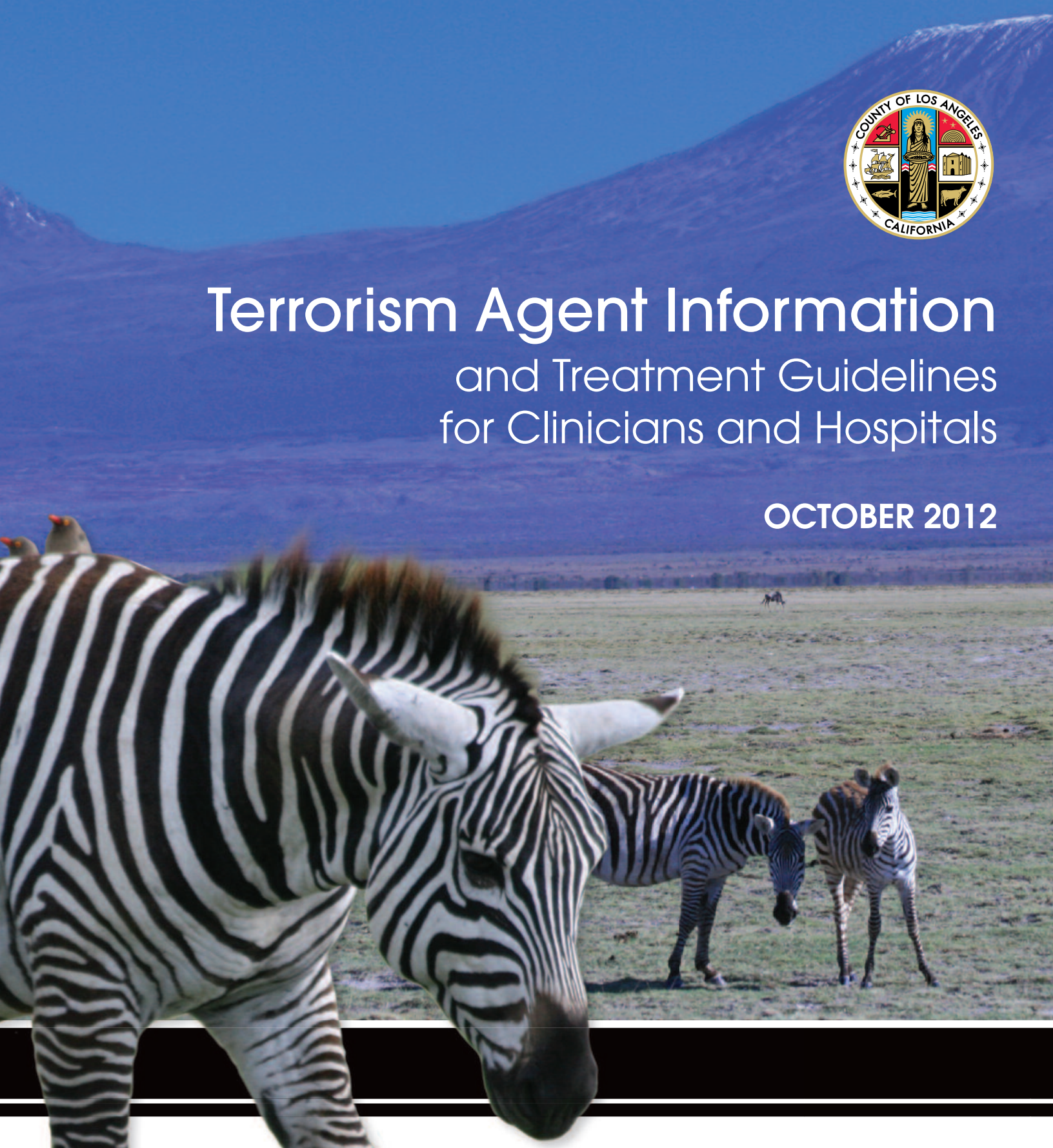

Terrorism Agent Information

and Treatment Guidelines for Clinicians and Hospitals

OCTOBER 2012

Published by:

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LOS ANGELES COUNTY

COUNTY OF LOS ANGELES
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IN THE EVENT OF A POSSIBLE BIOTERRORISM INCIDENT, PLEASE CALL THE:

Los Angeles County Department of Public Health

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After Hours (County Operator)	213-974-1234

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IMMEDIATELY CALL
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Acute Communicable Disease Control Program

Monday – Friday (8am – 5 pm):
(213) 240-7941

After Hours:
(213) 974-1234

Ask to Speak with the Public Health Physician on call

Other City and County Health Departments

Phone numbers are listed below

Long Beach City
Department of Health & Human Services
(562) 570-4000 (Business hours)
(562) 570-4302 (Epidemiology)
(562) 435-6711 (After hours)

Orange County
Health Care Agency
(714) 834-4722 (Business hours)
(714) 834-8180 (Epidemiology)
(714) 628-7008 (After hours)

Pasadena City
Public Health Department
(626) 744-6089 (Business hours)
(626) 744-6043 (After hours)

Riverside County
Health Services Agency
Department of Public Health
(951) 358-5107 (Business hours)
(951) 830-8041 (After hours)

San Bernardino County
Department of Public Health
(800) 722-4794 (Epidemiology)
(909) 356-3805 (After hours)

Ventura County
Public Health Department
(805) 981-5201 (Business hours)
(805) 656-9432 (After hours)

Compiled and edited by the staff of the Los Angeles County Department of Public Health and the Los Angeles County Emergency Medical Services Agency.

Acknowledgements:

The following documents were used in preparing this document:

California Department of Health Services, Surveillance and Epidemiology Response Plan, December 2002

California Department of Health Services, California Hospital Bioterrorism Response Planning Guide, October 2001

Santa Clara County Public Health Department, Zebra Packet: Bioterrorism Information for Clinicians, November 2011

Ventura County Health Care Agency, Public Health Division, Guidelines for Ventura County Hospitals During Biological Emergencies, March 2001

Saint Louis University Center for the Study of Bioterrorism and Emerging Infections, Bioterrorism Planning Guide, June 2002

Centers for Disease Control (CDC) fact sheets

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INTRODUCTION

Terrorism has become an undeniable reality in the United States today. In addition to conventional weapons, there is increasing concern that criminal individuals, terrorist groups, or nations may resort to the use of biological, chemical, or radiological weapons. There is a long history of use of biological and chemical weapons on the battlefield. While these weapons have been used on occasion in the United States, the events of September 11, 2001 and the anthrax mailings of October 2001 have made the potential danger evident. Physicians, nurses, first responders and other health care personnel in American cities can no longer afford to be uninformed about biological, chemical and radiological weapons. Rapid recognition of a clinical syndrome consistent with a bioterrorist agent will facilitate not only appropriate early treatment of the victim, but will give public health officials time to conduct a rapid epidemiologic investigation to identify other exposed individuals and deliver appropriate prophylactic measures to prevent or ameliorate disease. For many biological weapons, a narrow window of opportunity exists during which a prophylactic measure can be administered to prevent or treat disease. Delay in recognition will cost lives. Delayed recognition of contagious bioterrorist agents, chemical agents, and radiological contamination will harm the affected patients by depriving them of the necessary appropriate treatment or decontamination and lead to infection or contamination of health care workers.

In prior terrorist attacks 80% of victims who presented for healthcare had not been exposed or infected with the agent in question, but were suffering from psychological effects. Such psychological effects can mimic the signs and symptoms associated with the agent of concern. If such persons are not appropriately recognized and triaged they will complicate diagnostic issues and deplete pharmaceutical stockpiles.

Clinicians, as well as being first responders, must also be aware that they may be dealing with the perpetrator of the incident. Terrorists working with weapons of mass destruction (WMD) may be accidentally exposed to the agent during the perpetration of the attack. Clinicians should consider this possibility when dealing with patients exposed to WMD and act accordingly.

The Los Angeles County Department of Public Health (LAC DPH) has a long history of disaster preparedness and has been involved in preparing for terrorist events since 1998. The Public Health approach to terrorism preparedness is to develop an "all-hazards approach" and to emphasize a "dual purpose" approach to utilization of resources. Steps taken to combat a potential terrorist event also enhance preparedness for other types of disasters including natural disasters and natural disease outbreaks.

Bioterrorism attacks are likely to present as acute outbreaks of an unusual syndrome. Also, the outbreak of an illness in the "wrong" season or geographic area should raise suspicion. Clinical syndromes of bioterrorism can present as: acute severe pneumonia or respiratory distress, encephalopathy, acute onset of neuromuscular symptoms, otherwise unexplained rash with fever, fever with mucous membrane bleeding, unexplained acute icteric syndromes and massive diarrhea with dehydration and collapse. Atypical host characteristics would be expected. Thus

illness affecting the young (<50 years), immunologically intact, those with no underlying illness, and no recent history of international travel or other exposure to a potential source of infection should spark concern. Serious, unexpected, acute illness may be characterized by any of the following features: abrupt onset, prostration, cardiovascular collapse, respiratory distress, obtundation/change in mental status and disseminated intravascular coagulation. Multiple similarly presenting cases, especially geographically associated or closely clustered in time, would suggest a bioterrorist attack. Finally increases in common syndromes occurring out of season, such as influenza-like illness during summer, should be noted and reported.

This manual seeks to provide a comprehensive resource for clinical personnel to become educated on various aspects of biological, chemical, and radiological terrorism and to serve as an emergent guide book on what to do and where to seek information in the event of an attack. This manual also provides information for clinicians on how to report potential exposures to the Los Angeles County Department of Public Health.

In addition to the hardcopy, an electronic PDF version of this manual is also maintained on the LAC Acute Communicable Disease Control Program website:
http://publichealth.lacounty.gov/acd/HCPmaterials.htm
The electronic copy will be updated as new information becomes available.

To request a hardcopy of this manual and/or other educational material, planning guidelines, resources and protocols for professional healthcare providers, visit:
http://publichealth.lacounty.gov/acd/HCPmaterials.htm

This third edition updates the July 2006 edition and incorporates updates such as the definition of the Public Health Technical Advisory Group (TAG), and updates to the anthrax, botulism, plague, smallpox, ricin, glanders and melioidosis, chemical terrorism chapter, including the public health laboratory protocol for specimen collection for a chemical exposure event.

Additional resources for updates and information for professional healthcare providers:

LAC DPH Acute Communicable Disease Control Program
http://publichealth.lacounty.gov/acd/index.htm

LAC DPH Emergency Preparedness Response Program
http://publichealth.lacounty.gov/eprp/

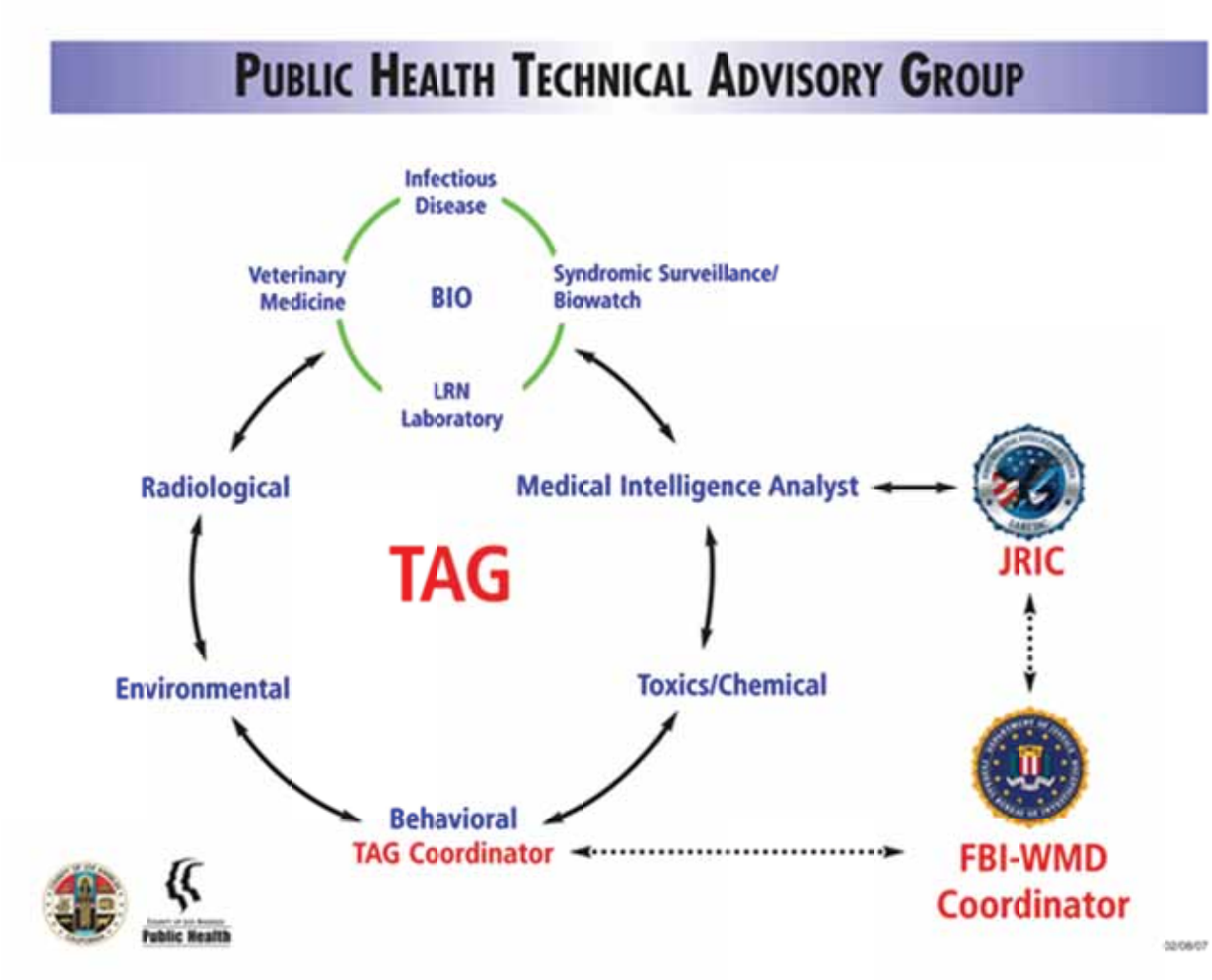
LAC DPH Laboratory
http://publichealth.lacounty.gov/lab/index.htm

LAC DHS Emergency Management Service Agency
http://ems.dhs.lacounty.gov/

PUBLIC HEALTH TECHNICAL ADVISORY GROUP (TAG)

The Los Angeles County Department of Public Health operates a 24/7 specialized medical team with expertise in the field of terrorism and weapons of mass destruction (WMD). This team, known as the WMD Technical Advisory Group (TAG), is comprised of medical personnel with security clearances whose work routinely involves the early detection of biological, chemical, and radiological threats within the County of Los Angeles. The TAG is linked to both the FBI and the Joint Regional Intelligence Center (JRIC), permitting real-time sharing and analysis of threat information and intelligence. The TAG responds to reports of individuals suspected of exposure to a WMD agent, reports of patients with possible clinical manifestations characteristic of a WMD agent, or other threats involving the use of a WMD. (See Figure 1)

Figure 1



SECTION I

BIOTERRORISM

INFORMATION and TREATMENT
GUIDELINES for HOSPITALS and CLINICIANS

INTRODUCTION

The threats of biological, chemical, radiological and nuclear terrorism within the United States continue to be a real concern and a top priority for the Los Angeles County Department of Public Health (LAC DPH). LAC DPH plays a key role in protecting the public's health and serves as a resource to hospitals and clinician to facilitate the early detection of terrorism agents.

The LAC DPH developed this handbook as a reference document for healthcare providers in various settings and to supplement their hospital or facility emergency preparedness plans. This handbook is organized into three primary sections. The first section provides an overview of bioterrorism, including bioterrorism event definitions and reporting requirements. The second section contains detailed information and treatment guidelines for those potential chemical agents that are of highest concern. The third section contains information on treatment guideline for nuclear and radiological events.

Hospitals and clinicians have the first opportunity to recognize and initiate a response to a bioterrorism attack. Healthcare facilities need to have infection control policies in place authorizing the infection control practitioner or designee to rapidly implement prevention and control measures in response to a suspected outbreak. In the case of a suspected terrorist event, communication must include infection control practitioners, healthcare administration, local and state health departments, the Joint Regional Intelligence Center (JRIC), the Federal Bureau of Investigation (FBI) field office and the Centers for Disease Control and Prevention (CDC).

A major component of a strong public health infrastructure is the capacity to monitor the ever-changing picture of disease in the community. While many new and improved methods of disease surveillance are currently being developed and implemented, public health is dependent on clinicians to promptly report all reportable diseases. A list of reportable diseases and procedures for disease reporting is located on the LAC DPH Acute Communicable Disease Control Program website: http://www.lapublichealth.org/acd/

Individual healthcare providers will be the first to recognize and respond to a bioterrorist event. **Early detection by astute clinicians and rapid reporting to the local health department will be critical in minimizing the impact of a bioterrorism event or other infectious disease emergency.**

In November 2001, Title 17 of the California Code of Regulations was amended to mandate immediate reporting by healthcare providers and clinical laboratory directors of the diseases/conditions/agents that pose the most serious threat for bioterrorism. For a complete list of reportable diseases and to report a disease visit http://www.lapublichealth.org/acd/

The diseases/conditions having potential bioterrorist implications that healthcare providers must report immediately (including nights, weekends and holidays) by telephone to the local health department are suspected or confirmed cases of:

- **Anthrax**
- **Botulism**
- **Brucellosis**
- **Plague**
- **Smallpox**
- **Tularemia**
- **Varicella deaths**
- **Viral hemorrhagic fevers**
- **Occurrence of any unusual disease**
- **Outbreaks of any disease**

Healthcare providers are defined as physicians, surgeons, veterinarians, podiatrists, nurses, nurse practitioners, nurse midwives, school nurses, infection control practitioners, physician assistants, dentists, coroners and medical examiners. The requirement for laboratories to report these diseases does not replace the healthcare provider's legal obligation to report. Moreover, public health action aimed at finding the source of an outbreak and implementing preventive treatment should not be delayed until a definitive laboratory diagnosis is made. Healthcare providers must immediately report suspected cases. Detailed information about reporting procedures can be found at http://www.lapublichealth.org/acd/.

Following notification, the local public health department will arrange for specialized laboratory testing, provide guidelines for treatment, prophylaxis, and infection control, begin a public health investigation, and activate local, state and federal emergency response systems.
Potential biological agents are numerous. Attention has been focused on those agents that would have the greatest impact on health and security. These agents are highly contagious or have the potential to be engineered for widespread dissemination via small-particle aerosols.

The CDC has classified potential bioterrorism agents into three categories, depending on easiness of dissemination or transmission, and the extent/severity of morbidity and mortality they impose. These are listed below. Of these, the Category A threats are considered the highest risk and Category C are considered emerging threats for disease.

Category A

Highest priority agents include those that:

- Can be easily disseminated or transmitted from person-to-person
- Cause high mortality with greatest potential for major public health impact
- May cause public panic and social disruption
- Require special action for public health preparedness

Category A agents include:

- Anthrax (*Bacillus anthracis*)
- Botulism (*Clostridium botulinum* toxin)
- Plague (*Yersinia pestis*)
- Smallpox (variola major)
- Tularemia (*Francisella tularensis*)

- Viral hemorrhagic fevers (filoviruses [e.g., Ebola, Marburg] and arenaviruses [e.g., Lassa, Machupo])

Category B

Second highest priority agents include those that:

- Are moderately easy to disseminate
- Cause moderate morbidity and low mortality
- Require specific laboratory diagnostic enhancements and enhanced disease surveillance

Category B agents include:

- Brucellosis (*Brucella* species)
- Epsilon toxin of *Clostridium perfringens*
- Food safety threats (e.g., *Salmonella* species, *Escherichia coli* O157:H7, *Shigella*)
- Glanders (*Burkholderia mallei*)
- Melioidosis (*Burkholderia pseudomallei*)
- Psittacosis (*Chlamydia psittaci*)
- Q fever (*Coxiella burnetii*)
- Ricin toxin from *Ricinus communis* (castor beans)
- Staphylococcal enterotoxin B
- Typhus fever (*Rickettsia prowazekii*)
- Viral encephalitis (alphaviruses [e.g., Venezuelan equine encephalitis, eastern equine encephalitis, western equine encephalitis])
- Water safety threats (e.g., *Vibrio cholerae*, *Cryptosporidium parvum*)

Category C

Are agents with the third highest priority that include emerging pathogens that could be engineered for mass dissemination because of:

- availability
- ease of production and dissemination
- potential for high morbidity and mortality rates and major health impact

Category C agents include:

- Nipah virus
- Hantavirus

Source: Center for Disease Control and Prevention, Emergency Preparedness and Response, Bioterrorism Agents available at: http://www.bt.cdc.gov/agent/agentlist-category.asp

The focus of this document is on the Category A agents and a few Category B agents including Brucellosis, Glanders, Melioidosis, Q Fever and Ricin due to the terrorism interests in these agents.

Reporting to the Health Department

To report a case or outbreak of any disease, contact the Communicable Disease Reporting System Hotline

Tel: 888-397-3993 FAX: 888-397-3778

IN THE EVENT OF A POSSIBLE BIOTERRORISM INCIDENT, PLEASE CALL THE:

Los Angeles County Department of Public Health

Business Hours	(8am-5pm)	213-240-7941
After Hours (County Operator)		213-974-1234

Ask to Speak with the Public Health Physician On-Call

Bioterrorism Event Description

The following table is designed to assist public health officials in identifying possible bioterrorism events. For the clinician, it is intended to reflect the importance of immediate notification to the Public Health Department of any of the reportable diseases listed.

