- A thorough travel and exposure history is key to distinguishing naturally occurring from intentional viral hemorrhagic fever cases.
- Viral hemorrhagic fevers can be transmitted via exposure to blood and bodily fluids.

Viral Hemorrhagic Fevers
Summary of Key Points

- Contact and airborne precautions are recommended for health care workers caring for infected patients.
- Diagnostic laboratory testing for viral hemorrhagic fevers must be done in a bio-safety level 4 lab (i.e., CDC); contact the local or state health department before specimen collection in suspected cases.

Case Studies and Reports

Viral Hemorrhagic Fevers
Case Studies and Reports


MMWR Morb Mortal Wkly Rep 2001 50(5)
Summary: Category A Critical Agents

- Decontamination of exposed persons
  - Showering or washing thoroughly with soap and water adequate for most; bleach not necessary

- Infection control
  - Standard precautions – all cases
  - Airborne and contact precautions – smallpox and viral hemorrhagic fevers
  - Droplet precautions – pneumonic plague
Resources

- Centers for Disease Control and Prevention
- Bioterrorism Web page: http://www.bt.cdc.gov/
- CDC Office of Health and Safety Information System (personal protective equipment)
  http://www.cdc.gov/od/oha/
- USAMRIID – includes link to on-line version of Medical Management of Biological Casualties Handbook
  http://www.usamriid.army.mil/
- Johns Hopkins Center for Civilian Biodefense Studies
  http://www.hopkins-biodefense.org
  Fact sheets and links to other info, including JAMA series from Working Group on Civilian Biodefense and BT-related anthrax case studies

- Office of the Surgeon General: Medical Nuclear, Biological and Chemical Information
  http://www.nbc-med.org

- St. Louis University Center for the Study of Bioterrorism and Emerging Infections – fact sheets and links
  http://bioterrorism.slu.edu

- Public Health - Seattle & King County
  http://www.metrokc.gov/health

- American College of Physicians – links to BT resources, including decision support tools and palm documents
  http://www.acponline.org

- Self-Assessment (case scenarios – chemical and biological)
  http://www.acponline.org/bioterr/self_assessment.htm

In Case of An Event...

The next two slides highlight Web-based resources valuable to clinicians during a BT event. Most of the links have been presented previously in the resources following the different sections of this curriculum. They are included here again because they contain answers to questions clinicians may have during the course of an event – updates on disease investigations and threats, current testing, treatment and prophylaxis recommendations, and contact numbers for additional information and reporting.
References

General Bioterrorism Information and Web sites


Bioterrorism Preparedness and Response


Diseases of Bioterrorist Potential
Advisory Committee on Immunization Practices (ACIP). Use of smallpox (vaccinia vaccine), June 2002: supplemental recommendation of the ACIP.

http://www.bt.cdc.gov/ncidod/hip/GUIDE/infectcont98.htm


CDC. Considerations for distinguishing influenza-like illness from inhalational anthrax. MMWR 2001;50(44):984-986.


Working Group on Civilian Biodefense Consensus Recommendations


**Psychological Aftermath of Crisis**