BIOTERRORISM EVENT	HIGHLY SUGGESTIVE OF BIOTERRORISM	MODERATELY SUGGESTIVE OF BIOTERRORISM	NOTES
ANTHRAX (inhalation)			
Single Case	✓		Definitely diagnosed or strongly suspected case.
ANTHRAX (Cutaneous)			
Single Case	✓		In a patient without compatible risk factors for naturally occurring disease.
PLAGUE (Pneumonic) or TULAREMIA			
Single Case		✓	Definitively diagnosed and occurring in a patient with no known compatible risk factors.
Greater Than One Case	✓		With at least 1 laboratory confirmed case, no known risk factors, and occurring in a brief time period.
SMALLPOX			
Single Case	✓		Definitely diagnosed or strongly suspected case.
VIRAL HEMORRHAGIC FEVER			
Single Case	✓		In a patient with no international travel history.
BRUCELLOSIS			
Cluster of Cases		✓	Occurring in persons with no known compatible risk factors.
BOTULISM			
Number Above Baseline		✓	Presumptively diagnosed cases with no known compatible risk factors occurring in a brief time period.
RESPIRATORY ILLNESS			
Number Above Baseline		✓	Unexplained severe respiratory illness requiring hospitalization occurring outside the usual flu season.
DEATHS			
Number Above Baseline		✓	Unexplained deaths occurring in a brief time period within a defined geographic region.
ANY UNUSUAL EPIDEMIOLOGIC FEATURES		✓	The occurrence of any unusual epidemiologic features in a seemingly natural outbreak (e.g., absence of the usual risk factors for disease, or the presence of unusual risk factors or greater than expected morbidity or mortality).

Source: Adapted from the State of California's Surveillance and Epidemiologic Response Plan
http://www.dhs.ca.gov/ps/dcdc/bt/index.htm

See the back of this manual for poster inserts on:

1. **Bioterrorism Syndromes**
2. **Evaluating Patients for Smallpox**

Both Posters will be available online at **http://publichealth.lacounty.gov/acd/HCPmaterials.htm**

Isolation Guidelines

Patient Management IMPORTANT PHONE NUMBERS Infectious Diseases: _____ - _____ Infection Control: _____ - _____ LACDPH Acute Communicable Disease Control Unit Business Hours: (213) 240-7941 After Hours: (213) 974-1234	BACTERIAL AGENTS	Anthrax	Brucellosis	Cholera	Glanders	Bubonic Plague	Pneumonic Plague	Tularemia	Q Fever	VIRUSES	Smallpox	Viral Encephalitis	Viral Hemorrhagic Fever	BIOLOGICAL	Botulism	Ricin	T-2 Mycotoxins	Staph. Enterotoxin
Isolation Precautions																		
Standard Precautions for all aspects of patient care		x	x	x	x	x	x	x	x		x	x	x		x	x	x	x
Contact Precautions (gown and gloves: wash hands after)				x***	x*	x*					x		x				x*	
Airborne Precautions (negative pressure room and N95)											x		x**					
Droplet Precautions (surgical mask)							x						x**					
Patient Placement																		
No restrictions		x	x	x	x			x	x			x			x	x	x	x
Cohort "like" patients when private room is not available				x***	x*	x	x				x		x				x*	
Private room				x***	x*	x*	x				x		x				x*	
Negative pressure											x		x**					
Door closed at all times											x		x**					
Patient Transport																		
No restrictions		x	x	x	x	x		x	x			x			x	x	x	x
Limit movement to essential medical purposes only				x***	x*	x*	x				x		x				x*	
Place mask on patient to minimize dispersal of droplets							x				x		x**					
Cleaning and Disinfection																		
Routine cleaning of room with hospital approved		x	x	x	x	x	x	x	x		x	x			x	x	x	x
Disinfect surfaces with 10% bleach solution or phenolic													x					
Dedicated equipment (disinfect prior to leaving room)					x***	x*	x*				x		x				x*	
Linen management as with all other patients		x	x	x	x	x	x	x	x			x	x		x	x	x	x
Linens autoclaved or laundered in hot water with bleach											x							
POST-MORTEM CARE																		
Follow principles of Standard Precautions		x	x	x	x	x	x	x	x		x	x	x		x	x	x	x
Droplet Precautions (surgical mask)							x											
Contact Precautions (gown and gloves)					x*	x*					x		x				x*	
Avoid autopsy or use Airborne Precautions and HEPA							x				x		x**					
Routine terminal cleaning of room with hospital approved		x	x	x	x	x	x	x	x		x	x	x		x	x	x	x
Disinfect surfaces with 10% bleach solution or phenolic													x					
Minimal handling of body; seal body in leak-proof material													x					
Cremate body whenever possible											x							
DISCONTINUATION OF ISOLATION																		
48 hours of appropriate antibiotic and clinical							x											
Until all scabs separate											x							
Until skin decontamination completed (1 hour contact)																	x	
Duration of illness				x***	x*	x*							x					

Standard Precautions – Prevent direct contact with all body fluids (including blood), secretions, excretions, non-intact skin (including rashes) and mucous membranes. Standard Precautions routinely practiced by healthcare providers include: splash/spray and gowns to protect skin and clothing during procedures.

*Contact Precautions needed only if patient has skin involvement (bubonic plague: draining bubo) or until decontamination of skin is complete (T2 Mycotoxins).

**A surgical mask and eye protection should be worn if you come within 3 feet of patient. Airborne Precautions are needed if patient has cough, vomiting, diarrhea or hemorrhage.

***Contact Precautions needed only if the patient is diapered or incontinent.

Designed by LTC Suzanne E. Johnson, RN, MSN, CIC, Walter Reed Army Medical Center; Revised by Center for the Study of Bioterrorism and Emerging Infections

Standard Precautions

Standard precautions are employed in the care of ALL patients.

- Wash hands after patient contact
- Wear gloves when touching blood, body fluids, secretions, excretions and contaminated items
- Wear a mask and eye protection, or a face shield and a gown during procedures likely to generate splashes or sprays of blood, body fluids, secretions or excretions
- Handle used patient-care equipment and linen in a manner that prevents the transfer of microorganisms to people or equipment
- Use care when handling sharps and use a mouthpiece or other ventilation devices as an alternative to mouth-to-mouth resuscitation when practical
- Ensure that the hospital has adequate procedures for the routine care, cleaning and disinfection of environmental surfaces, beds, bedrails, bedside equipment, and other frequently touched surfaces
- Handle, transport and process used linen soiled with blood, body fluids, secretions and excretions in a manner that prevents skin and mucous membrane exposures and contamination of clothing and that avoids transfer of microorganisms to other patients and environments.
- Take care to prevent injuries when using needles, scalpels and other sharp instruments or devices
- Place a patient who contaminates the environment or who does not (or cannot be expected to) assist in maintaining appropriate hygiene or environmental control in a private room. If a private room is unavailable, consult with infection control professionals regarding patient placement or other alternatives

Airborne Precautions

Standard precautions plus:

- Place the patient in a private room that has a monitored negative airflow room, with six to twelve air exchanges per hour, and appropriate filtration of air (high efficiency particulate air) before it is discharged from the room
- Wear a properly fitted N95 or higher quality mask when entering the room
- Limit movement and transport of the patient. Place a mask on the patient if s/he needs to be moved from their room

Droplet Precautions

Standard precautions plus:

- Place the patient in a private room or cohort them with someone with the same infection. If not feasible, maintain at least 3 feet between patients
- Wear a mask when working within 3 feet of the patient
- Limit movement and transport of the patient. Place a mask on the patient if s/he needs to be moved from their room.

Contact Precautions

Standard Precautions plus:

- Place the patient in a private room or cohort them with someone with the same infection if possible
- Wear gloves when entering the room. Change gloves after contact with infective material. Remove gloves before leaving the patient's room
- Wear a gown when entering the room if contact with patient is anticipated or if patient has diarrhea, colostomy or wound drainage not covered by a dressing
- Limit the movement and transport of patient from the room
- Daily cleaning of patient-care objects, bedside equipment and frequently touched surfaces
- Dedicate use of medical equipment. If not feasible adequate disinfection between patients is necessary

VHF-specific Barrier Precautions

- Strict adherence to hand hygiene
- Place the patient in a private room that has monitored negative airflow room, with six to twelve air exchanges per hour, and appropriate filtration of air (high efficiency particulate air filter) before it is discharged from the room.
- Wear a properly fitted N95 mask or higher quality mask, double gloves, impermeable gown, leg and shoe covering, face shield and goggles when entering the room
- Dedicate use of medical equipment
- Disinfect environment with an EPA-registered hospital disinfectant or a 1:100 dilution of household bleach
- Limit the movement or transport of the patient from the room

(Please note these precautions are more stringent than recommended in health care settings in developing nations). For more information see
http://www.cdc.gov/ncidod/dvrd/spb/mnpages/vhfmanual.htm

For more information on Isolation precautions, please see
http://www.cdc.gov/hicpac/pdf/isolation/Isolation2007.pdf

ANTHRAX

ALL SUSPECTED CASES OF ANTHRAX MUST BE REPORTED IMMEDIATELY TO THE DEPARTMENT OF PUBLIC HEALTH ACUTE COMMUNICABLE DISEASE CONTROL PROGRAM:

Monday - Friday (8am – 5pm)
(213) 240-7941

After Hours (County Operator)
(213) 974-1234

Ask to Speak with the Public Health Physician On-Call

Quick Reference: Anthrax *(Bacillus anthracis)*

ALL SUSPECTED CASES OF ANTHRAX MUST BE REPORTED IMMEDIATELY TO THE DEPARTMENT OF PUBLIC HEALTH ACUTE COMMUNICABLE DISEASE CONTROL PROGRAM

During Business Hours	213-240-7941
After Hours (County Operator)	213-974-1234

Epidemiology:

- Anthrax disease occurs in humans through 3 routes of infection: inhalational, cutaneous, and gastrointestinal.
- However there are 4 major clinical presentations: meningitis, inhalational, cutaneous, and gastrointestinal. Cutaneous anthrax is the most common naturally occurring form and results from direct contact with infected animals or animal products. Gastrointestinal anthrax results from ingestion of inadequately cooked meat from infected animals and is rare. Meningitis is most likely to occur after inhalational exposure but can occur after cutaneous or gastrointestinal infection.
- Anthrax spores are highly resistant to physical and chemical agents; spores can persist in the environment for years
- In the United States, in October 2001, anthrax-contaminated mail resulted in 22 cases (inhalational and cutaneous) with 5 deaths.
- Sporadic cases have occurred in U.S. related to animal hides and drumming. Outbreaks in heroin users have occurred in Europe.

Clinical:

Inhalational anthrax:

- Incubation period 1 -7 days (range up to 43 days in humans and 60 days in non-human primates)
- Presence of hemorrhagic mediastinal adenopathy; development of hemorrhagic pleural effusions; pulmonary parenchymal disease (infiltrates or consolidation).
- Mediastinal widening by chest X-ray or CT in previously healthy, non-trauma patient is virtually pathognomonic
- A newly proposed 3 level clinical staging system describes an early-prodromal stage (nonspecific flu-like symptoms), an intermediate-progressive stage, and a late-fulminant state (shock, respiratory failure). This new staging system can help distinguish those patients with a high probability of cure (intermediate-progressive stage) from those with a lower probability of cure (late-fulminant state).
- Without a high index of suspicion, the diagnosis of inhalational anthrax is difficult during nonspecific prodromal illness.
- Mortality ranges from 90% (historic) to 45% (2001 attack)

Anthrax Meningitis:

- Hemorrhagic meningitis in 50% of inhalational anthrax cases
- Was the presenting manifestation of the index case in the 2001 anthrax attacks
- CSF with presence of hemorrhage and long box-car shaped Gram-positive rods
- Treat with drugs that have CSF penetration.

Cutaneous anthrax:

- Incubation period 1 -7 days (up to 12 days)
- Presents as papule, progressing to vesicle and ulcer with black eschar over 3-10 days

Gastrointestinal Anthrax:

- Incubation period 1 -7 days (up to 12 days)
- Presents initially with nonspecific nausea, vomiting, anorexia, and fever
- Progresses to abdominal pain, hematemesis, bloody diarrhea, and ascities

Laboratory Diagnosis:

- Gram stain of primary specimens shows Gram-positive non-motile bacilli, occurring singly or in short chains, often with squared-off ends ("bamboo rod" appearance); additionally a capsule may be visible as clear zones around the bacilli or be demonstrated by negative staining with India ink on a wet mount. In advanced disease, Gram stain of unspun blood may be positive. Sputum is rarely positive.
- Distinguishing characteristics on culture include: non-hemolytic, non-motile, spore-forming rods; encapsulated bacteria may be seen from positive blood culture bottles and from growth on specialized solid media (not sheep-blood agar) under elevated CO_2 conditions.
- Primary isolation and Gram stain can be performed at the hospital laboratory (Sentinel/Level A, BSL-2)
- Processing of environmental specimens and powders requires BSL-3 laboratory facilities and should not be performed in clinical laboratories; contact the Public Health Laboratory 562-658-1300 or after hours at 213-974-1234.

Treatment:

- Prompt initiation of antibiotic therapy and antibiotic susceptibility testing
- Ciprofloxacin or doxycycline, combined with 1 or 2 other antibiotics for inhalational anthrax, are the antibiotics of choice for penicillin-resistant anthrax or for empiric therapy while awaiting susceptibility results; treatment should be continued for at least 60 days.
- Ciprofloxacin is favored over doxycycline for treatment of anthrax cases with serious systemic illness such as inhalational anthrax, gastrointestinal anthrax, or cutaneous anthrax with systemic involvement; cases with suspected meningeal involvement; and fulminant cases with bacteremia.
- Early and aggressive drainage of pleural effusions in all patients with inhalational anthrax is recommended.
- Immunotherapeutic: Anthrax immune globulin (AIG) and Raxibacumabs (monoclonal antibody) are available through the CDC's Strategic National Stockpile

Management of Exposed Persons:

- If vaccine is available, all exposed persons (as determined by local and state health departments) should be vaccinated with 3 doses of anthrax vaccine (0, 2 weeks, and 4 weeks)
- Start antibiotic prophylaxis immediately after exposure with ciprofloxacin (or acceptable alternative fluoroquinolone) or doxycycline. If strain is penicillin susceptible, therapy can be changed to penicillin or amoxicillin.
- Compliance with the full course of antibiotic prophylaxis must be reinforced regardless of the perceived level of exposure; no "short courses" should be administered.
- For PEP, the CDC recommends 60 days of selected oral antibiotics in conjunction with a 3-dose regimen (0, 2 weeks, 4 weeks) of anthrax vaccine.

Infection Control:

- Standard Precautions - anthrax is NOT transmitted from person-to-person

Introduction and Epidemiology

Anthrax is a disease caused by *Bacillus anthracis* that can infect animals, including man. In humans, anthrax disease occurs through 3 routes of infection: inhalational, cutaneous, and gastrointestinal. There are four major clinical presentations of anthrax disease: inhalational, meningitis, cutaneous, and gastrointestinal. Transmission to humans usually occurs through contact with infected animals or contaminated animal products. In September 2001, letters containing anthrax spores were sent via the United States mail to media and Senate offices on the East Coast. Twenty-two confirmed or suspected anthrax cases (11 inhalational and 11 cutaneous) resulted, with five deaths from inhalational anthrax.

The spore form of *B. anthracis* is highly resistant to physical and chemical agents. The organism has been shown to persist for decades in soil and in factories contaminated during the processing of infected animal products. Animal products that can transmit anthrax include wool, hair, meat, bones, bone-meal, hides, or other contaminated foodstuffs. Soil is the major reservoir for anthrax.

Although human anthrax is infrequent and sporadic in the United States, human cases (primarily cutaneous) continue to be reported from Africa, Asia, Europe, and the Americas. While anthrax-contaminated soil exists in many foci throughout the United States, the number of cases reported annually, prior to the 2001 bioterrorism-related outbreak, had declined over the last five decades; From 1980 through 2000, only seven cases of anthrax were reported to the Centers for Disease Control and Prevention (CDC). However sporadic cases have occurred. Inhalational and gastrointestinal anthrax was reported in the U.S. in 2006 and 2009 associated with animal hides and a drumming event. In 2011, a case of inhalational anthrax occurred in Minnesota, thought to be natural acquired. Anthrax has also been associated with heroin use in a large outbreak occurring in Scotland, England, and Germany between 2009 and 2011. Most patients had skin and soft tissue infections that were not typical of other cutaneous anthrax cases. There are no data to support person-to-person transmission of anthrax.

A suspected case of anthrax in a patient without a clear exposure history (e.g., a traveler returning from an area with known animal cases or a person with exposure to imported animal hides) may be the first clue of a bioterrorist attack. Therefore, even a single, suspect case should be immediately notified to the Department of Public Health Acute Communicable Disease Control Unit (Business Hours: (213) 240-7941 or After Hours: (213) 974-1234).

Significance as a Potential Bioterrorist Agent

- Anthrax was successfully used as a bioterrorist agent in the United States in September 2001, resulting in 22 cases, 5 deaths, and massive societal disruption
- Anthrax has been weaponized by many countries during the last 50 years, including the United States (during the 1950s) and Iraq during the 1990 Gulf War
- Accidental release of anthrax from military facility into the air over the city of Sverdlovsk, Russia in 1979 resulted in civilian deaths
- Anthrax is easy to cultivate and spores are readily produced

- Anthrax spores are highly resistant to heat and disinfection
- If aerosolized spores are inhaled, a severe hemorrhagic mediastinitis can occur with high mortality rate despite appropriate treatment
- Currently, anthrax vaccine is in limited supply in the United States

Clinical Manifestations

Clinical manifestations of anthrax infections resulting from a bioweapons attack will depend on the method of dissemination. An aerosol release would result in most infected individuals presenting with symptoms of inhalational anthrax, with fewer having the cutaneous form of the disease. High-dose powder dissemination, i.e., letters contaminated with finely milled spores, resulted in cases of both inhalational and cutaneous anthrax in the 2001 anthrax attacks. A terrorist may present with cutaneous or inhalational anthrax after working with the agent. Therefore, any anthrax case should raise suspicions. There is little information on the potential effectiveness of intentional food or water contamination in causing gastrointestinal anthrax. Gastrointestinal anthrax is extremely rare and requires the ingestion of vegetative cells such as those found in infected animal flesh. Unlike spores, vegetative cells do not survive for long periods in the environment. Studies have shown that when animals are given high doses of anthrax spores by a feeding tube they do not develop gastrointestinal anthrax. However, heavy contamination of food with spores could potentially cause inhalational anthrax if spores were inhaled during ingestion.

Inhalational Anthrax

Presenting findings include acute hemorrhagic mediastinal adenopathy, pulmonary infiltrate with blood pleural effusions, or pulmonary parenchymal disease after inhalation of aerosolized *B. anthracis* spores. Inhalational anthrax does not usually present as an acute pneumonia. CT scans without contrast were more sensitive that chest x-rays for identifying mediastinal adenopathy due to anthrax in the 2001 anthrax attacks.

Incubation period
Illness usually occurs within 1-7 days of exposure (possibly up to 43 days). Viable spores have been found in mediastinal lymph nodes of nonhuman primates up to 100 days following aerosolized exposure.

Signs and Symptoms
Historically, inhalational anthrax was divided into an initial (early) and acute (late) stage, where the patients who developed into the acute phase progressed rapidly to death. However, based on the 2001 inhalational anthrax cases, a new 3 stage clinical staging system was proposed (Lucey D.) which includes an "intermediate-progressive" stage when blood cultures are positive, mediastinal adenopathy, and pleural effusions are present, but cure can still occur with pleural drainage, appropriate antibiotics, and meticulous supportive care. All six survivors in the 2001 anthrax attacks presented for medical care in the "intermediate-progressive stage".

Early clinical diagnosis of inhalation anthrax is difficult. Initial symptoms, such as myalgia, fever, and malaise mimic those of influenza. However, nasal congestion, rhinorrhea, and sore throat are features of most ILI cases not commonly associated with anthrax. Two to three days later, infected patients become dramatically sicker with the development of respiratory symptoms, including severe

dyspnea and hypoxemia. An important diagnostic finding is widening of the mediastinum on chest x-ray, reflecting the mediastinitis. However, initial radiographs are not as sensitive as Chest CT and might miss classic findings associated with inhalational anthrax in the early disease stages.

TABLE 1
Proposed Staging of Inhalational Anthrax*

*From Lucey D. Anthrax. In Mandell, Douglas, and Bennett's Principles and *Practice of Infectious Diseases.* 6th ed. Philadelphia: Elsevier Churchill Livingstone; 2005.

Stage	Comments
1: Asymptomatic	Usually < 1 week and rarely > 1 month
2: Early-prodromal	Nonspecific malaise, myalgias, low-grade fever, mild headache, nausea, general "flu-like" prodromal illness.
3: Intermediate-progressive	Blood cultures are positive in < 24 hours; mediastinal adenopathy present; pleural effusions that are often hemorrhagic, large, and require repeated drainage. Findings may include high fever, dyspnea, confusion or syncope, increasing nausea/vomiting. Patients in this stage can still be cured with appropriate antibiotics and intensive support.
4: Late-fulminant	Respiratory failure requiring intubation, meningitis, end-organ hypoperfusion ("shock"). Cure currently less likely in this stage. Future therapies for this stage may require inhibitors of both anthrax toxin and systemic inflammatory response mediators, in addition to antibiotics and intensive care.
This proposed staging system incorporates information from historical "early" and "late" stages with new timing of microbiologic and radiologic information (i.e., an "intermediate-progressive stage") from the 11 patients in the 2001 bioterrorism attacks	

TABLE 2
Diagnosis of Inhalational Anthrax Infection*
(Inglesby, et. al. JAMA 2002; 287:2236-2252)

Category	Findings
Epidemiology	Sudden appearance of several cases of severe acute febrile illness with fulminant course and death Or Acute febrile illness in persons identified as being at risk following a specific attack (e.g. those in the 2001 attacks; postal workers, members of the news media, and politicians and their staff
Diagnostic tests	Chest radiograph: widened mediastinum, infiltrates, pleural effusion. Chest CT scan: hyperdense hilar and mediastinal nodes, mediastinal edema, infiltrates, pleural effusion Thoracentesis: hemorrhagic pleural effusions
Microbiology	Peripheral blood smear: Gram-positive bacilli Blood culture: growth of large Gram-positive bacilli with preliminary identification of Bacillus species
Pathology	Hemorrhagic mediastinitis, hemorrhagic thoracic lymphadenitis, hemorrhagic meningitis; DFA stain of infected tissues**
* See Table 4 for symptoms ** Most rapid assays are available only at laboratories participating in the Laboratory Response Network (LRN)	

TABLE 3
Differential Diagnosis of Inhalational Anthrax

Condition	Features of Condition that Distinguishes from Anthrax
Mycoplasma pneumonia	Marked patchy infiltrates, + cold agglutinins
Legionnaire's disease	May have high fever with relative bradycardia, diarrhea, infiltrates
Psittacosis	History of exposure to birds, pneumonitis
Plague	More likely to have pulmonary infiltrate
Tularemia	More likely to have pulmonary infiltrate, less fulminant disease
Invasive group A streptococcal pneumonia	More likely to have pulmonary infiltrate
Q fever	Animal exposure history, phase I antibodies
Histoplasmosis	Long standing X-ray findings, chronic onset
Traumatic mediastinitis	History of trauma
Coccidioidomycosis	Residence in or travel to southwestern U.S.
Acute bacterial mediastinitis	Post-surgical infection, esophageal perforation, continuous spread from head neck or thoracic infection
Inhalation of staphylococcal enterotoxin B (as a bioterrorist agent)	No prodrome present
Superior vena cava syndrome	Other clinical symptoms of SVC syndrome
Ruptured aortic aneurysm	No prodrome

Clinical Laboratory Values

The white blood cell count (WBC) may be slightly elevated at time of initial visit, often with left shift. Later in the illness there may be a marked elevation of WBC with left shift. Transaminases may be elevated, hypoxemia may be present and patients may have metabolic acidosis. Hypocalcemia, hypoglycemia, and hyperkalemia have been reported in animal models. Cerebrospinal fluid in hemorrhagic meningitis may show red blood cells (RBC), elevated WBC, elevated protein, Gram-positive rods and decreased glucose. Detailed descriptions of the first 10 bioterrorism-related inhalational anthrax cases in the 2001 bioterrorism-associated outbreak are summarized in the following tables.

TABLE 4

Symptoms for 10 patients with bioterrorism-related inhalational anthrax in October and November 2001

Jernigan J, et al. Emerg Infect Dis. 2001; 7(6):933-43.

Symptoms	n = 10
Fever, chills	10
Fatigue, malaise, lethargy	10
Cough (minimal or nonproductive)	9
Nausea or vomiting	9
Dyspnea	8
Sweats (often drenching)	7
Chest discomfort or pleuritic pain	7
Myalgias	6
Headache	5
Confusion	4
Abdominal pain	3
Sore throat	2
Rhinorrhea	1
Physical findings	
Fever (>37.8°C) (100.04°F)	7/10
Tachycardia (heart rate > 100/m in)	8/10
Hypotension (systolic blood pressure < 110 mm Hg)	1/10
Laboratory results	
WBC (median)	$9.8 \times 10^3/mm^3$
(range)	$7.5\text{-}13.3 \times 10^3/mm^3$
Differential - neutrophilia (>70%)	7/10
bands (>5%)	4/5
Elevated transaminases (SGOT or SGPT >40 U/L)	9/10
Hypoxemia Alveolar-arterial oxygen gradient (>30 mm Hg) O_2 saturation on room air (<94%)	6/10
Metabolic acidosis	2/10
Elevated creatinine (>1.5 mg/dl)	1/10
Chest X-ray findings	
Any abnormality	10/10
Mediastinal widening	7/10
Pleural effusion	8/10
Infiltrates or consolidation	7/10
Chest computed tomography findings	
Any abnormality	8/8
Mediastinal lymphadenopathy, widening	7/8
Pleural effusion	8/8
Infiltrates or consolidation	6/8

Anthrax Meningitis

Presents as hemorrhagic meningitis or meningoencephalitis. CSF shows hemorrhage and Gram-positive rods. Case-fatality surpasses 90%. In Sverdlovsk, 50% with inhalational anthrax also had meningitis. Meningitis can occur as manifestation of infection by the cutaneous or gastrointestinal route but is most likely to occur after inhalational infection.

Cutaneous Anthrax

Presents as a "malignant pustule or malignant carbuncle" resulting from introduction of anthrax spores beneath the skin by inoculation or contamination of a pre-existent break in the skin.

Incubation period

Ranges from 1-7 days (up to 12 days). The typical incubation period is 2-5 days.

Signs and Symptoms

An evolving skin lesion, usually located on exposed parts of the body (face, neck, arms), with varying degrees of associated edema. The skin lesion typically progresses as follows:

- Small, painless, red macule (contrast to spider bite which is usually painful)
- Pruritic papule
- Small ring of vesicles that coalesce into a single large vesicle
- Vesicle ruptures to form depressed ulcer
- 1-3 cm black necrotic eschar develops in center (7-10 days from onset of lesion) often with significant edema
- Eschar falls off after 1 -2 weeks, often leaving no permanent scar
- Edema, redness, and/or necrosis without ulceration may also occur
- Lesions are generally not purulent unless there is superinfection.
- Systemic symptoms include fever, headache, myalgias, and regional lymphangitis or lymphadenopathy (7 of the 11 cutaneous cases in the US 2001 anthrax attacks had systemic symptoms).
- Lesions on the face and neck may be associated with significant edema and narrowing of the trachea from neck swelling can occur.
- "Malignant edema" describes a syndrome with marked edema, induration, and multiple bullae at the site of inoculation associated with generalized toxemia.
- Septicemia is rare.
- Untreated cutaneous anthrax progresses to systemic anthrax in 10-20% of cases.
- Systemic anthrax has a case fatality rate of up to 20%.
- Fatalities are rare (<1%) with primary cutaneous anthrax if effective antibiotic treatment is given.
- Despite antibiotic treatment, the lesion will progress through all stages.

TABLE 5
Differential Diagnosis of Cutaneous Anthrax

Condition	Features of Condition that Distinguish from Cutaneous Anthrax
Insect bite	History of insect bite, often painful
Brown recluse spider bite	History of insect bite (lesion becomes painful, and may manifest the "red, white, and blue" sign)
Ulceroglandular tularemia	More tender than pruritic; local edema typically less than in anthrax
Scrub typhus	Generalized macular-papular or papular-vesicular rash; papular base is discernible under the vesicle or eschar; history of residence or travel to endemic areas
Rickettsial spotted fevers	Generalized macular-papular or papular-vesicular rash; papular base is discernible under the vesicle or eschar; history of residence or travel to endemic areas
Ecthyma gangrenosum	Usually associated with frank cellulitis or with known immunosuppression
Plague	Sudden onset of painful lymphadenopathy; skin lesions are rare in U.S. cases
Glanders	Travel to or residence in endemic area
Orf virus disease	Animal exposure; contact with sheep, goats, or musk oxen; lesion associated with crusts and scabbing
Staphylococcal lymphadenopathy	Lesion purulent with palpable lymph nodes; primary wound is associated with red, linear streaks toward regional lymph node
Cutaneous leishmaniasis	Travel to or residence in endemic area; eschar is absent
Cat scratch disease	Contact with kittens or cats with fleas; primary lesion is a papule or vesicle, tender lesion and lymphadenopathy

Clinical Laboratory Values

Laboratory values are within normal limits if not disseminated and similar to inhalational anthrax if dissemination has occurred.

Gastrointestinal Anthrax

Primary infection occurs after the ingestion of contaminated food, particularly raw or undercooked meat from infected animals.

Incubation period
Ranges from 1-7 days (up to 12 days).

Signs and Symptoms

Two clinical presentations, intestinal, and oropharyngeal, have been described. The symptoms of intestinal anthrax are initially nonspecific and include nausea, vomiting, anorexia, and fever. As the disease progresses, abdominal pain, hematemesis, and bloody diarrhea develop, occasionally accompanied by ascites. The patient may present with the findings of an acute surgical abdomen. Oropharyngeal anthrax is associated with cervical edema and necrosis. A lesion, resembling a cutaneous anthrax lesion, may be seen in the oral cavity on the posterior wall, the hard palate or the tonsils. Patients typically complain of fever, dysphagia, and lymphadenopathy. Toxemia, shock, and cyanosis characterize the terminal stages of both forms of the disease. The case fatality rate for gastrointestinal anthrax ranges from 25% to 60% (role of early antibiotic treatment is undefined).

Laboratory Diagnosis

The Laboratory Response Network (LRN) for bioterrorism consists of over 100 state and local public health and military laboratories located throughout the United States. These laboratories have protocols and reagents that enable them to rapidly identify *B. anthracis* and other potential agents of bioterrorism. The LRN laboratory levels A-D have been replaced with the designations Sentinel Laboratory, Reference Laboratory or National Laboratory, based on capacity to perform testing for biological agents and the biosafety level (BSL). **Most hospital laboratories are Sentinel/Level A facilities. These possess BSL-2 capabilities and can culture clinical specimens to either rule out or refer isolates to a higher level laboratory for confirmation.** ASM sentinel level clinical microbiology laboratory guidelines can be accessed at **http://www.asm.org/index.php/public-policy/issues/sentinel-laboratory-guidelines**.The Level B and Level C laboratory categories have been merged into the Reference laboratory category and are either state or local public health laboratories or other federal laboratories that possess standardized protocols, validated reagents, advanced technologies for confirmatory testing, and the capacity to perform testing on environmental specimens. Reference laboratories possess BSL-3 facilities, or have BSL-2 facilities and use BSL-3 practices, and have molecular analysis and reference capabilities. As of 2006 there are two National/Level D laboratories: CDC and United States Army Medical Research Institute of Infectious Diseases (USAMRIID). These laboratories are responsible for the development and standardization of both traditional and molecular assays for detection, identification and strain characterization of bioterrorism agents. The Public Health Laboratory (PHL) is a Reference laboratory for anthrax testing.

As a reminder, if anthrax is suspected, clinicians are required to *immediately* call the Department of Public Health Acute Communicable Disease Control Program (Business Hours: (213) 240-7941 or After Hours: (213) 974-1234). Clinical laboratories should not attempt to handle environmental specimens, letters or packages containing powder. These should be referred to the PHL after consulting with local law enforcement and with PH Laboratory personnel (Business Hours: (562) 562-658-1300 or After Hours: (213) 974-1234).

Microbiology

Culture is the definitive test for anthrax. *B. **anthracis*** is a Gram-positive spore-forming bacillus that forms flat to slightly convex unevenly round colonies that are grayish in color with a ground-glass appearance and uneven borders. It is non-hemolytic (weak hemolysis may be seen on older cultures), non-motile, gamma phage susceptible, and usually penicillin susceptible, and able to produce the characteristic capsule under appropriate conditions.

B. anthracis can be isolated from blood, pleural fluid, CSF, ascitic fluid, vesicular fluid or lesion exudate. Sputum cultures are rarely positive. When culturing a lesion, either vesicular fluid or exudate from the ulcer itself should be collected. If there is no visible exudate, the edge of the eschar can be lifted with a pair of forceps and the fluid near the edge collected.

Obtain specimens whenever possible prior to antibiotic therapy.

- Blood cultures may be positive for bacterial growth in 12-48 hours using standard technology. A capsule may be demonstrated directly from the blood culture bottle. From growth on sheep blood agar, the organism is non-motile, non-hemolytic, and unencapsulated.
- Isolates must be sent to the PHL for definitive identification if ***B. anthracis*** **cannot be ruled out (presumptive identification).** Presumptive identification of anthrax by the microbiology laboratory is based upon the following characteristics:
  - Rapid aerobic growth on a blood or nutrient agar isolation plate
  - Gram stain showing large Gram-positive rods with square or concave ends having oval subterminal-to-central spores that do not cause swelling of the vegetative cell (spores are evident only from cultures grown in a non-CO_2 atmosphere)
  - Colonies on blood agar are non-hemolytic, rough, gray-white, tenacious colonies with comma-shaped protrusions giving an undulated appearance to the border ("Medusa-head" colony)
  - Organisms are non-motile as determined by wet mount or motility medium, and are catalase positive

Confirmatory criteria for distinguishing ***B. anthracis*** from other ***Bacillus*** **species include:**

- Capsule production
- Lysis by gamma phage and
- DFA assay.

Nasal Cultures

Nasal cultures are used only for epidemiologic investigation, to detect aerosol contamination of contaminated environments. **They should only be performed by public health personnel in the context of epidemiologic investigations.** Nasal cultures are not performed for detection of *B. anthracis* in an individual patient because it is regarded as insensitive and untested. **Decisions regarding postexposure prophylaxis should not be based on an individual's nasal swab culture results.**

Gram Stain

Gram stain should be performed on vesicular fluid or exudate from ulcerative lesions for suspected cutaneous anthrax, pleural fluid for suspected inhalation anthrax and CSF for suspected meningeal involvement. **In advanced disease, a Gram stain of unspun blood may be positive.** The Gram stain shows Gram-positive bacilli, usually occurring singly or in short chains (2-4 cells), often with squared-off ends ("bamboo-rod" appearance). India ink will clearly demonstrate the capsule where the Gram stain may not.

Direct Fluorescent Antibody (DFA) Test

Rapid diagnostic staining technique. This test has been used to examine exudate from cutaneous lesions, CSF, and tissue. It is not generally helpful for inhalational anthrax because respiratory/ pleural

fluid specimens are usually negative in the early stages of disease when rapid diagnosis is most critical. This test is currently available only at LRN Laboratories.

Rapid Diagnostic Test

PCR for detection of nucleic acid can provide a preliminary diagnosis of anthrax within several hours. Currently, these tests are only available at reference laboratories.

Serology

Not helpful for rapidly establishing the diagnosis during the acute illness.

Autopsy Findings

Identifying thoracic hemorrhagic necrotizing lymphadenitis and hemorrhagic necrotizing mediastinitis in a previously healthy patient is essentially pathognomonic for inhalation anthrax. Hemorrhagic meningitis would also be a distinct clue to the diagnosis of anthrax.

Laboratory Diagnosis of Cutaneous Anthrax

A negative culture does not exclude the diagnosis of anthrax, especially if collected when the lesion has ulcerated or after antibiotic treatment has begun. Definitive diagnosis requires immunohistochemical staining of biopsy specimens at CDC. Please call Public Health Laboratory (PHL) or the Department of Public Health Acute Communicable Disease Control Unit to arrange testing. A digital photograph of the lesion, if available, will facilitate testing.

****NOTE: In the event of a bioterrorist event, the anthrax strain may be penicillin resistant. Currently, there are no NCCLS standards for susceptibility testing for *B. anthracis*. Microbiology laboratories must alert the Department of Public Health Acute Communicable Disease Program (Business Hours: (213) 240-7941 or After Hours: (213) 974-1234) as soon as *B. anthracis* is identified so that susceptibility testing at a national reference laboratory can be arranged. Susceptibility testing is crucial in guiding both therapy and prophylaxis for potentially infected persons.**

Handling Laboratory Specimens

BSL-2 practices, containment equipment, and facilities are recommended for procedures on clinical materials suspected as being positive for anthrax. Laboratory staff handling specimens from persons who might have anthrax must wear surgical gloves, protective gowns, and shoe covers. Laboratory tests should be performed in BSL-2 cabinets and blood cultures should be maintained in a closed system. Every effort should be made to avoid splashing or creating an aerosol, and protective eye wear and masks should be worn if work cannot be done in a BSL-2 cabinet.

Accidental spills of potentially contaminated material should be decontaminated immediately by covering liberally with a disinfectant solution 0.5% hypochlorite (10% household bleach) or 10% formalin), **left to soak for 30 minutes,** and wiped up with absorbent material soaked in disinfectant. All biohazardous waste should be decontaminated by autoclaving. Contaminated equipment or instruments may be decontaminated with a hypochlorite solution, hydrogen peroxide, iodine, peracetic acid, 1% glutaraldehyde solution, formaldehyde, ethylene oxide, irradiation, or other OSHA-approved solutions, or by autoclaving.

Sources of information for this section are the 12 CDC documents *[MMWR* 2001;50:889, 909, 906, 941, 960, 961, 973, 984, 987, 991, 1008, and 1014], and the comprehensive review "Anthrax as a Biological Weapon, 2002: Updated Recommendations for Management,"[JAMA. 2002;287:2236-2252].

Treatment of Inhalational Anthrax

Clinicians must be aware that the treatment recommendations for inhalational anthrax contained in this guideline are based on a very small series of cases in humans and limited studies in experimental animals; they are conditional pending laboratory characterization of the strain involved in a specific event and may need to be altered in the mass casualty setting. Specific treatment recommendations for other bioterrorism-related outbreaks might change, depending on the characteristics of the anthrax strain involved.

TABLE 6
Initial Management
(adapted from John G. Bartlett, MD, CDC Medical Epidemiologist, Anthrax Update, CDC web site 11/26/01)

Initial Treatment of Inhalational Anthrax	
Ciprofloxacin	Preferred if sensitivities are unknown
Doxycycline:	Considered comparable to ciprofloxacin for prophylaxis and treatment for susceptible strains
Fluoroquinolones:	Levofloxacin, gatifloxacin and moxifloxacin - probably comparable to ciprofloxacin, but not FDA-approved for anthrax
Rifampin:	May be added as adjunct
Clindamycin:	Stops protein (toxin) synthesis
NOT cephalosporins:	B. anthracis produces a cephalosporinase. These agents should not be used.

Note: CNS penetration: Penicillin, chloramphenicol, ciprofloxacin, and rifampin Poor CSF penetration: Clindamycin and doxycycline

The key to successful treatment is prompt initiation of appropriate antimicrobial therapy at the first suspicion of anthrax. Strains of *B. anthracis* engineered to be resistant to penicillin and tetracycline have reportedly been developed. Consequently, the choice of primary and adjunctive antimicrobials must be empiric until susceptibility-testing results are available. Ciprofloxacin, in combination with one or two additional antibiotics, is the recommended initial treatment for inhalational anthrax. Other fluoroquinolones are also likely to be effective, but are not FDA-approved for this indication. The choice of adjunctive agent would be empirical pending susceptibility testing results. Antimicrobial agents suggested for combination therapy, based on susceptibility testing of the strain involved in the 2001 US outbreak include rifampin, vancomycin, clindamycin, and chloramphenicol. Naturally-occurring strains of *B. anthracis* are resistant to extended-spectrum cephalosporins, which are often used in empirical regimens for treatment of sepsis. Penicillin has

been previously recommended as the antibiotic of choice for treating infections due to penicillin-sensitive anthrax. However, while the 2001 outbreak strain was sensitive to penicillin with standard in *vitro* testing, it produced an inducible beta-lactamase. Penicillin should not be given as a single agent in clinical syndromes associated with a high microbial load until the presence of an inducible betalactamase has been ruled out.

In adults (including pregnant women* and immunocompromised) treatment considerations are as follows:

- **Initial intravenous therapy:** Ciprofloxacin, 400 mg every 12 hours in combination with one or two other antimicrobials with in vitro activity against anthrax, such as rifampin, vancomycin, clindamycin, imipenem or chloramphenicol. Clinical or subclinical meningitis in patients with inhalational anthrax is likely and should be suspected. Therefore, IV ciprofloxacin is recommended (for better CNS penetration) instead of doxycycline (which has poor CNS penetration). Antibiotics should be continued for 60 days, with adjustment of the regimen based on patient's clinical course.

*High death rates from infection outweigh risk of fluoroquinolones in pregnant women.

- **Switch to oral therapy when clinically appropriate:** Ciprofloxacin, 500 mg twice daily or doxycycline, 100 mg twice daily. Continue antimicrobial therapy for at least 60 days.

Supportive therapy is often required (e.g., volume expanders, vasopressor agents, and oxygen). A tracheotomy may be needed if cervical edema compromises the airways.

In children (including immunocompromised) recommendations are given below:

- **Initial intravenous therapy:** Ciprofloxacin, 10-15 mg/kg every 12 hours (not to exceed 1 g daily) **OR**, if susceptible, doxycycline, >8 years and >45 kg, 100 mg every 12 hours; > 8 years and < 45 kg or $\leq$ 8 years, 2.2 mg/kg every 12 hours **AND** one or two additional antimicrobials.

- **Switch to oral therapy when clinically appropriate:** Ciprofloxacin, 10-15 mg/kg twice daily (not to exceed 1 g daily) **OR**, if susceptible, doxycycline, >8 years and >45 kg, 100 mg twice daily; >8 years and $\leq$ 45 kg or < 8 years, 2.2 mg/kg twice daily. Continue antimicrobial therapy for at least 60 days.

Consider adjunctive steroids in patients with meningitis.

Also in anthrax meningitis, doxycycline may be less optimal than ciprofloxacin for CSF penetration.

Management with pleural fluid drainage in additional to antibiotics may have increased survival in the 2001 anthrax cases who had repeated drainage of large, bloody, and recurrent pleural effusions. Early and aggressive drainage of pleural effusions in all patients with inhalational anthrax is recommended.

Anthrax Meningitis — The optimal management of anthrax meningitis is unknown. There is a high likelihood of clinical or subclinical meningitis in cases of severe systemic anthrax, such as inhalation anthrax or gastrointestinal anthrax. Due to the potential for meningeal involvement, systemic cases of anthrax (even in the absence of proof of meningitis) should be treated using intravenous antimicrobial therapy, including ciprofloxacin plus one or two additional antimicrobial agents with good central

nervous system (CNS) penetration (meropenem or imipenem, rifampin, vancomycin, penicillin or ampicillin) and in vitro activity against *B. anthracis.*

Immunotherapeutics

Anthrax Immune Globulin (AIG) antitoxin is a therapy derived from the plasma of individuals previously immunized with the anthrax vaccine. This investigational product consists of antibody directed against the anthrax protective antigen. Patients already presenting with symptoms of anthrax infection may be treated with AIG in addition to antibiotic therapy. AIG has been purchased for the CDC's Strategic National Stockpile and may be released for use in an emergency.

Raxibacumab (ABthrax), is a human IgG1-gamma monoclonal antibody directed against protective antigen developed by Human Genome Sciences (HGS), It targets anthrax toxins after they have been released by anthrax bacteria, when antibiotics might not be effective. Raxibacumab has also been purchased by the U.S Dept. of Health and Human Services for the Strategic National Stockpile.

Treatment of Cutaneous Anthrax

Treatment is based on three assumptions. First, cutaneous anthrax is generally associated with a relatively low microbial load. Secondly, anyone with cutaneous anthrax is also at risk for the inhalational form. Finally, the organism may persist in vivo in the spore state so that late reactivation is plausible. In general, debridement of cutaneous anthrax lesions is contraindicated due to the risk of systemic spread.

In adults (including pregnant or breastfeeding women and immunocompromised):

- **Initial Oral Therapy:** Ciprofloxacin, 500 mg twice daily OR, if tetracycline susceptible, doxycycline, 100 mg twice daily. May change to amoxicillin, if susceptible, 500 mg every eight hours, after clinical improvement in patients with a contraindication to tetracyclines and fluoroquinolones. Continue therapy for at least 60 days.

In children (including immunocompromised):

- **Initial Oral Therapy:** Ciprofloxacin, 10-15 mg/kg twice daily (not to exceed 1 g daily) **OR**, if susceptible, doxycycline, >8 years and >45 kg, 100 mg twice daily; >8 years and $\leq$ 45 kg or $\leq$ 8 years, 2.2 mg/kg twice daily. May change to amoxicillin, 80 mg/kg/day, divided into 3 doses, after clinical improvement. Continue for at least 60 days.

Patients with systemic involvement, extensive edema, or lesions on head or neck require intravenous therapy and combination therapy (see inhalational anthrax). Cutaneous lesions will continue to evolve despite the use of effective antibiotics, but severe edema and systemic symptoms will be prevented. Corticosteroids (prednisone 1-2 mg/kg/day or dexamethasone 0.75-0.9 mg/kg/day) for the first 3-4 days of treatment may reduce morbidity and mortality in severe cutaneous anthrax (malignant edema), particularly in the setting of laryngeal edema.

Anthrax Vaccination and Duration of Therapy

Anthrax vaccine adsorbed (AVA) is marketed as BioThrax (Emergent BioSolutions, Lansing, Michigan) and is licensed for use in persons aged 18–65 years who are at high risk for exposure. AVA is not licensed for use in children (i.e., persons aged <18 years) or pregnant women. It is an alum-absorbed, inactivated cell-free vaccine for anthrax that has been developed and used primarily by the military as well as laboratory and veterinarian workers. The efficacy of the vaccine against

anthrax in the pre-exposure setting has been documented in humans.

The anthrax vaccine is FDA-licensed for used in the pre-exposure setting but it has not been licensed for use in the post-exposure setting and therefore in the post-exposure context, it can only be administered under an Investigational New Drug application. For postexposure prophylaxis, the vaccine is given parenterally (0.5 ml subcutaneously, deltoid region) in three doses 2 weeks apart (0, 2 weeks, and 4 weeks). (See below under Management of Exposed Persons)

Mild local reactions occur in 30% of vaccine recipients and consist of slight tenderness and redness at the injection site. Severe local reactions are infrequent and consist of extensive swelling of the forearm in addition to the local reaction. Systemic reactions occur in fewer than 0.2% of recipients. (NOTE: The FDA has only licensed the vaccine for use in healthy adults aged 18-65 years; the safety and efficacy of the vaccine for children and pregnant women have not been studied).

Management of Exposed Persons

In the event of a bioterrorist release of *B. anthracis* spores, it may be difficult to define who has been exposed. Once the site of the attack is determined, all persons at the site of the release or downwind from the release (assuming aerosol dispersal) would be considered potentially exposed.

Decisions regarding postexposure prophylaxis will be made in consultation with public health. **Contacts (e.g., household contacts, friends, coworkers) do not require postexposure prophylaxis unless they were exposed to the aerosol or other source of contamination at the site of attack.** It is important to establish that both the patient and the patient's household members understand that anthrax is not contagious. Neither exposed nor infected patients present any infectious risk.

Elevated fear and anxiety within the community will result in unexposed individuals seeking medical treatment. These individuals will present with vague somatic symptoms which in some cases may mimic symptoms of infection.

There will most likely be a significant number of anxious persons who were not actually exposed. These persons should still be considered victims. Most will exhibit anxiety, some will exhibit somatic symptoms that they will attribute to exposure and/or infection referred to as disaster somatization reaction (DSR). These symptoms range from general anxiety to mimicking symptoms of infection. Mental health referral should be made AFTER appropriate medical triage. Mental health treatment must include reassurance and possible treatment with anxiolytic medications. If these measures do not address the person's concerns, consideration of "against medical advice" prophylactic antibiotics might be considered for mental health reasons. These patients should be treated in the same manner as patients who were exposed and compliance with the full 60-day (or more) duration of antibiotics must be reinforced. No "short courses" of antibiotics should be administered.

Patients treated for exposure should be informed of the importance of completing the full course of antibiotic prophylaxis regardless of an absence of symptoms. It is the responsibility of the prescribing clinician to convey this message.

Inhalational exposures

In adults (including immunocompromised):

- Initiation of **oral** antibiotic therapy quickly after exposure has been shown to markedly reduce the mortality of inhalational anthrax in animal studies. The best available prophylactic regimen is the combination of antibiotic therapy and vaccination. Antibiotic susceptibility information on clinical isolates should guide prophylactic antibiotic choices. While awaiting antibiotic susceptibility test results, or if susceptibility results confirm **penicillin resistance,** begin therapy immediately with ciprofloxacin, 500 mg twice daily or doxycycline, 100 mg twice daily. Most authorities agree that other fluoroquinolones, such as levofloxacin, gatifloxacin, and moxifloxacin, may be equally effective. Levofloxacin is FDA-approved for anthrax post-exposure prophylaxis.

  Alternate regimens for **penicillin susceptible** isolates include potassium penicillin V, 30 mg/kg/day in 4 divided doses or amoxicillin, 500 mg every 8 hours.

  Side effects of ciprofloxacin and doxycycline appeared to be comparable in follow-up of those who took prophylaxis during the 2001 anthrax letter attacks in the U.S.

In pregnant women:

- Initial **oral** therapy includes: ciprofloxacin, 500 mg twice daily or alternative therapy (if strain is proved to be susceptible) amoxicillin, 500 mg every eight hours.

In children (including immunocompromised):

- Recommendations for oral antibiotic therapy of children, while awaiting antibiotic susceptibility results or if susceptibility results confirm **penicillin resistance,** include: ciprofloxacin, 15 mg/kg twice daily, not to exceed 1 g daily or doxycycline, >8 years and >45 kg, 100 mg twice daily; >8 years and $\leq$ 45 kg or $\leq$ 8 years, 2.2 mg/kg every 12 hours. If the isolate is **penicillin-susceptible,** children should be treated with a penicillin antibiotic. For children weighing $\geq$ 20 kg, amoxicillin, 500 mg three times daily; for children <20 kg, amoxicillin, 80 mg/kg/day in three divided doses.

Duration of antibiotic Post-exposure prophylaxis (PEP) and anthrax vaccine for PEP

The CDC recommends 60 days of selected oral antibiotics in conjunction with a 3-dose regimen (0, 2 weeks, 4 weeks) of anthrax vaccine (BioThrax, also known as AVA) as an emergency public health intervention. Two major U.S. national advisory bodies have considered strategies for post-exposure prophylaxis for prevention of inhalation anthrax among individuals exposed to potentially aerosolized *B. anthracis* spores. Both groups, the Advisory Committee on Immunization Practices (ACIP) and the John Hopkins Working Group on Civilian Biodefense, concluded that based on available data, the best means for prevention of inhalation anthrax is prolonged antibiotic therapy in conjunction with anthrax vaccination. In addition, a recent Institute of Medicine Report on anthrax vaccine safety and efficacy also concluded that based on limited animal studies, anthrax vaccine administered in combination with antibiotics following exposure to *B. anthracis* spores may help to prevent the development of inhalation anthrax. BioThrax is not licensed for post-exposure prophylaxis for prevention of inhalation anthrax, or for use in a 3-dose regimen; therefore, this program would be conducted under an Investigational New Drug (IND) application.

Pregnant Women

In a post event setting that poses a high risk for exposure to aerosolized *B. anthracis* spores, pregnancy or breastfeeding is neither a precaution nor a contraindication to PEP. Pregnant or breastfeeding women at risk for inhalation anthrax should receive AVA and 60 days of antimicrobial therapy as described.

Children

The use of AVA in children (age 0-17) is not contraindicated in a post event setting that poses a high risk for exposure to aerosolized *B. anthracis* spores.

Detailed information on use of the anthrax vaccine is available: see Use of Anthrax Vaccine in the United States Recommendations of the Advisory Committee on Immunization Practices (ACIP), 2009. MMWR July 23, 2010, Vol. 59 (No.RR-6).

Exposures through cuts, abrasions or injections

Immediately wash the infected part with soap and water, and apply a disinfectant solution approved for topical use. Promptly begin therapy as outlined under the treatment section for cutaneous anthrax and continue therapy for 7-10 days. If there is an exposure risk for inhalational anthrax, therapy should be continued for at least 60 days.

Ingestional exposures

Treat GI exposure for 60 days. **All persons exposed to anthrax should be instructed to watch for signs or symptoms of flu-like illness (e.g., fever, cough, chills, malaise, etc.), abdominal pain, nausea, vomiting, or diarrhea.** Should such symptoms occur, patients must be immediately evaluated by a physician for initiation of intravenous antibiotic therapy.

For current information about the availability of human anthrax vaccine, call the Department of Public Health Acute Communicable Disease Control Program at (213) 240-7941.

TABLE 7
Inhalational Anthrax Treatment Protocol* for Cases Associated with Bioterrorist Events

Category	Initial therapy (intravenous)	Duration
Adults (Including pregnant women** and immunocompromised)	Ciprofloxacin[a] 400 mg Q 12 hrs **OR** Doxycycline 100 mg Q 12 hrs **AND** One or two additional antimicrobials***	Switch to oral therapy when clinically appropriate: Ciprofloxacin 500 mg BID **OR** Doxycycline 100 mg BID Continue for at least 60 days (IV and PO combined)
Children** (Including immunocompromised)	Ciprofloxacin[a]**** 10-15 mg/kg Q 12 hrs **OR** Doxycycline >8 yrs and >45 kg: 100 mg Q 12 hrs >8 yrs and ≤ 45 kg: 2.2 mg/kg Q 12 hrs ≤ 8 yrs: 2.2 mg/kg Q 12 hrs **AND** One or two additional antimicrobials***	Switch to oral therapy when clinically appropriate: Ciprofloxacin**** 10-15 mg/kg BID **OR** Doxycycline >8 yrs and >45 kg: 100 mg BID >8yrs and ≤ 45 kg: 2.2 mg/kg BID ≤ 8 years: 2.2 mg/kg BID Continue for at least 60 days (IV and PO combined)

*Source: MMWR 2001;50:909-19 and JAMA. 2002;287:2236-2252

**High death rate from infection outweighs theoretical risk from antimicrobials.

***Vancomycin, clindamycin, chloramphenicol, imipenem show in vitro activity against anthrax

**** Ciprofloxacin not to exceed 1 gram daily in children. Other fluoroquinolones may be effective alternatives.

[a] Ciprofloxacin is favored over doxycycline for treatment of anthrax cases with serious systemic illness such as inhalational anthrax, gastrointestinal anthrax, or cutaneous anthrax with systemic involvement; cases with suspected meningeal involvement; and fulminant cases with bacteremia.

TABLE 8
Cutaneous Anthrax Treatment Protocol* for Cases Associated with Bioterrorist Events

Category	Initial Therapy (Oral)	Duration
Adults (Including pregnant women** and immunocompromised)	Ciprofloxacin[a] 500 mg BID **OR** Doxycycline 100 mg BID	At least 60 days
Children** (Including immunocompromised)	Ciprofloxacin[a]*** 10-15 mg/kg BID **OR** Doxycycline: >8 years and >45 kg: 100 mg BID >8 years and ≤45 kg: 2.2 mg/kg BID ≤ 8 years kg: 2.2 mg/kg BID	At least 60 days Change to amoxicillin if susceptible

Note: Cutaneous anthrax with signs of systemic involvement, extensive edema, or lesions on the head or neck requires intravenous therapy and a multidrug approach as for inhalational anthrax.

*Source: MMWR 2001;50:909-19; JAMA 2002;287:2236-2252

**High death rate from infection outweighs risk of antimicrobials.

*** Ciprofloxacin not to exceed 1 gram daily in children.

[a] Ciprofloxacin is favored over doxycycline for treatment of anthrax cases with serious systemic illness such as inhalational anthrax, gastrointestinal anthrax, or cutaneous anthrax with systemic involvement; cases with suspected meningeal involvement; and fulminant cases with bacteremia.

TABLE 9
Recommended Postexposure Prophylaxis Protocol* to Prevent Inhalational Anthrax Associated with Bioterrorist Events

Category	Initial Therapy (Oral)	Duration
Adults (Including pregnant women** and immunocompromised)	Ciprofloxacin 500 mg BID **OR** Doxycycline 100 mg BID	At least 60 days Alternate therapy if susceptible, amoxicillin, 500 mg TID
Children** (Including immunocompromised)	Ciprofloxacin*** 10-15 mg/kg BID OR ~ Doxycycline: >8 years and >45 kg: 100 mg BID >8 years and ≤ 45 kg: 2.2 mg/kg BID ≤ 8 years kg: 2.2 mg/kg BID	At least 60 days Alternate therapy if susceptible, amoxicillin, ≥ 20 kg: 500 mg TID <20 kg: 80 mg/kg in 3 divided doses

* MMWR 2001;50:909-19, JAMA. 2002;287:2236-2252

**High death rate from infection outweighs risk of antimicrobials.

*** Ciprofloxacin not to exceed 1 gram daily in children

Infection Control

There are no data to suggest that person-to-person transmission of inhalational, cutaneous or gastrointestinal anthrax occurs. Standard precautions are indicated for hospitalized patients with suspected or confirmed inhalational or gastrointestinal anthrax infection. Standard precautions for cutaneous anthrax; contact precautions if uncontained copious drainage. High-efficiency particulate air filtration masks are not indicated. Patients do not require isolation rooms (Working Group on Civilian Biodefense, JAMA. 2002;287:236-2252). Articles contaminated with infective material including bandages should be discarded, bagged, and labeled before being sent for decontamination and reprocessing. Contaminated surfaces should be cleaned with a hospital-approved disinfectant such as hypochlorite.

Disposal of Infectious Waste

Use of tracking forms, containment, storage, packaging, treatment, and disposal methods should be based upon the same rules as all other regulated medical wastes.

Autopsy and Handling of Corpses

All postmortem procedures should be performed using Standard precautions. All persons performing or assisting in postmortem procedures must wear mandated personal protective equipment (PPE) as delineated by OSHA guidelines. Surfaces contaminated during postmortem procedures should be decontaminated with an appropriate chemical germicide such as iodine, 10% hypochlorite or 5% phenol (carbolic acid). Cremation is preferable.

Reporting to the Health Department

Human and animal anthrax are reportable diseases in California. All suspected human cases should be reported immediately by phone to the:

Los Angeles County Department of Public Health

Business Hours (8am-5pm)	**213-240-7941**
After Hours (County Operator)	**213-974-1234**

Ask to Speak with the Public Health Physician On-Call

BOTULISM

ALL SUSPECTED CASES OF BOTULISM MUST BE REPORTED IMMEDIATELY TO THE DEPARTMENT OF PUBLIC HEALTH ACUTE COMMUNICABLE DISEASE CONTROL PROGRAM:

Monday - Friday (8am – 5pm)
(213) 240-7941

After Hours (County Operator)
(213) 974-1234

Ask to Speak with the Public Health Physician On-Call

Quick Reference Sheet: Botulinum Toxin

ALL SUSPECTED CASES OF BOTULISM MUST BE REPORTED IMMEDIATELY TO THE DEPARTMENT OF PUBLIC HEALTH ACUTE COMMUNICABLE DISEASE CONTROL PROGRAM

During Business Hours	213-240-7941
After Hours (County Operator)	213-974-1234

Infant botulism suspects: contact the California Infant Botulism Treatment and Prevention Program: 510-231-7600

Epidemiology:

- Botulinum neurotoxins (A-G) could be transmitted by aerosol or contamination of food and/or water supplies
- Wound botulism results from toxin elaboration in an abscess from self injection, surgical wound, or puncture wound.
- Intestinal botulism arises from elaboration of toxin from *C. botulinum* organisms in the gut; infant botulism is the most common form of intestinal botulism
- Botulism is NOT transmitted from person to person

Clinical:

- Incubation period is typically 12-72 hours (range 2 hours to 8 days)
- Early symptoms include blurred vision, diplopia and dry mouth
- Later symptoms include dysarthria, dysphagia, dysphonia, ptosis and the development of a *symmetrical,* descending progressive paralysis and respiratory failure
- Patients are usually alert with normal mental status, afebrile and with normal sensory nerve function

Laboratory Diagnosis:

- Initial diagnosis is primarily based on clinical presentation
- Spinal fluid protein is normal and characteristic findings are seen on EMG (facilitation of the compound muscle action potential on repetitive nerve stimulation)
- Toxin can be detected in serum, stool, and gastric contents (foodborne botulism) by mouse neutralization bioassay
- Laboratory confirmation is available through LAC Public Health Laboratory, arrange by calling Public Health ACDC

Treatment:

- Supportive care is the mainstay of therapy; prolonged ventilatory support is often required for severe cases
- Botulinum antitoxin (heptavalent A-G) is available after approval by Public Health ACDC. Prompt administration is essential after hypersensitivity testing

Management of Exposed Persons:

- Currently, there is no available postexposure prophylaxis

Infection Control:

- Standard Precautions - botulism is not transmitted from person to person

Introduction and Epidemiology

Botulism is a neuroparalytic disease caused by a neurotoxin produced by the anaerobic spore-forming bacterium, *Clostridium botulinum.* Two additional bacteria, *Clostridium baratii* and *Clostridium butyricum,* can also rarely produce botulinum toxin. Botulinum toxins are designated A through G based on antigenic differences. These are among the most poisonous substances known. Human botulism is caused by toxin types A, B, E and rarely, type F; botulism associated with toxin type A is most severe. In the eastern United States, botulism is primarily caused by botulinum toxin type B, while type A predominates in the west, and type E in Canada and Alaska. Botulism is classically acquired by the ingestion of preformed neurotoxin **(foodborne botulism),** although botulism can also be caused by localized infection with *C. botulinum* **(wound botulism)** or *C. botulinum* colonization of the intestine with in vivo toxin production **(infant botulism).**

Botulinum neurotoxins irreversibly bind to presynaptic receptors of peripheral nerves and subsequently inhibit release of acetylcholine. Both the neuromuscular junctions and cholinergic autonomic synapses are affected, resulting in skeletal muscle and bulbar paralysis. Recovery can take weeks to months, requiring the regeneration of presynaptic axons and formation of new synapses.

Foodborne botulism in the United States has been most commonly recognized in small clusters or single cases related to home-canned foods or vegetables of low acidity (e.g., beans, peppers, carrots and corns). Recent examples of foodborne botulism due to non-preserved foods include Alaskan fermented fish, foil-wrapped baked potatoes, chopped garlic in soybean oil, carrot juice, potato salad and sautéed onions. Heating food sufficiently before eating destroys botulinum toxins. Waterborne botulism has never been reported. Deliberate contamination of food or water supplies is also possible. However, an extremely large volume of toxin would be required to contaminate a municipal water supply and the toxin is inactivated by chlorination.

Wound botulism can occur if a wound becomes infected with *C. botulinum* with subsequent production of toxin in vivo. This occurs most frequently in intravenous or subcutaneous drug abusers ("skin poppers" injecting black tar heroin), intranasal cocaine users with sinusitis, or following trauma with gross contamination.

Intestinal (Infant) botulism occurs when the spores are ingested, germinate in the intestine and produce toxin, which is then absorbed through the gastrointestinal tract. Intestinal botulism in young infants has been associated with ingestion of honey. It is extremely rare past the infant stage.

Airborne transmission of botulinum neurotoxin does not usually occur naturally (although three persons were affected by aerosolized toxin while disposing of rabbits and guinea pigs whose fur had been coated with previously aerosolized botulinum toxin during a laboratory accident in Germany in 1962). The clinical manifestations of disease would be identical to foodborne botulism with the absence of prodromal gastrointestinal symptoms that may accompany ingestion of spoiled food.
Botulism is not transmitted from person to person.

Multiple, simultaneous cases of acute flaccid paralysis with prominent bulbar palsies with a common geographic factor, but no common food history, multiple simultaneous outbreaks with no common source, or cases with an unusual toxin type should raise suspicion of a bioterrorist attack.

Significance as a Potential Bioterrorist Agent

- Botulinum toxin is one of the most potent toxic substances known (it is 100,000 times more toxic than sarin gas)
- Toxin could be released as an aerosol or used to contaminate water or food supplies
- Iraq manufactured 19,000 liters of botulinum toxin and deployed 10,000 liters in over 100 munitions during the 1991 Gulf War
- The Aum Shinrikyo cult attempted to release botulinum toxin during a failed bioterrorist attack in Japan
- A massive outbreak of botulism would easily overwhelm both the existing supply of botulinum antitoxin and intensive care support (ventilator) capacity at acute care hospitals

Clinical Manifestations

Based on experience from 3 human cases and laboratory aerosol exposure in monkeys, it is assumed that the clinical presentation of inhalational botulism is similar to foodborne botulism, with the exception that gastrointestinal prodromal symptoms may not occur with inhalational botulism.

Incubation period

Typically 12-72 hours (range 2 hours to 8 days depending on dose).

Signs and Symptoms

Patients may exhibit some or all of the following signs or symptoms:

Early Signs and Symptoms (cranial nerve abnormalities precede peripheral muscle weakness):

- Blurred vision
- Diplopia (double vision)
- Dry mouth

Late Signs and Symptoms (more severe disease):

- Dysphonia (hoarse voice)
- Dysarthria (difficulty articulating words)
- Dysphagia (difficulty swallowing)
- Ptosis (drooping eyelids)
- Symmetrical, descending, progressive muscular weakness demonstrating fatigability with repetitive muscle activity
- Respiratory failure
- Normal mental status (although communication may be impaired due to cranial nerve deficits)
- Normal sensory nerve function
- Afebrile (unless secondary infection is present, e.g., aspiration pneumonia)

The patient may have dilated or fixed pupils. Patients are typically alert and responsive and sensory deficits (other than blurred vision) do not occur. Deep tendon reflexes may be symmetrically depressed or remain normal. Fever does not occur unless there is a complicating infection.

Differential Diagnosis of Botulism

Condition	Features of condition that distinguish from botulism
Guillain-Barré	History of recent gastrointestinal infection; sensory changes, ascending paralysis; increased CSF protein; characteristic EMG changes
Myasthenia gravis	EMG findings; recurrent paralysis; response to anticholinesterase inhibitor therapy; Tensilon test can be falsely positive in botulism.
Tick paralysis	Presence of ticks; sensory findings; ascending paralysis beginning with affected limb. Tick removal leads to rapid recovery of motor functions.
Stroke	Asymmetry; abnormal CNS imaging; sensory findings
Acute intoxication	Exposure history; drug or toxin levels
Lambert-Eaton Syndrome	Increasing strength with effort; malignancy present
Polio	Asymmetric paralysis; cells in CSF; history of febrile illness
CNS infections	Mental status changes; CSF abnormalities; EEG changes
CNS tumor	Abnormal CNS imaging; asymmetric findings; sensory changes
Inflammatory myopathy	Elevated muscle enzymes
Diabetes mellitus	Sensory abnormalities; elevated blood glucose and ketones
Hypothyroidism	Abnormal thyroid function tests
Laryngeal trauma	Trauma history; absence of bulbar palsies
Psychiatric conditions	Absence of disconjugate gaze and other cranial palsies

Clinical Laboratory Findings

Routine clinical lab findings are usually within normal limits.

Diagnosis

The diagnosis of botulism requires a very high index of suspicion, and is most often based on epidemiologic evidence of a potential exposure. **It is important to ask detailed questions (before patient decompensates) including:**

- Recent history of eating home-canned foods
- Other known individuals with similar symptoms
- Recent travel to Alaska or consumption of Alaskan or Native American specialties (fermented fish, walrus, whale blubber)
- Recent history of intravenous or subcutaneous "skin popping" drug use (especially with black tar heroin or cocaine use)
- Presence of puncture wound, infected surgical wound, or abscess

In the event of a bioterrorist attack, a recognized source of exposure may be absent.

Laboratory Diagnosis

Contact the Department of Public Health Acute Communicable Disease Control Program (Business Hours: (213) 240-7941 or After Hours: (213) 974-1234) to obtain antitoxin and to arrange for laboratory testing. Laboratory results take at least 24 hours to confirm, however if the clinical syndrome is compatible with botulism, antitoxin will be released emergently.

In LAC, laboratory testing for toxin is available through the Public Health Laboratory (PHL) after consultation with the Acute Communicable Disease Control Program (Business Hours: 213-240-7941 or After Hours: 213-974-1234).

The diagnosis of botulism requires a compatible clinical presentation. The detection of botulinum neurotoxin in the patient's serum and/or stool (in the case of foodborne botulism) serves to confirm the diagnosis. The detection of toxin will be dependent on the total dose absorbed and the time from onset of symptoms to testing. The specimens are evaluated by mouse neutralization bioassay, currently the gold standard assay. This assay can detect as little as 0.03ng of botulinum toxin with results available usually in 1-4 days.

Processing of Specimens

Obtain serum (at least 30 ml), stool (at least 25-50 g) and gastric aspirate if available. Immediately call the Acute Communicable Disease Control Program (Business Hours: 213-240-7941 or After Hours: 213-974-1234) to arrange for testing.

Serum specimens must be taken ***before*** antitoxin treatment to demonstrate the presence of botulinum toxin. All specimens should be refrigerated, not frozen, and examined as quickly as possible after collection. Freezing will hamper recovery of *Clostridium botulinum,* but will not interfere with detection of toxin.

Toxin testing may take up to 4 days to complete after specimens are received. The lack of detection of toxin in serum of patients with clinically compatible illness does not necessarily rule out the diagnosis of botulism, particularly in the event of inhaled botulism neurotoxin.

Bacterial Cultures, Antibody Tests and Routine Laboratory Tests

Blood, stool, sputum and urine cultures are not helpful in confirming a diagnosis of botulism. Viable clostridial organisms may be isolated from wound botulism cases if the specimen is collected properly and grown anaerobically, as well as in infant botulism caused by bacterial infection of the gut. Patients do not generally develop an antibody response due to the sub-immunogenic amount of toxin necessary to produce disease; repeated episodes of botulism in the same person have been documented.

Routine laboratory tests, including chemistries and hematologic profiles are generally within normal limits unless a secondary process (e.g., nosocomial infection) has occurred.

Cerebrospinal fluid tests are generally normal in botulism (compared to the elevated CSF protein generally present in Guillain-Barré syndrome).

Electrophysiologic Studies

Electromyelography (EMG) should be performed on clinically involved muscles. EMG may support the diagnosis of botulism but a normal EMG does not rule out disease. Characteristic findings of botulism include:

- Normal sensory nerve function
- Normal nerve conduction velocity
- Incremental response (facilitation) to repetitive stimulation (often seen only at 50 Hz)
- Normal Tensilon (edrophonium) test (differentiates botulism from myasthenia gravis)

Handling Laboratory Specimens

Biosafety Level (BSL)-2 practices, containment equipment, and facilities are recommended for all activities with materials potentially containing toxin. Laboratory staff handling specimens from persons who might have botulism must wear surgical gloves, protective gowns and shoe covers if performing procedures with high splash potential or risk of aerosolization. Laboratory tests should be performed in BSL-2 cabinets and blood cultures should be maintained in a closed system. Every effort should be made to avoid splashing or creating an aerosol. Protective eye wear and masks should be worn if work cannot be done in a BSL-2 cabinet.

Accidental spills of potentially contaminated material should be decontaminated immediately by covering liberally with a disinfectant solution (a strong alkaline solution [e.g., 0.1 M sodium hydroxide] for botulinum toxin and a 1:10 bleach solution for the *Clostridium* organisms and spores) **for at least 15 minutes** to ensure effective inactivation. If the material is suspected to contain both toxin and organisms, the spill must be sequentially treated with both bleach and sodium hydroxide.

All biohazardous waste should be decontaminated by autoclaving. Contaminated equipment or instruments may be decontaminated with a hypochlorite solution, hydrogen peroxide, peracetic acid, 1% glutaraldehyde solution, formaldehyde, ethylene oxide, or other OSHA approved solutions, or by autoclaving for 60 minutes; toxin can be inactivated by boiling for 10 minutes.

Treatment

Supportive care and timely administration of botulinum antitoxin are the keys to successful management of botulism. With modern improvements in intensive care support and early administration of antitoxin, mortality rates for botulism have dropped to approximately 6% in recent years. Respiratory failure due to paralysis of respiratory muscles is the most serious complication as well as the most common cause of death.

Botulinum Antitoxin

Contact the Department of Public Health Acute Communicable Disease Control Program (Business Hours: 213-240-7941 or After Hours: 213-974-1234) to obtain antitoxin and to arrange for laboratory testing. If the clinical syndrome is compatible with botulism, antitoxin will be released emergently.

In uncontrolled studies, use of antitoxin has been associated with lower mortality rates and, if administered early after onset of symptoms, a shorter course of illness. However, antitoxin will not

reverse symptoms; it can only halt further progression of symptoms. Antitoxin need not be repeated since the circulating antibodies have a half-life of 5 to 8 days.

In 2010, the Centers for Disease Control announced the availability of a new heptavalent botulinum antitoxin (HBAT, Cangene Corporation) through a CDC-sponsored Food and Drug Administration (FDA) Investigational New Drug (IND) protocol. HBAT replaces a licensed bivalent botulinum antitoxin AB and an investigational monovalent botulinum antitoxin E (BAT-AB and BAT-E, Sanofi Pasteur) with expiration of these products on March 12, 2010. As of March 13, 2010, HBAT became the only botulinum antitoxin available in the United States for naturally occurring noninfant botulism. The trial is expected to continue for several years.

The antitoxin is of equine origin and requires skin testing (follow instructions in the package insert) for hypersensitivity before administration of the antitoxin. About 9-21 % of patients will develop either acute or delayed-type sensitivity reactions. Serum sickness reactions appear to be dose-related and may be less likely with the newer dosing recommendations.

Infant botulism is treated with BabyBIG®, Botulism Immune Globulin Intravenous (Human) (BIG-IV), an orphan drug that consists of human-derived botulism antitoxin antibodies that is approved by the U.S. Food and Drug Administration for the treatment of infant botulism types A and B. It is available from the California Department of Public Health, Infant Botulism Treatment and Prevention Program, http://www.infantbotulism.org/ at 510-231-7600.

Supportive Therapy

Improvements in intensive care have significantly decreased mortality rates from botulism. Monitoring vital capacity is crucial. Intubation is usually indicated when vital capacity falls below 12 ml/kg, without waiting for a rise in PCO_2 or fall in oxygen saturation. Ventilatory support may be required for weeks to months.

Therapy in pediatric patients over the age of 1 year and pregnant women is identical to the recommendations outlined above.

Aminoglycoside antibiotics and clindamycin are contraindicated for treatment of secondary infections since they can exacerbate the neuromuscular blockade

Management of Exposed Persons

An exposed person is defined as a person who has been directly exposed to botulinum neurotoxin. In the case of a bioterrorist event, the exposure would most likely occur by inhalation of toxin.

There is currently no available postexposure prophylaxis for asymptomatic exposed persons. Such persons should be educated regarding the signs and symptoms of clinical botulism and instructed to seek medical care immediately if symptoms occur. As there is no prophylactic measure for botulism exposure other than observation and early treatment in the event of symptoms, exposed persons and their families will likely experience anxiety and require supportive mental health intervention. These individuals may also experience somatic symptoms that may include neurologic symptoms. These patients should be carefully assessed. Antitoxin therapy is for patients with neurological findings consistent with botulism poisoning.

Infection Control

Botulism is not transmitted from person to person. All staff should observe **Standard Precautions** when caring for patients with suspected or confirmed botulism. Patients do not require isolation rooms.

Disposal of Infectious Waste

Use of tracking forms, containment, storage, packaging, treatment and disposal methods should be based upon the same rules as all other regulated medical waste.

Autopsy and Handling of Corpses

All postmortem procedures are to be performed using Standard Precautions.
All persons performing or assisting in postmortem procedures must wear mandated PPE as delineated by OSHA guidelines. Instruments should be autoclaved or sterilized with a 10% bleach solution or other solutions approved by OSHA. Surfaces contaminated during postmortem procedures should be decontaminated with an appropriate chemical germicide such as 10% hypochlorite or 5% phenol (carbolic acid).

Reporting to the Health Department

Botulism is a reportable disease in California. All suspected cases should be reported immediately by phone to the:
Los Angeles County Department of Public Health

Business Hours (8am -5pm)	**213-240-7941**
After Hours (County Operator)	**213-974-1234**

Ask to Speak with the Public Health Physician On-Call

PLAGUE

ALL SUSPECTED CASES OF PLAGUE MUST BE REPORTED IMMEDIATELY TO THE DEPARTMENT OF PUBLIC HEALTH ACUTE COMMUNICABLE DISEASE CONTROL PROGRAM:

Monday - Friday (8am – 5pm)
(213) 240-7941

After Hours (County Operator)
(213) 974-1234

Ask to Speak with the Public Health Physician On-Call

Quick Reference Sheet: Plague (Yersinia pestis)

ALL SUSPECTED CASES OF PLAGUE MUST BE REPORTED IMMEDIATELY TO THE DEPARTMENT OF PUBLIC HEALTH ACUTE COMMUNICABLE DISEASE CONTROL PROGRAM

During Business Hours	213-240-7941
After Hours (County Operator)	213-974-1234

Epidemiology:

- Naturally occurring plague is a zoonotic disease of rodents that can be transmitted to humans from the bite of a plague-infected flea. Occurs naturally in 17 Western states in the US.
- There are 3 forms of plague: bubonic, primary septicemic and pneumonic
- Pneumonic form is thought to be the most likely to be seen in a bioterrorist attack
- Intentional aerosol release should be suspected if human cases occur in nonendemic areas or in persons with no known risk factors in the absence of prior rodent deaths

Transmission:

- Exposure to respiratory droplets (within 6.5 ft of human or animal with pneumonic form)
- Direct contact with infected animals or exposure to persons with pneumonic plague
- Bite of plaque-infected flea
- Direct contact with infected draining buboes

Clinical:

- Pneumonic Plague: Characterized by fulminant pneumonia with acute onset of fever, chills, headache, malaise and a productive cough, that is initially watery before becoming bloody. Untreated, rapid progression to dyspnea, stridor, sepsis, cyanosis and death
- Bubonic Plague: Characterized by painful lymphadenitis, high fever, malaise
- Septicemic Plague: 80% of persons with bubonic form become septic; 5-15% develop secondary pneumonic plague

Laboratory Diagnosis:

- Presumptive: Gram-negative bacillus, sometimes coccobacillus, with bipolar ("safety-pin") staining on Gram, Wright, Giemsa, or Wayson stain of blood, sputum, CSF or lymph node aspirate
- Organism grows slowly on standard blood and MacConkey agar
- Confirmatory: Immunofluorescent staining for capsule (F1 antigen) and phage lysis

Treatment:

- Streptomycin or gentamicin are the preferred antibiotics
- Doxycycline, tetracycline or fluoroquinolones are alternative choices
- Chloramphenicol should be used to treat plague meningitis

Management of Exposed Persons:

- Oral antibiotic prophylaxis is recommended for all persons exposed to aerosol or persons in close physical contact with a confirmed case
- Doxycycline, tetracycline or fluoroquinolones are recommended for 7 days
- Contacts who develop fever or cough should begin IV or IM antibiotic treatment
- FDA approved levofloxacin for Post Exposure Prophylaxis based on animal data

Infection Control:

- Droplet Precautions with confirmed or suspected pneumonic plague.
- Contact Precautions with confirmed or suspected bubonic plague until the patient has received at least 48-72 hours of antibiotics AND the patient is showing clinical signs of improvement

Introduction and Epidemiology

Plague is transmitted by a gram-negative bacillus, Yersinia pestis, of the family Enterobacteriaceae. Naturally occurring plague is a disease primarily affecting rodents. Transmission between rodents is via plague-infected fleas. Transmission to humans can occur by respiratory droplets from rodents, from infected animals or materials, or person-to-person. Plague has three clinical forms: bubonic, primary septicemic and pneumonic disease. **Pneumonic plague is thought to be the most likely presentation in the event of a biological attack.**

In the United States, transmission to humans has been primarily from the bites of plague-infected fleas from infected rodents. Less frequently, infection is caused by direct contact with body fluids or tissues while handling an infected animal. Currently, in the United States, infected cats are the only source of primary pneumonic plague for humans. Persons who develop secondary plague pneumonia usually receive appropriate isolation and treatment before secondary transmission can occur.
Five-15% of cases with bubonic or primary septicemic plague develop secondary pneumonic disease, and therefore can transmit primary pneumonic plague to other individuals.

Human plague has been reported most often from the four western states: New Mexico, Arizona, Colorado and California. During 1990--2005, a total of 107 cases of plague were reported in the United States (CDC, unpublished data, 2006), a median of seven cases per year. In 2006, a woman received the first diagnosis of plague in Los Angeles County, California, since 1984. The woman was hospitalized with fever, septic shock, and a painful right axillary swelling; blood cultures grew *Y*. pestis and she had handled raw meat from an infected animal.

Since primary pneumonic plague can be transmitted from person-to-person, a patient with compatible clinical symptoms should be placed on droplet precautions until the patient has received at least 48-72 hours of antibiotics.

Significance as a Potential Bioterrorist Agent

- Could be released as an aerosol during a bioterrorist attack
- Has been weaponized by the former Soviet Union and Japan; Japan purportedly dropped ceramic bomblets containing plague-infected fleas over China during World War II
- United States worked with plague as a weapon before the offensive program was terminated
- Potential for secondary transmission is highest with pneumonic plague
- Aerosolized plague would cause pneumonic disease, with high mortality rates if untreated
- Paranoia and panic due to infectivity and historical implications

Clinical Manifestations

Primary Pneumonic Plague

Incubation period
Typically 2-4 days (range 1 -6 days).

Signs and Symptoms
Patients exhibit acute and often fulminant onset of high fever, malaise, headache, myalgias, chest pain and productive cough (watery, purulent or bloody). Pneumonia rapidly progresses to become severe, with sepsis, multiorgan system failure and death. Other signs and symptoms may include:

- Chest pain
- Dyspnea
- Ecchymoses
- Petechiae
- Acral necrosis
- Cyanosis
- Stridor
- Respiratory failure
- Shock
- Consumptive coagulopathy
- Coma
- Plague meningitis (may occur in 6-7% of cases and tends to occur more commonly in children)
- Death rate is near 100% if appropriate antibiotics are not given within 12-24 hours

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Differential Diagnosis of Pneumonic Plague

Condition	Features of Condition that Distinguish from Pneumonic Plague
Community acquired pneumonia	Lobar pneumonia; less severe; culture and Gram stain
Hantavirus pulmonary syndrome	Thrombocytopenia, circulating immunoblasts and myelocytes, elevated transaminases and LDH, hemoconcentration, gastrointestinal symptoms, exposure to rodents
Meningococcemia,	Headache and meningitis, petichial or maculopapular rash, gram-negative diplococci on CSF
Rickettsiosis	Eschar at site of initial insect bite, disseminated erythematous papulovesicular rash, infiltrate not common leukopenia, thrombocytopenia
Q fever	Animal exposure, antiphase I antibodies
Ricin	Pulmonary edema
Staphylococcal enterotoxin B as an aerosolized weapon	Normal chest X-ray
Pulmonary tularemia	Cough not as productive; pulse temperature dissociation may occur
Mycoplasma	Marked patchy infiltrates, + cold agglutinins
Inhalational anthrax	Widened mediastinum

Clinical Laboratory Values
Patients with pneumonic plague may have clinical laboratory values consistent with severe illness, sepsis and multisystem organ failure such as an elevated WBC with left shift and toxic granulation, disseminated intravascular coagulation (DIC), elevated creatinine and abnormally high liver enzymes.

Primary Septicemic Plague

Incubation period
1-7 days.

Signs and Symptoms
Clinically resembles septicemia caused by other gram-negative bacteria. Patients are febrile and often have chills, headache, malaise and gastrointestinal disturbances. Septicemic plague may progress rapidly to septic shock, consumptive coagulopathy, meningitis and coma. Patients may develop secondary plague pneumonia.

Differential Diagnosis of Septicemic Plague

Condition	Features of Condition that Distinguish from Septicemic Plague
Meningococcemia,	Headache and meningitis; petechiae or maculopapular rash; gram-negative diplococci on CSF
Appendicitis	Right lower quadrant abdominal pain
Gram-negative sepsis	May be difficult to distinguish clinically; epidemiological history and labs
Rickettsiosis	Eschar at site of initial insect bite; disseminated erythematous papulovesicular rash; infiltrate not common; leukopenia and thrombocytopenia
Malaria	Appropriate travel history

Clinical Laboratory Values
Patients with septicemic plague may have clinical laboratory values consistent with severe illness, sepsis and multisystem organ failure (elevated WBC with left shift, toxic granulations, disseminated intravascular coagulation (DIC), elevated creatinine and abnormally high liver enzymes).

Bubonic Plague

Incubation period
2-8 days.

Signs and Symptoms
Patients develop fever, headache, chills and swollen, extremely painful lymph nodes (buboes). Nausea, vomiting and diarrhea are common. Swollen nodes typically involve the nodes that drain the site of initial infection. Patients generally do not have overlying skin lesions. Patients may develop secondary septicemic plague or secondary plague pneumonia.

Differential Diagnosis of Bubonic Plague

Condition	Features of Condition that Distinguish from Bubonic Plague
Tularemia	Inoculation site usually clear; sepsis rare
Cat-scratch disease	Inoculation site usually clear; sepsis rare
Lymphogranuloma venereum	Sexual contact history; presence of genital lesions
Chancroid	Less local pain; indolent course; no sepsis; sexual contact history; presence of genital lesions
Tuberculosis	Less local pain; indolent course; no sepsis
Streptococcal adenitis	Node may be less tender; sepsis less common

Clinical Laboratory Values

Patients with bubonic plague may have clinical laboratory values consistent with severe illness, sepsis and multisystem organ failure such as an elevated WBC with left shift and toxic granulations, disseminated intravascular coagulation (DIC), elevated creatinine and liver enzymes.

Laboratory Diagnosis

Laboratory work with clinical specimens must be done under Biosafety Level (BSL)- 2 conditions. If plague is suspected, please immediately call the Department of Public Health Acute Communicable Disease Control Program (Business Hours: (213) 240-7941 or After Hours: (213) 974-1234) to arrange for submission of specimens for confirmatory testing. Staff from the public health laboratory are available for consultation at (562) 658-1300 or After Hours: (213) 974-1234.

The diagnosis of plague may be suspected based on characteristic findings on microscopic staining of appropriate body fluids and confirmed by immunofluorescent staining for the capsule or bacterial culture. Serology is generally used retrospectively to confirm suspect cases.

Staining of Specimens

- Appropriate clinical specimens include: blood, bubo aspirates, sputum, CSF (if signs/ symptoms of meningitis) and skin scrapings (if a lesion is present).

- On Gram stain there are polymorphonuclear leukocytes and gram-negative rods or coccobacilli that may demonstrate bipolar staining ("safety pin" appearance). Identification of such organisms in bubo aspirate, blood, sputum or CSF is highly suggestive of plague.

With **Wayson staining,** *Yersinia pestis* appears as a light blue bacillus with dark blue polar bodies on a contrasting pink background.

Immunofluorescent staining of the capsule (F1) in fresh clinical specimens is presumptive for plague diagnosis. This test is available only at LRN laboratories. Public Health Laboratory (PHL) is an LRN laboratory.

Bacterial Cultures
Blood, bubo aspirates, sputum, CSF and skin scrapings can be cultured.

Materials should be inoculated onto blood and MacConkey agar plates and infusion broth. It generally takes 2 days to identify visible colonies. **Rapid biochemical identification systems may not be reliable for identification due to slower growth rate of *Y. pestis.***

Serologic Testing
Several serologic tests are available including a passive hemagglutination/ hemagglutination inhibition test and an ELISA (PHL and CDC, respectively). An elevated serum antibody titer to the F1 antigen of > 1:10 or positive ELISA (unvaccinated individual or persons without history of prior plague infection) is presumptively diagnostic. A fourfold or greater rise in titer from acute to convalescent serum confirms the diagnosis of plague. Serology is not useful for rapid diagnosis.

Handling Laboratory Specimens

Biosafety Level (BSL) - 2 practices containment equipment and facilities are recommended for all activities with materials potentially containing infectious material. Laboratory staff handling specimens from persons who might have plague must wear surgical gloves, protective gowns, and shoe covers if performing procedures with high splash potential or risk of aerosolization. Laboratory tests should be performed in BSL-2 cabinets and blood cultures should be maintained in a closed system. Every effort should be made to avoid splashing or creating an aerosol. Protective eye wear and masks should be worn if work cannot be done in a BSL-2 cabinet.

All biohazardous waste should be decontaminated by autoclaving. Contaminated equipment or instruments may be decontaminated with a hypochlorite solution, hydrogen peroxide, peracetic acid, 1% glutaraldehyde solution, formaldehyde, ethylene oxide, irradiation, or other OSHA approved solutions, or by autoclaving or boiling for 10 minutes.

Treatment

The Working Group on Civilian Biodefense has developed consensus-based recommendations for measures to be taken by medical and public health professionals following the use of plague as a biological weapon against a civilian population (JAMA. 2000;283:2281-2290). Treatment guidelines included in this section reflect these recommendations.

Supportive care combined with the rapid administration of parenteral antibiotics are the keys to successful management of plague. Plague pneumonia is almost always fatal if antibiotics are not begun within 12-24 hours of onset of symptoms.

Therapy in adults:
- The drug of choice for primary pneumonic plague is streptomycin, 1 g, administered by intramuscular injection every 12 hours for 10 days (maximum daily dose 2 g). Gentamicin, 2 mg/kg loading dose followed by 1.7 mg/kg intravenously or intramuscularly every 8 hours for 10 days can also be used.

- Chloramphenicol should be used for plague meningitis due to its better CNS penetration. Dosage is 25 mg/kg intravenously every six hours; continue for 10 days after clinical improvement.

Antibiotic choice may need to be altered as susceptibility information becomes available.

- **Alternative Antibiotics:** Doxycycline, 200 mg intravenous loading dose, followed by 100 mg intravenously every 12 hours for 10-14 day; ciprofloxacin, 400 mg intravenously every 12 hours; levofloxacin, 500 mg intravenously every 24 hours; and ofloxacin, 400 mg orally every 12 hours, are acceptable alternative agents. In 2012, the FDA approved levofloxacin for treatment of plague and for post-exposure prophylaxis based on animal studies.

Third generation cephalosporins are not considered effective therapy.

- **Supportive therapy:** Supportive care is essential, including intravenous fluids and hemodynamic monitoring.

Therapy in pediatric patients:

- First-line agents: Streptomycin, 15 mg/kg intramuscularly every 12 hours or gentamicin, 2.5 mg/kg intramuscularly or intravenously every 8 hours. *Alternatively,* doxycycline, >8 yrs and > 45 kg, 100 mg intravenously every12 hrs; >8 years and <45 kg or < 8 years, 2.2 mg/kg intravenously every 12 hrs.

Therapy in pregnant women:

- Avoid streptomycin in pregnancy due to its association with irreversible deafness in children exposed in utero. Gentamicin is the preferred choice, 2 mg/kg loading dose followed by 1.7 mg/kg intramuscularly or intravenously every 8 hours. Doxycycline, 100 mg intravenously twice daily or ciprofloxacin, 400 mg intravenously twice daily, are acceptable alternatives. Liver function should be monitored if tetracyclines are used due to potential hepatotoxicity of this agent during pregnancy.

Management of Exposed Persons

An exposed person is defined as a person who has been exposed to aerosolized *Yersinia pestis* or has been in close physical contact with a confirmed case-patient. Close contact is defined as contact with a patient at less than 6.5 feet (two meters) during a period when the case was symptomatic and before the case had received 48 hours of antibiotic therapy. Household contacts and healthcare worker contacts should be considered exposed and should receive prophylaxis. In a community experiencing a pneumonic plague epidemic, all persons developing a temperature of 38.5°C (101.3°F) or higher or a new cough should promptly seek medical attention and begin parenteral antibiotic treatment.

Antibiotics: All prophylactic antibiotic therapy should continue for 7 days from *last exposure* to the case. The Working Group on Civilian Biodefense recommends the use of doxycycline as the first antibiotic of choice for postexposure prophylaxis, pending susceptibility results. Other recommended antibiotics include tetracycline, ciprofloxacin and chloramphenicol for adults and children older than two years.

Table 6:
Treatment of Patients with Pneumonic Plague in the Contained and Mass Casualty Settings and for Postexposure Prophylaxis (adapted from JAMA. 2000;283: 2281-2290)

Patient Category	Recommended Therapy
Adults	**Contained Casualty Setting** ***Preferred choices*** Streptomycin, 1 g IM twice daily Gentamicin, 5 mg/kg IM or IV once daily or 2 mg/kg loading dose followed by 1.7 mg/kg IM or IV 3 time daily†
	Alternative choices Doxycycline, 100 mg IV twice daily or 200 mg IV once daily Ciprofloxacin, 400 mg IV twice daily‡ Chloramphenicol, 25 mg/kg IV 4 times daily§
Children	***Preferred choices*** Streptomycin, 15 mg/kg twice daily (maximum daily dose, 2 g) Gentamicin, 2.5 mg/kg IM or IV 3 times daily† ***Alternative choices*** Doxycycline > 8 years and ≥ 45 kg, 100 mg IV twice daily > 8 years and < 45 kg, 2.2 mg/kg IV twice daily (maximum, 200 mg/d) ≤ 8 years, 2.2 mg/kg IV twice daily (maximum, 200 mg/d)
Pregnant women	***Preferred choice*** Gentamicin, 5 mg/kg IM or IV once daily or 2 mg/kg loading dose followed by 1.7 mg/kg IM or IV 3 times daily†
	Alternative choices Doxycycline, 100 mg IV twice daily or 200 mg IV once daily Ciprofloxacin, 400 mg IV twice daily‡
	Mass Casualty Setting and Postexposure Prophylaxis#
Adults	***Preferred choices*** Doxycycline, 100 mg orally twice daily†† Ciprofloxacin, 500 mg orally twice daily!
	Alternative choice Chloramphenicol, 25 mg/kg orally 4 times daily§¶
Children	***Preferred choices*** Doxycycline†† > 8 years and ≥ 45 kg, 100 mg orally twice daily > 8 years and < 45 kg, 2.2 mg/kg orally twice daily (maximum, 200 mg/d) ≤ 8 years, 2.2 mg/kg orally twice daily (maximum, 200 mg/d) Ciprofloxacin, 20 mg/kg orally twice daily
	Alternative choice Chloramphenicol, 25 mg/kg orally 4 times daily§**¶
Pregnant women	***Preferred choices*** Doxycycline, 100 mg orally twice daily†† Ciprofloxacin 500 mg orally twice daily
	Alternative choice Chloramphenicol, 25 mg/kg orally 4 times daily§**¶

†Aminoglycosides must be adjusted according to renal function. Evidence suggests that gentamicin, 5 mg/kg IM or IV once daily, would be efficacious in children, although this is not yet widely accepted in clinical practice. Neonates up to 1 week of age and premature infants should receive gentamicin, 2.5 mg/kg IV twice daily.

‡Other fluoroquinolones can be substituted at doses appropriate for age. Ciprofloxacin should not exceed 1 g/d in children.

§Concentration should be maintained between 5 and 20 ug/ml. Concentrations greater than 25 ug/ml can cause reversible bone marrow suppression.

#Duration of treatment in mass casualty setting is 10 days and for postexposure prophylaxis is 7 days.

**Children younger than 2 years should not receive chloramphenicol.

††Tetracycline can be substituted for doxycycline.

¶Oral formulation only available outside the U.S.

Levofloxacin (500 mg orally once daily for 10 days) may be an acceptable alternative for those who cannot take doxycycline. FDA has approved levofloxacin for PEP based on animal data.

INFECTION CONTROL

Pneumonic plague can be spread from person-to-person by respiratory droplet transmission (coughing, sneezing). All staff should observe **Droplet Precautions** and **Standard Precautions** when caring for patients with suspected or confirmed pneumonic plague. **Contact** and **Standard Precautions** should be observed when caring for patients with suspected or confirmed bubonic plague, until **48-72 hours of appropriate antibiotics** have been administered AND the patient is showing clinical improvement. As 5-15% of patients with bubonic plague will develop secondary pneumonic plague, Droplet Precautions should be observed in all patients with bubonic plague until therapy has been initiated and pneumonitis has been ruled out. Droplet Precautions require that the patient be placed in a private room and that persons entering the patient room wear a surgical mask, especially when within three feet of the patient. *Negative air pressure isolation rooms are not indicated.*

In addition to respiratory droplet transmission, transmission can occur from plague skin lesions such as draining buboes or abscesses. Wound and skin precautions should be followed if skin lesions are present.

Multiple patients with pneumonic plague may be cohorted as long as all patients are receiving appropriate therapy.

Disposal of Infectious Waste

Use of tracking forms, containment, storage, packaging, treatment and disposal methods should be based upon the same rules as all other regulated medical wastes.

Autopsy and Handling of Corpses

All postmortem procedures are to be performed using Standard Precautions. Efforts should be made to avoid aerosolization. All persons performing or assisting in postmortem procedures must wear mandated PPE as delineated by OSHA guidelines. Instruments should be autoclaved or sterilized with a 10% bleach solution or other solutions approved by OSHA. Surfaces contaminated during postmortem procedures should be decontaminated with an appropriate chemical germicide such as 0.5% sodium bleach (10% household bleach) or 5% phenol (carbolic acid).

Reporting to the Health Department

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Los Angeles County Department of Public Health

Business Hours (8am -5pm)	**213-240-7941**
After Hours (County Operator)	**213-974-1234**

Ask to Speak with the Public Health Physician On-Call

SMALLPOX

ALL SUSPECTED CASES OF SMALLPOX MUST BE REPORTED IMMEDIATELY TO THE DEPARTMENT OF PUBLIC HEALTH ACUTE COMMUNICABLE DISEASE CONTROL PROGRAM:

Monday - Friday (8am – 5pm)
(213) 240-7941

After Hours (County Operator)
(213) 974-1234

Ask to Speak with the Public Health Physician On-Call

Quick Reference Sheet: Smallpox (variola major)

ALL SUSPECTED CASES OF SMALLPOX MUST BE REPORTED IMMEDIATELY TO THE DEPARTMENT OF PUBLIC HEALTH ACUTE COMMUNICABLE DISEASE CONTROL PROGRAM

During Business Hours	213-240-7941
After Hours (County Operator)	213-974-1234

Epidemiology:

- Declared eradicated worldwide in 1980 by the World Health Organization (WHO)
- Transmission person to person, primarily by droplet nuclei or aerosols but can occur by direct contact
- Transmission does not occur until onset of rash
- No animal reservoir

Clinical:

- Incubation period is 12-14 days (range 7-17 days)
- Characteristic rash appears 1-4 days after nonspecific, flu-like prodrome (high fever, malaise, and prostration, with headache and backache)
- Maculopapular rash begins on face, hands, forearms and spreads to legs and centrally to trunk; lesions are more predominant on the face and extremities than on the trunk
- Lesions progress synchronously from macules to papules to vesicles to pustules to crusty scabs over course of about two weeks

Diagnosis:

- A vaccinated member of the Public Health Smallpox Response Team should perform all lab specimen collections on patients classified as high risk by the CDC algorithm '
- Specimen examination requires Biosafety Level (BSL) -4 containment facilities (CDC or USAMRIID) for confirmation by electron microscopy, PCR, RFLP or cell culture

Treatment:

- Supportive care is the mainstay of therapy.
- In vitro antiviral activity against poxviruses has been shown with adefovir, cidofovir, dipivoxil and ribavirin. Animal studies suggest that cidofovir may be most effective

Management of Exposed Persons:

- Smallpox vaccine is required for all persons exposed at the time of a bioterrorist attack, anyone with close personal contact to a smallpox case during the infectious period, and household or other close contacts of the primary contacts
- Vaccine is most effective if given before or within 3 days of exposure

Infection Control:

- Strict Airborne and Contact Precautions from the onset of the rash until all scabs separate
- Confirmed and suspected cases should be isolated in negative air pressure isolation rooms. In an outbreak setting, confirmed and suspected cases should be isolated in designated smallpox receiving facilities.

- Only healthcare workers who have been vaccinated within the past 5-10 years and with a confirmed "take" should be exposed to a suspected or confirmed smallpox case.
- Asymptomatic contacts must be placed under fever surveillance for 18 days after their last exposure or until 14 days following successful vaccination (whichever comes first)
- Asymptomatic contacts to a smallpox case may be monitored in their homes or in a designated residential setting as directed by the local health officer.
- Asymptomatic afebrile contacts are not contagious and do not need to be isolated
- The authority to impose community or population-wide quarantine measures, (such as closing schools and offices, and recommending that the community remain in their homes) resides in Public Health, although implementation would require a multi-jurisdictional approach

Introduction and Epidemiology

Smallpox is caused by variola, a large enveloped DNA virus of the genus orthopoxvirus. The last natural occurrence of endemic smallpox was in Somalia in 1977. The last human cases were laboratory-acquired infections in 1978. The World Health Organization declared smallpox eradicated in 1980.

Person-to-person transmission of variola virus normally occurs by inhalation of virus-containing droplet nuclei or aerosols expelled from the oropharynx of infected persons with subsequent infection of the oropharyngeal region of the susceptible individual. Transmission occurs most efficiently during the early stages of the rash illness; it is generally believed that close (< 6.5 feet) person-to-person proximity is required for reliable transmission to occur. After an incubation period of 7 to 17 days (mean: 12 days), the period of infectivity begins as an enanthem and a rash characterized by maculae progressing to papules, vesicles, and pustules developing on the face and extremities first, all in the same stage. Patients remain contagious until the scabs have been shed. Transmission via contact with material from the smallpox pustules or crusted scabs can also occur, however, scabs are much less infectious than respiratory secretions. During the smallpox era, smallpox cases were generally limited to those who came into close contact (< 6.5 feet) with patients, usually in the household or in hospitals. There is no known animal reservoir for smallpox.

The stability of variola virus released into the environment is not known with certainty. It is believed that variola virus would exhibit properties similar to vaccinia virus, which if released as an aerosol, may persist for up to 24 hours (slightly longer, under ideal conditions of low temperature and humidity in the absence of UV light). Variola virus in scabs, in bedding and in clothing of smallpox patients, however, remains viable for extended periods.

During the past century, the prototypical disease, variola major, had a mortality rate of 3% in those with a history of vaccination sometime in the past and 30% in those never vaccinated. The key to control and eventual eradication of endemic smallpox was rigorous case identification followed by immunization of contacts. Routine smallpox vaccination was discontinued in the United States in 1972. Immunity from prior smallpox vaccination wanes with time and, at this point, the entire United States' civilian population is likely susceptible. However, persons who have been vaccinated in the remote past may experience less severe disease and have a decreased mortality rate.

Significance as a Potential Bioterrorist Agent

- Allegations that the former Soviet Union produced large quantities of smallpox virus and adapted it for use in bombs and intercontinental ballistic missiles
- Speculation regarding existence of clandestine smallpox virus stockpiles outside the stockpiles at the Centers for Disease Control and Prevention (Atlanta, United States) and the State Research Center of Virology and Biotechnology (Koltsovo, Russia)
- Probable low infectious dose
- Increasing susceptibility of the population
- High mortality rate in the non-immune

- Potential for significant ongoing transmission due to secondary spread

- Major media attention, widespread public fear and misconceptions about smallpox will add to the effectiveness of smallpox as an agent of mass panic

Clinical Manifestations

Historically, there were four forms of smallpox: variola major, variola minor (or alastrim), hemorrhagic smallpox and malignant (or flat) smallpox. Variola major accounted for approximately 90% of cases. Variola minor (or alastrim), was a milder form of the disease and accounted for a minority of cases. In some circumstances, variola minor was caused by a separate virus (variola minor) and in some circumstance was thought to result from some degree of host immunity. Hemorrhagic and malignant (flat) smallpox were both severe forms of the disease with high mortality. These forms are thought to be due to problems with host immunity, rather than to a different strain of virus.

As a terrorist agent, smallpox might be disseminated through an overt or covert aerosol attack or a "suicide patient." It is unclear how a smallpox epidemic in the United States today would progress. Many sociological factors related to disease transmission are different today than in the past. The immunity of the population has waned and there is a much larger population of immunosuppressed individuals. The mortality rate may be higher than the historic mortality rate of 30% because of these factors. There may be an increased frequency of hemorrhagic and malignant forms of smallpox in immunosuppressed populations. One would not anticipate cases of variola minor (alastrim) as this milder strain of the virus is less likely to have been weaponized. At the same time, advances in supportive care technology might be expected to lead to a lowered mortality rate. The aggregate effect is hard to predict.

CDC and other smallpox experts suggest that clinicians focus on identifying a classic case of variola major, as the clinical presentation of a classic case of smallpox is rather specific, and should be easily recognizable once the characteristic features are understood.

This section will focus primarily on variola major, with some additional information on the hemorrhagic and malignant forms.

Variola major

Incubation period

Typically 12-14 days (range 7-17 days).

Signs and Symptoms

- **Prodrome:** Acute onset of malaise, prostration, high fever, rigors, myalgias, abdominal pain, vomiting, headache and backache. 15% develop delirium. 10% of light-skinned patients have a transient erythematous rash.

- **Exanthem:** Appears as soon as 1-4 days after prodrome, just as fever peaks, with a discrete maculopapular rash on the mucous membranes of mouth and pharynx, face, hands, and forearms. Involvement of palms and soles is common. Rash spreads to the

legs and then centrally to the trunk during the second week. Lesions quickly progress from sparse macules (day 1), to papules (day 2), to vesicles (days 2-3), to pustules, often with central umbilication, (days 5 to approximately 12), and scabs (days 13-18) for a total duration of 2-3 weeks.

- ***History and Physical Examination:*** Ask detailed questions about any symptoms preceding rash onset, including prodromal symptoms and clinical features in the 1-4 days before rash onset, contact with any ill individuals (especially those with a rash illness), history of prior varicella or herpes zoster, and history of varicella vaccination (vaccine available since 1995). In persons born before 1972 and those who served in the military or worked in medical laboratories, ask about smallpox vaccination and look for a vaccination scar (Children in the United States were routinely vaccinated until 1971, military personnel until 1990, and persons working with orthopoxviruses continue to be vaccinated. Since early 2003, some public health personnel, healthcare workers, and first responders have been vaccinated). In addition, determine if the patient is immunocompetent, which medications (prescription and over-the-counter) the patient has taken and where the patient has traveled. This information will be helpful in evaluating the patient, determining which illnesses should be considered in the differential diagnosis, and finally, if smallpox is a consideration, will be used to classify a case patient into low, moderate or high risk categories for smallpox.

Clinical Course

- Fever may decrease somewhat after the initial onset of rash
- Multiorgan involvement and secondary bacterial infections do not commonly occur. Encephalitis may occur similarly to the encephalitis that occurs in vaccinia, measles or varicella.
- Complications may include arthritis, pneumonia, osteomyelitis and keratitis.
- Historically mortality is 30% in unvaccinated individuals and 3% in previously vaccinated individuals (without specifying the remoteness of vaccination).
- Death typically occurs in the second week from high-level viremia and circulating immune complexes.

Differential Diagnosis of Smallpox

Condition	Features of condition that distinguish from smallpox
Varicella (chickenpox)	Smallpox has many more lesions on face and extremities than trunk (centrifugal spread). Smallpox lesions are synchronous in their stage of development on any one region of the body. Smallpox lesions are more common on palms and soles. Smallpox lesions are more deeply imbedded in the dermis than the superficial lesions of chickenpox. Smallpox lesions are more often painful than pruritic. Typical prodrome in varicella is mild or brief. Varicella cases with no history of varicella or varicella vaccination may have exposure history.
Monkeypox	Difficult to distinguish. Monkeypox often has lymphadenopathy and lower fever
Disseminated herpes zoster	Begins dermatomally, often in the elderly or immunocompromised, with lesions in various stages and similar to varicella.
Disseminated herpes simplex	Typically immunocompromised host, lesions in various stages; superficial lesions; rash appears similar to varicella
Impetigo	No prodrome, localized rash; not disseminated
Drug rash	History of medication; rash may be generalized; often not severely ill
Enterovirus	Milder fever; pharyngitis; lesions on hands, feet, mouth, evolve into grayish flat vesicles that appear more superficial
Contact dermatitis	No viral prodrome; often localized; pruritic
Scabies	Localized rash; pruritic; no febrile prodrome
Insect bites	Localized rash; pruritic; no febrile prodrome
Acne	Predominantly face, chest & back; chronic; no febrile prodrome
Molluscum contagiosum	Immunocompromised; no febrile prodrome
Measles	Cough and coryza
Rubella	Lymphadenopathy
RMSF	Intense prodromal headache; thrombocytopenia, anemia and leukopenia common
Syphilis	No prodrome

Clinical laboratory Values

Severe cases can have leukopenia, differential may show granulocytopenia, increased lymphocytes and elevated basophils.

(see "Evaluating the Patient with Acute, Generalized Vesicular or Pustular Rash Illness and Determining the Risk of Smallpox,").

http://www.bt.cdc.gov/agent/smallpox/diagnosis/pdf/spox-poster-full.pdf

To order a Smallpox Reference Poster from LA County Department of Public Health, visit: http://publichealth.lacounty.gov/acd/HCPmaterials.htm

Variations in variola major

Malignant (flat-type) Smallpox

- Occurs in 2-5% of smallpox cases
- May be more contagious due to increased viral burden
- Often due to lack of adequate cell-mediated immune response in the host
- Historically, malignant or hemorrhagic cases were often the index cases (due to shorter incubation period) but were often misdiagnosed and not recognized as smallpox

Incubation period

May be somewhat shorter than seen in classic smallpox. Typically 12-14 days (range 7-17 days).

Signs and Symptoms

- Malignant smallpox is notable for severe systemic toxicity with extreme, severely prostrating viral prodromic phase
- Abdominal pain can be severe enough to be mistakenly diagnosed as appendicitis or other cause of acute surgical abdomen
- Rash begins as a slow evolution of flat, soft, focal skin lesions. These papules coalesce and never become pustular. Skin develops a fine-grained reddish color, resembling crepe rubber.
- Occurs more frequently in children
- The mortality among unvaccinated persons is 95%.
- In survivors, the lesions may either resolve without scarring, or lead to large areas of desquamation.

Differential Diagnosis of Malignant (flat-type) Smallpox

Condition	Features of condition that distinguish from smallpox
Hemorrhagic varicella	History of exposure to varicella; no history of varicella vaccination
Acute surgical abdomen	No development of rash; no abdominal findings or imaging

Clinical Laboratory Values
Severe cases can have leukopenia; differential may show granulocytopenia, increased lymphocytes and elevated basophils.

Hemorrhagic-type smallpox

- Occurs in less than 3% of smallpox cases.
- May be more contagious due to increased viral burden.
- Historically, malignant or hemorrhagic cases were often the index case (due to shorter incubation period) but were often misdiagnosed and not recognized as smallpox.
- Hemorrhagic-type smallpox occurs among all ages but more commonly in adults. Both sexes are affected equally.

Incubation period
May be somewhat shorter than seen in classic smallpox. Typically 12-14 days (range 7-17 days).

Signs and Symptoms
- Hemorrhagic smallpox presents with severe systemic toxicity with extreme, severely prostrating viral prodromic phase (high fevers, headache, backache and abdominal pain).
- Rash begins as a dusky erythema, followed by extensive petechiae, mucosal hemorrhage and intense toxemia.
- Seen more commonly in pregnant women.
- Patients usually die before development of typical pox lesions.

Differential Diagnosis of Hemorrhagic-type Smallpox

Condition	Features of condition that distinguish from smallpox
Meningococcemia	Gram-negative diplococci in blood and CSF; shorter interval between onset of symptoms and rash; bacterial meningitis
Acute leukemia.	Possible recent history of easy bleeding; fatigue; weight loss with malignancy
Viral hemorrhagic fever	May have travel history
Rickettsial sepsis	History of tick bite
Ehrlichiosis	History of tick bite
Stevens Johnson	No febrile prodrome
Kawasaki syndrome	"Strawberry tongue"
Scarlet fever	No febrile prodrome, "strawberry tongue"
Toxic shock syndrome	No febrile prodrome, "strawberry tongue"
Erysipelas	No febrile prodrome
Measles	Koplik spots; cough and coryza

Clinical Laboratory Values
Hemorrhagic smallpox patients may have granulocytopenia with relative lymphocytosis. In early hemorrhagic cases, patients may have thrombocytopenia, prolonged PT and/or PTT, circulating antithrombin and an increase in immature lymphoid cells.

Laboratory Diagnosis

If smallpox is suspected, please immediately call the Department of Public Health Acute Communicable Disease Control Program (Business Hours: (213) 240-7941 or After Hours: (213) 974-1234) to arrange for submission of specimens to a reference laboratory for rule-out and confirmatory testing.

In the event of a bioterrorist release of smallpox, confirmation by a reference laboratory will be necessary for the earliest (index) cases. After a smallpox outbreak is confirmed, diagnosis of subsequent cases will need to be based on a compatible clinical presentation.

NOTE: specimen collection should only be performed by an individual wearing appropriate PPE and **vaccinated within the last 5-10 years.** For a case deemed high risk for smallpox, contact the **Department of Public Health Acute Communicable Disease Control Program (Business Hours: (213) 240-7941 or After Hours: (213) 974-1234) immediately.** A vaccinated Public Health Smallpox Rapid Response Team member(s) will respond and assist with assessment of the patient, sample collection, epidemiologic investigation, contact identification and tracing, risk communication, security and coordination with criminal investigation.

All moderate or high risk cases should be immediately reported by telephone to the above numbers. For high risk patients, all confirmatory viral laboratory testing on materials obtained from skin lesions should ONLY be performed at an appropriate reference laboratory. For moderate risk patients, all laboratory testing to rule in varicella and other orthopox viruses should be performed at the Public Health PHL.

Specimen Collection

Label all tubes, vials and microscope slide holders with: patient's name, unique identifier, date of collection, source of specimen (vesicle, pustule, scab or fluid) and name of person collecting the specimen. Wear personal protective equipment (N95 mask, goggles, gloves, gown and shoe covers or Tyvek coveralls).

Specimen Collection Procedure

1. Clean patient's skin with an alcohol wipe and allow skin to dry.
2. Open the top of a firm, fresh vesicle or pustule with a sterile tuberculin syringe or 26-gauge needle or scalpel. Place the skin of the vesicle or pustule top into a dry, sterile screw-capped container (Blue Top).
3. Take slide and at different sites on the slide, touch the open lesion at least three times. Allow fluid to air-dry 10 minutes without smearing. Label the slide as touch prep and place in the slide holder.
4. Scrape the base of the vesicle or pustule vigorously (without drawing blood) with the plastic end of an applicator stick or swab and smear the scrapings onto a glass microscopic slide. Allow to dry for 10 minutes. To prevent cross-contamination, do not place slides from more than one patient in the same slide holder. If slide is not available, swab the base of the lesion with a swab, place in a dry, sterile 15ml screw-capped container (Blue Top), break off applicator handle.

5. Again, scrape the base of the vesicle or pustule vigorously (without drawing blood) with a second applicator stick or swab and place in a 15 ml screw-capped container with standard viral transport medium.
6. Repeat above procedures on at least 2 more lesions.

Please consult with the Department of Public Health for additional sampling protocols including testing of scab material and punch biopsy.

Specimens will be tested at the CDC Biosafety Level 4 Reference Laboratory using the following tests:

Electron Microscopy
Scrapings of vesicular lesions can be examined by electron microscopy for characteristic brick-shaped virions. This method does not distinguish variola from vaccinia, monkeypox or cowpox.

Viral Cultures
Requires isolation of virus and characterization of its growth on chorioallantoic membrane or cell culture.

Other Testing
Polymerase chain reaction and restriction fragment length polymorphisms are diagnostic techniques that promise a more accurate and less cumbersome method of identifying variola virus. These techniques are currently only available at certain LRN laboratories, such as the LAC PHL and the California State Viral Rickettsial Disease Laboratory.

Treatment

While there is no proven effective treatment for smallpox, there are potential medical therapies that may be beneficial. Supportive care is the mainstay of therapy and antibiotics should be used for any secondary bacterial infections. Historically, smallpox in unvaccinated individuals has a mortality of 30%. This figure may be decreased with modern supportive care or may be increased due to a different population pool (higher prevalence of the immunosuppressed). Therapies include:

- Meticulous skin care and hygiene
- Ophthalmological consultation and care for keratitis or other ocular lesions should be obtained
- Dehydration and electrolyte abnormalities can occur during the vesicular and pustular rash stages requiring careful monitoring of electrolytes and fluid status, with hydration and nutritional support as needed
- Appropriate analgesia should be maintained
- Currently, there are no anti-viral drugs of proven efficacy. Although, adefovir, dipivoxil, cidofovir and ribavirin have significant in vitro antiviral activity against poxviruses, their efficacy as therapeutic agents for smallpox is currently uncertain. Cidofovir is FDA-licensed and shows the most promise in animal models.
- The use of cidofovir to treat smallpox should be evaluated and monitored by experts at the CDC. Cidofovir is available from the CDC and is available through the Strategic National Stockpile in large amounts, but there are a number of precautions and contraindications

- VIGIV is only available through the Strategic National Stockpile from CDC. It is administered intravenously. It is used to treat complications from smallpox vaccination, such as: eczema vaccinatum, progressive vaccinia, severe generalized vaccinia, vaccinia infections in individuals who have skin conditions, and aberrant infections induced by vaccinia virus (except in cases of isolated keratitits).
- Under a contract awarded in 2011, the Federal Government is acquiring Tecovirimat (St-246) for the Strategic National Stockpile, for potential treatment of individuals who are symptomatic and/or diagnosed with smallpox disease.
- Bacterial superinfection of lesions was not common historically but should be watched for and treated as appropriate.
- In an outbreak situation, if patients are cohorted, any patient with a suspected but not laboratory confirmed case of smallpox should be vaccinated prior to exposure to known smallpox patients. This is to prevent inadvertent transmission of smallpox to a misdiagnosed patient.

Management of Exposed Persons

An exposed person is defined as a person who has been in close personal contact with a patient with suspected or confirmed smallpox. Close personal contact includes persons residing in the same household as the case-patient or persons with face-to-face contact with the case AFTER the case has developed febrile illness.

During outbreaks in Europe in the 1960s, up to 10-20 secondary cases occurred after exposure to a single case-patient if vaccination efforts were delayed. The majority of these secondary cases were household contacts or healthcare workers.

In the less likely scenario of an overt aerosolized attack, the extent of exposure, and definition of an exposed person (to the primary aerosolization of virus) will be described by public health authorities in conjunction with environmental health, and the appropriate local, state, and federal authorities.

All exposed persons should be immediately referred to **the Department of Public Health Acute Communicable Disease Control Program (Business Hours: (213) 240-7941 or After Hours: (213) 974-1234.**
Exposed individuals will be:

- Medically triaged to rule out active infection with smallpox
- Assessed for level of exposure
- Assessed for contraindications to vaccination **(NOTE: There are no absolute contraindications to vaccination in the context of actual exposure to smallpox)**
- Counseled about the level of risk
- Vaccinated if appropriate
- Potentially queried by law enforcement (to facilitate the investigation of the criminal terrorist act of a smallpox attack, including potential exposure information)
- Information on the primary contact's household and close personal contacts will be obtained to facilitate vaccination efforts
- Placed on fever surveillance
- Offered mental health support (patient and household members)

Individuals who are exposed to smallpox are not contagious until after development of rash. A febrile prodrome precedes the onset of rash by 1-4 days. Thus fever in an individual who was exposed to a case and subsequently vaccinated could be a reaction to vaccination, an unrelated illness, or an indicator that the individual is in the viral prodrome phase of smallpox and will become contagious within 1-4 days. Afebrile vaccinated exposed individuals will not be "quarantined," but placed on twice daily fever surveillance.

Vaccinated contacts may continue their daily activities, including work, as long as they are compliant with twice-daily temperature checks for 18 days, remain afebrile and remain within the area. Although the majority of vaccinated contacts may remain in their homes and workplaces during this period, some individuals may be referred to a Category R (residential) facility (such as a designated hotel or shelter) if they are unable to comply with such surveillance.

A vaccinated contact who develops a fever will require isolation and close observation for development of a rash.

A contact who develops a rash will be considered high risk for smallpox, and require either isolation in a negative air pressure isolation room or in a designated smallpox facility.

Please refer to the Public Health Smallpox Preparedness, Response and Recovery Plan for additional details on contact management.

Smallpox Vaccine

Smallpox vaccine is a highly effective immunizing agent (95% efficacy). In fact, smallpox vaccination is the only way to prevent smallpox. Smallpox vaccine is a live vaccine composed of a virus called vaccinia. Vaccinia is another orthopoxvirus (related to smallpox) but cannot spread or cause smallpox. It helps the body develop immunity to smallpox. Because the virus in the vaccine is a “live” virus, it can spread to other parts of the body or to other people from the vaccine site. This can be prevented through proper care of the vaccination site (e.g. hand washing and careful disposal of used bandages).

The smallpox vaccine, Dryvax (licensed by the FDA in 1931), was used in the focused ring vaccination campaigns during the global smallpox eradication effort. The campaigns utilized intensive surveillance and contact tracing to bring about global eradication of smallpox disease.

The last case of smallpox in the U.S. was in 1949. The last naturally occurring case in the world was in Somalia in 1977. Routine vaccination of the American public against smallpox stopped in 1972. Since the disease was eradicated, it was not necessary to prevent it through vaccination so vaccine production ceased. However, CDC (Centers for Disease and Prevention) kept a stockpile of Dryvax for emergency use. After the event of September 11, 2001, The U.S. government took measures to improve its level of preparedness against terrorism. In 2003, the U.S. government offered doses of Dryvax to civilian volunteer healthcare workers in the Preparedness and Response Program. Currently, the new smallpox vaccine (ACAM2000) is provided only to scientists and medical professionals who work with smallpox or similar viruses in a research setting. It is also used by the Department of Defense for protection against smallpox among the military personnel.

ACAM2000 is the current smallpox vaccine that has replaced Dyvax, as the primary smallpox vaccine stockpiled for use in an emergency, such as a terrorist attack. It was developed under

contracts with CDC. Dryvax is no longer available since CDC's contract with Wyeth (the manufacturer of Dryvax) expired in February 2008. CDC oversees the strategic national stockpile of ACAM2000 in the U.S.

ACAM2000 was licensed by the Food and Drug Administration (FDA) in September of 2007. It is manufactured by ACAMBIS using modern cell-culture techniques. This allows for rapid and large-scale production with consistent product quality. The vaccinia virus is grown in vero cells instead of on the skin of calves like Dryvax. As a second generation vaccine, ACAM2000 is derived from Dryvax.

ACAM2000, a lyophilized powdered vaccine, is supplied in a multiple-dose 3 mL clear glass vial. The lyophilized powder is reconstituted with packaged diluent. The diluent is supplied in a 3 mL clear glass vial containing 0.6 mL solution. One hundred bifurcated needles are supplied in a box. (5X5X1 in). A 1 mL tuberculin syringe with 25 gauge needle is supplied for vaccine reconstitution. After reconstitution, each vial has approximately 100 doses of 0.0025 mL.

IMVAMUNE®, also known as modified vaccinia Ankara (MVA), is an attenuated smallpox vaccine that is being developed for individuals with HIV infection or atopic dermatitis (AD).

Vaccine Indications

ACAM2000 is indicated for active immunization against smallpox disease for persons determined to be at high risk for smallpox infection. In a preparedness setting (or "pre-event" setting), indications for vaccination are largely dependent on an individual's occupation, willingness to volunteer, absence of any contraindications, and the suspected level of threat reported by the Federal government. **It is important to note that there are NO contraindications to vaccination in the event of actual exposure to the virus or an individual with smallpox.**

All exposed persons, including all household and face-to-face contacts of patients, should be vaccinated immediately, if vaccine is available. Additionally, all healthcare workers who might care for smallpox patients, emergency personnel who might transport patients and mortuary staff should be vaccinated as soon as vaccine is available. **Vaccination is most effective at protecting against smallpox if given either before or within 3 days of exposure.**

Contraindications in Pre-event Smallpox Vaccination

Currently, ACAM2000 is not recommended for the general public. People who should not receive the vaccine in a non-emergency setting include:

1. Anyone who is allergic to the vaccine or any of its components
2. Women who are pregnant or planning to become pregnant within 4 weeks after vaccination
3. Women who are breastfeeding
4. Anyone under 12 months of age
5. People who have, or have had certain skin conditions (especially eczema and atopic dermatitis
6. People with weakened immune systems, such as those who have received a transplant, are HIV positive, are receiving treatment for cancer, or are taking medications (like steroids) that suppress the immune system
7. People who have been diagnosed as having a heart condition, or who have 3 or more known major cardiac risk factors.

Common Adverse Reactions

Common adverse reactions observed in ACAM2000 vaccination include: itching at the vaccination site, sore arm, fever, headache, body ache, mild rash and fatigue.

Storage and Handling

ACAM2000 is stored by the CDC in freezer with temperature of -15°C to -25° C (+5° F to -13° F). Unreconstituted vaccine once received can be stored refrigerated at 2° C to 8° C (35° F to 46° F) for up to 18 months (The expiration date is set when the vaccine leaves the national stockpiles). Diluent is stored at room temperature. Its expiration date is 5 years. Reconstituted vaccine may be administered within 6-8 hours if kept at temperature (20° to 25° C, 68° to 77° F); it should then be discarded as biohazardous material. Reconstituted vaccine may be returned to refrigerated storage overnight for future use if it has been exposed to room temperature conditions for less than 6-8 hours at a time. This cycle can be repeated for as many times as is practical (so long as it is within 30 days of reconstitution date). Unused reconstituted vaccine may be stored in a refrigerator at 2° C to 8° C (35° F to 46° F) no longer than 30 days.

Methodology

Preparation/Handling Precautions and instructions for Disposal:

When preparing and administering the vaccine, personnel should wear protective gloves and avoid contact of vaccine with skin or mucous membranes.

The vaccine vial, its stopper, the diluents syringe, the vented needle used for reconstitution, the bifurcated needle used for administration, and any gauze or cotton that came in contact with the vaccine should be discarded in leak-proof biohazard containers. These containers should then be disposed of appropriately.

Reconstitution of ACAM2000:

The vaccine vial should be removed from cold storage and brought to room temperature before reconstitution. The flip cap seals of the vaccine and diluent vials are removed, and each rubber stopper is wiped with an isopropyl alcohol swab and allowed to dry thoroughly. Using aseptic technique and a sterile 1 mL syringe fitted with a 25 gauge x 5/8” needle (provided), draw up 0.3 mL of diluent and transfer entire contents of the syringe to the vaccine vial. Gently swirl to mix but try not to get product on the rubber stopper. The reconstituted vaccine should be clear to slightly hazy, colorless to straw-colored liquid free from extraneous matter. Inspect the vaccine after reconstitution for particulate matter and discoloration before administration. If particulate matter is observed, the vaccine should not be used and the vial should be disposed of safely.

Vaccination Instructions:

Vaccinators must receive education on the proper administration of ACAM2000 prior to administering the vaccine. A Medication Guide (used as a smallpox vaccine information statement) should be provided to the vaccinee.

Gather vaccine and supplies for administration (i.e., bifurcated needle, alcohol prep pads, 2x2 sterile gauze, semipermeable dressing such as Tegaderm, tape, gloves, biohazard sharps container, biohazard bag, and towel/bib). Verify the patient's identity, review and/or clarify screening questions. Clarify other questions and concerns. Ensure that consent was signed and screenings completed. Document that the ACAM2000 Medication Guide was given to the recipient. Place vaccine vial in vaccine holder to stabilize the vaccine vial. Remove vaccine vial stopper and place it inverted onto gauze, and cover with another gauze. Wash or sanitize hands with soap and water or alcohol based, anti-bacterial hand sanitizer. Don gloves. Ensure that consent was signed and screenings completed.

Select a vaccination site (currently the deltoid region is the recommended site) and assess if skin cleaning is necessary. If the site is obviously dirty, soap and water may be used to clean the area. (If an alcohol pad is used to clean the site, the skin must be allowed to dry thoroughly to prevent inactivation of the vaccine by alcohol).

Tear off packet containing a single bifurcated needle. Peel back wrapper about halfway, exposing butt-end of needle. Hold butt-end and gently pull bifurcated point-end free from wrapper. Dip bifurcated end of needle into the vaccine and visually confirm drop of vaccine is present between the prongs. (**Caution:** Needles should never be dipped into the vaccine vial more than once to avoid contamination of the vial.)

Pull the skin taut on the deltoid region of the upper arm with the other hand. Rest the wrist that is holding the bifurcated needle on the arm of the vaccinee. Position the needle perpendicular to the site of insertion. Make 15 rapid insertions into an area less than 5mm in diameter; the punctures should evoke a trace of blood after 15 to 30 seconds. Dispose of the contaminated needle in a biohazard sharp container. Use a 4x4 gauze to blot off any excess vaccine and blood and dispose into a biohazard bag.

Loosely cover the vaccination site with gauze and secure with a piece of tape. (If the vaccinee is involved in direct patient care, the gauze should be covered with a semipermeable dressing-Tegaderm). If the vaccine is not to be used further during that clinic, reinsert the rubber stopper and return to the refrigerator or placed it properly prepared cooler. Remove and discard gloves in the biohazard bag.

Record the vaccination and instruct the vaccinee on how to take care of the site.

Instructions on Taking Care of the Vaccination Site:

Cover the vaccination site loosely with a gauze bandage, using first aid adhesive tape to keep in place. Keep it covered until the scab falls off on its own. This bandage will provide a barrier to protect against the spread of the vaccinia virus. Apply a semipermeable dressing if involved in direct patient care. Wear a shirt that covers the vaccination site as an extra precaution to prevent the spread of the vaccinia virus. This is important in situations of close physical contact. Change the bandage every 1 to 3 days, or when dressing is soiled. Wash hands with soap and hot water or with alcohol-based hand sanitizer after direct contact with the vaccination site, the bandage or clothes, towels or sheets that might be contaminated with the virus from the vaccination site. Keep the vaccination site dry. Cover it with a waterproof bandage when bathing. Remove and change back to the loose gauze bandage after bathing. Put the contaminated bandages in a sealed plastic bag and throw them away in the trash. Keep a

separate laundry hamper for clothing, towels, bedding or other items that may have come in direct contact with the vaccination site or drainage from the site. Wash clothing or any other material that comes in contact with the vaccination site using hot water with detergent and/or bleach. Wash hands afterwards. Throw scab away in a sealed plastic bag when it falls off, and then wash hands.

The vaccinee should be instructed to return to the clinic in 6 to 8 days for the evaluation of the vaccination site for a "take".

Vaccination Failures

If a primary vaccination "take" or "major reaction" did not result, the vaccinee should be revaccinated in an attempt to achieve a satisfactory "take". A "take" indicates successful vaccination and it's characterized by a pustular lesion or an area of definite induration or congestion surrounding a central lesion. In the case of vaccination failure, the vaccination procedures should be checked, and vaccination repeated with a vaccine from another vial or vaccine lot. If a repeat vaccination is conducted using vaccine from another vial or vaccine lot fails to produce a major reaction, consult CDC at (404) 639-3670 before giving another dose.

Revaccination

The CDC recommends that personnel whose only occupational exposure to orthopoxviruses is through administering smallpox vaccine to others, (e.g., people who administer vaccine to poxvirus researchers, lab workers, etc.) be revaccinated every 10 years. For laboratory workers who handle virulent strains of orthopoxviruses, the ACIP recommends that these laboratory workers be revaccinated every 3 years.

CDC is currently recommending revaccination of volunteer responders from the pre-event smallpox program (2003) on an as-needed or "out-the-door" basis. "Out-the-door" basis is defined as receiving revaccination only after there is a determination of a credible smallpox threat to public health and prior to engaging in activities involving a risk for exposure to smallpox virus. "Out-the-door" revaccination would only apply to first responders who had been vaccinated as part of the US Civilian Smallpox Preparedness and had a documented vaccine "take". A "take" typically appears as a vesicle surrounded by a red areola, which becomes umbilicated and then pustular by days 7-11 after vaccination. Skin reactions after revaccination are typically less pronounced with more rapid progression and healing than those after primary vaccinations. The "out-the-door" recommendation would be activated only after a smallpox outbreak is confirmed or highly suspected, or there is credible evidence of a release or imminent release of smallpox virus.

For additional information on vaccination instructions, vaccine reconstitution, vaccine administration and care of the vaccination, visit:
http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM142572.pdf

Infection Control

Contact and Airborne Precautions

Smallpox is transmissible from person to person by exposure to respiratory secretions (particularly from coughing patients), contact with pox lesions and by fomites (although not efficiently). All staff should observe **both Airborne and Contact Isolation Precautions, in addition to Standard Precautions,** when caring for patients with suspected or confirmed smallpox.

If a patient presents to an emergency department or clinic with an acute generalized vesicular or pustular rash illness, care should be taken to decrease the risk of disease transmission.

- A surgical mask should be immediately placed on the patient.
- The patient should not be left in common waiting areas but placed without delay in a private, negative airflow room with the door kept closed.
- Alert the infection control department.
- Institute appropriate Airborne and Contact Precautions.
- Patient should be placed in a closed-door, negative air pressure isolation room with 6 to 12 air exchanges per hour and HEPA filtration of exhausted air.
- Keep the door closed at all times, except when staff or the patient must enter or exit.
- Staff and visitors should wear respirators (N95 or higher quality), gloves and gowns.
- Patient should wear surgical mask whenever patient must be outside of the negative air pressure isolation room and must be gowned or wrapped in a sheet so that the rash is fully covered.
- Patient should remain on strict isolation from the onset of eruptive exanthem until all pox scabs have separated (generally 14-28 days).

In the event of a large-scale smallpox outbreak due to a bioterrorist attack, there may be massive numbers of victims. In this case, there may be a need to cohort patients due to limited availability of respiratory isolation rooms. If this is done, then **all patients should receive smallpox vaccine within 3 days of exposure, in the event that some of these patients are misdiagnosed with smallpox.**

All healthcare workers providing direct patient care to persons with smallpox should be vaccinated within the last 3 years. If vaccinated staff are unavailable, then only staff who have previously received smallpox vaccine and who do not have contraindications to vaccine *(e.g., persons born before 1972 or persons who were in the military before 1989)* should be caring for patients with suspected or confirmed smallpox.

Disposal of Infectious Waste

- Use of tracking forms, containment, storage, packaging, treatment and disposal methods should be based upon the same rules as all other regulated medical wastes.
- There is no specific data on susceptibility of the smallpox virus to any current decontamination products. Recommendations are based on extrapolation from vaccinia virus.
- The concentration of EPA registered germicides used in routine healthcare decontamination is more than adequate for smallpox disinfection of environmental surfaces.
- FDA approved high-level disinfectants or chemical sterilants are effective at inactivating smallpox virus for semi-critical instruments and devices.
- For reusable medical equipment, routine cleaning and disinfection are adequate.
- There is no evidence of transmission of variola virus for non-porous surfaces. Routine cleaning and disinfection are adequate. There is no indication to use extraordinary procedures to clean and disinfect the interior surfaces of ambulances or other spaces occupied by smallpox patients.
- Regulated medical waste can be handled with approved methods of medical waste decontamination and can be expected to inactivate poxviruses.
- Air space decontamination (fumigation) is not indicated.

Laundry

- Contaminated textiles and fabrics such as clothing and bed linens from patients should be handled with minimum agitation to avoid re-aerosolization of virus.
- Textiles and clothing should be bagged or contained at the point-of-use in accordance with Occupational Safety and Health Administration (OSHA) regulations.
- Do NOT sort prior to laundering.
- Wet textiles should be bagged first and then placed in a leak-proof container.
- Reusable fabric laundry bags commonly used for laundry transport can be laundered along with the clothing and other fabrics.
- The use of a water-soluble bag is another option for minimizing direct contact and manipulation of these fabrics and clothing prior to washing.
- If laundry is transported to an off-site facility, the procedures that are currently used for transporting and safe handling of contaminated textiles off-site will be adequate for these situations.
- Laundry should be labeled in such a way that laundry staff should be prompted to wear appropriate PPE and handle potentially contaminated laundry with a minimum of agitation.
- The laundry area in a healthcare facility that receives potentially contaminated textiles and clothing should be set at negative air pressure as per normal operating standards and be physically separate from the area where clean laundry is dried, folded, and packed for transport and distribution.
- Textiles and fabrics from care areas for smallpox patients can be laundered using routine protocols for healthcare facilities (i.e., hot water [71 °C or 160°F] washing with detergent and bleach and hot air drying).
- No special laundering protocols are needed, nor is it necessary to launder materials from smallpox care areas separately from laundry generated elsewhere in the facility.
- If contaminated clothing and bed linens are to be washed at home, use the hot water cycle at the highest temperature possible with detergent followed by hot air drying.

- The use of chlorine bleach during hot water washing can provide an additional measure of safety. The use of cold water washing has not been evaluated with respect to inactivation of variola virus.
- If no other wash cycles other than cold water are available, use detergents and laundry additives that are specifically formulated for cold water washing and dry using a hot air cycle for the dryer.

Please refer to the CDC: Smallpox Response Planning Guidelines: http://www.bt.cdc.gov/agent/smallpox/response-plan/#guidef (Updated 3/21/2003) for further detail and the latest updates on decontamination guidelines.

Autopsy and Handling of Corpses

All postmortem procedures are to be performed using Standard Precautions. In addition, due to concerns about aerosolization of the virus, personnel should use particulate respirators as recommended under **Airborne Precautions.** All persons performing or assisting in postmortem procedures must wear mandated PPE as delineated by OSHA guidelines. Instruments should be autoclaved or sterilized with a 10% bleach solution or other solutions approved by OSHA. Surfaces contaminated during postmortem procedures should be decontaminated with an appropriate chemical germicide such as 10% hypochlorite or 5% phenol (carbolic acid).

The public health authority may choose to exercise the powers regarding the safe disposal of human remains, as outlined in Section 504 of the Model State Emergency Health Powers Act, if it is determined that a state of public health emergency exists.

Reporting to the Health Department

Smallpox is an international emergency and even an isolated suspected case MUST be reported immediately by phone to the:

Los Angeles County Department of Public Health

Business Hours (8am -5pm) **213-240-7941**
After Hours (County Operator) **213-974-1234**

Ask to Speak with the Public Health Physician On-Call

TULAREMIA

ALL SUSPECTED CASES OF TULAREMIA MUST BE REPORTED IMMEDIATELY TO THE DEPARTMENT OF PUBLIC HEALTH ACUTE COMMUNICABLE DISEASE CONTROL PROGRAM:

Monday - Friday (8am – 5pm)
(213) 240-7941

After Hours (County Operator)
(213) 974-1234

Ask to Speak with the Public Health Physician On-Call

Quick Reference Sheet: Tularemia (Francisella tularensis)

ALL SUSPECTED CASES OF TULAREMIA MUST BE REPORTED IMMEDIATELY TO THE DEPARTMENT OF PUBLIC HEALTH ACUTE COMMUNICABLE DISEASE CONTROL PROGRAM

During Business Hours	213-240-7941
After Hours (County Operator)	213-974-1234

Epidemiology:

- Highly infectious after aerosolization
- Infectious dose can be as low as 10-50 aerosolized organisms

Clinical:

- Incubation period is 3-5 days (range 1-14 days)
- Aerosolization would most likely result in primary pleuropneumonic or typhoidal tularemia
- Typhoidal tularemia is a nonspecific illness, with fever, headache, malaise and non-productive cough (mortality rates can be as high as 30-60% if untreated) without cutaneous or mucosal membrane lesions or regional lymphadenitis. Secondary pleuropulmonary involvement is common.
- Ingestion of contaminated food or drinking contaminated water may result in oropharyngeal tularemia

Diagnosis:

- Requires a high index of suspicion given nonspecific presentation
- Organism is difficult to culture and grows poorly on standard media; cysteine-enriched media is required
- Diagnosis of tularemia is usually confirmed serologically; antibody titers may not be elevated until 10 or more days after onset
- Bacterial cultures should be handled under Biosafety Level 3 conditions

Treatment:

- Parenteral streptomycin or gentamicin for 7-14 days is recommended
- Tetracyclines are alternative choices although they are bacteriostatic and associated with higher relapse rates and must be continued for at least 14 days

Management of Exposed Persons:

- Antibiotic prophylaxis is most effective if begun within 24 hours after exposure
- Tetracyclines are recommended for 14 days

Infection Control:

- Person-to-person transmission does **not** occur
- Standard Precautions are sufficient; isolation is not required
- Alert laboratory if suspicion for tularemia as additional precautions needed in laboratory

Introduction and Epidemiology

Tularemia is a zoonotic disease caused by *Francisella tularensis,* a gram-negative intracellular coccobacillus. *F. tularensis* has several biovars; *F. tularensis* biovar tularensis (type A) is the most common naturally occurring isolate in the United States, and typically results in a more severe illness. The organism is primarily recovered from lagomorphs (rabbits), rodents and arthropods (ticks and deer flies) in the United States. The rabbit is the vertebrate most commonly associated with tularemia in North America. Tularemia cases have occurred in all regions of the United States, with the highest number of cases occurring in Arkansas, Missouri, Oklahoma, Kansas, and Martha's Vineyard. More cases occur in persons aged 5-9 and over 75 and in males; this is probably related more to risk factors such as exposure to ticks, hunting and butchering rather than to innate susceptibility. In recent years, the reported incidence of tularemia has declined to less than 200 cases per year in the United States. *F. tularensis* biovar palaeartica (type B) may be found in the United States but is more commonly found in Europe and Asia. *F. tularensis* (type B), has been isolated from water, mosquitoes and aquatic mammals, and is associated with a milder clinical illness. *F. tularensis* biovar novicida (type C) has been isolated from water, but only rarely causes human disease.

Tularemia is acquired under natural conditions by direct inoculation (such as an arthropod bite), animal contact (such as skinning or eating infected animals) or via the airborne route (from inhalation of contaminated aerosols generated during farming activities). Waterborne and foodborne outbreaks have occurred. Domestic cats have occasionally transmitted tularemia by bites or scratches. *F. tularensis* may survive for prolonged periods in water, mud and animal carcasses. Even after being frozen (for example as a frozen killed rabbit), *F. tularensis* remains highly infectious. When inhaled as an aerosol as few as 10-50 virulent organisms can cause infection in humans; as few as 10 organisms can cause infection when administered percutaneously. In the event of a bioterrorist attack, aerosolization is thought to be the most likely route of infection.

Transmission of tularemia from person-to-person has never been reported, even with patients having pneumonia. Persons exposed to an aerosol of *F. tularensis* do not present a risk for secondary infection of others or for re-aerosolization of the organism.

Significance as a Potential Bioterrorist Agent

- Weaponized by the United States military during the biologic offensive program in the 1950s and1960s
- Highly infectious after aerosolization; infectious dose can be as low as 10-50 microorganisms when inhaled
- Aerosolized *F. tularensis* would cause pneumonic or typhoidal tularemia (a non specific, febrile illness), with high mortality rates (30-60%) if untreated
- Natural outbreaks of oropharyngeal or gastrointestinal tularemia have occurred after contamination of food or water
- Contamination of food and water might also result in ulceroglandular or oculoglandular tularemia

Clinical Manifestations

There are several different classification systems for clinical tularemia. The most straightforward classifies tularemia into pneumonic tularemia, ulceroglandular tularemia, typhoidal tularemia, oculoglandular tularemia and oropharyngeal or gastrointestinal tularemia.

During an act of bioterrorism, release of an aerosol is thought to be the most likely route of dissemination with pneumonic or typhoidal tularemia being the most likely clinical presentations. Contamination of food or water with resultant oropharyngeal tularemia is also a possibility. Ulceroglandular or oculoglandular tularemia may also result from either an aerosol release or from contamination and these may be the initial presentation of a bioterrorist attack.

Pneumonic Tularemia

Pneumonic tularemia is rarely acquired naturally. This form occurs after inhalation of the organism or as the result of secondary hematogenous spread to the lung. The infectious dose for primary pneumonic tularemia is thought to be as low as 10 organisms.
Pneumonic tularemia would present as a non-specific febrile illness with progression to pleuropneumonitis and systemic infection.

Incubation period

3-6 days (range 1-14 days).

Signs and Symptoms

Initial symptoms of systemic illness may resemble an acute non-specific febrile illness with fever, chills, headache, generalized myalgias and arthralgias and no prominent signs of respiratory disease. Pleuropneumonitis may follow after several days or weeks. The chest exam may be normal; rales may be present in the affected lung. Infiltrates will not respond to beta lactam antibiotics. The following signs and symptoms may be present:

- Dry cough
- Dyspnea
- Pleuritic-type chest pain
- Pharyngitis
- Bronchiolitis
- Pleuropneumonitis
- Hemorrhagic airway inflammation
- Hilar lymphadenopathy
- Pleuritis
- Pleural adhesions
- Pleural effusions
- 20% may have generalized maculopapular rash with possible progression to a pustular rash
- Rarely erythema nodosum may occur
- Tender hepatomegaly
- Rhabdomyolysis

May rapidly progress to:

- Severe pneumonia
- Sepsis
- Systemic inflammatory response syndrome
- Respiratory failure
- Death

Patchy, ill-defined infiltrates in one or more lobes, pleural effusions, pleural adhesions, cavitary lesions and/or hilar adenopathy may be seen on chest X-ray. Patients may develop acute respiratory distress syndrome and require mechanical ventilation.

Differential Diagnosis of Pneumonic Tularemia

Condition	Features of condition that distinguish from pneumonic
Plague	Plague has more rapid onset, more severe illness, higher mortality, productive cough with bloody, watery or purulent mucus and gram-negative diplococci on sputum.
Anthrax	Anthrax has more rapidly progressive respiratory illness, less pulmonary parenchymal involvement, widened mediastinum on chest X-ray and gram-positive rods on blood and/or CSF.
Q fever	Difficult to distinguish, laboratory confirmation may be needed.
Mycoplasma	Clinical picture more mild, sore throat may precede cough by a week or more; may have lesions on tympanic membrane; cold agglutinins
Psittacosis	Difficult to distinguish clinically; psittacosis patients may have exposure to birds; radiographic changes may be more severe than symptoms suggest
Coccidioidomycosis	Symptoms may be milder; may have erythematous maculopapular rash or erythema nodosum may occur; disseminated disease rare
Histoplasmosis	Most often asymptomatic; acute histoplasmosis can present as flu-like illness followed by infiltrates, hilar adenopathy, non-pleuritic chest pain and pulmonary infiltrate. Both tularemia and histoplasmosis may form granulomas.
Legionellosis	Difficult to distinguish clinically

Clinical Laboratory Values

In severe illness patients may exhibit leukocytosis, lymphocytosis, elevated creatinine and BUN, elevated LFTs and elevated CK. Pleural fluid may contain predominantly mononuclear leukocytes (PMNs) or RBCs. Sterile pyuria may occur. Elevated C reactive protein and ESR are common.

Oropharyngeal or Gastrointestinal Tularemia

Oropharyngeal or gastrointestinal tularemia can occur via ingestion of contaminated food, undercooked meat, contaminated water or droplets and oral inoculation from the hands after contact with contaminated material. Oropharyngeal or gastrointestinal tularemia presents as acute pharyngitis with cervical lymphadenopathy or ulcerative gastrointestinal lesions with abdominal pain, diarrhea, nausea, vomiting, mesenteric lymphadenopathy and gastrointestinal
bleeding. Severity can range from mild diarrhea to overwhelming ulceration with frank gastrointestinal bleeding and sepsis.

It is estimated that approximately 100,000,000 organisms are required to transmit disease orally.

Incubation Period
3-5 days (up to 21 days); probably dose dependent.

Signs and Symptoms
Oral Inoculation signs and symptoms may include:
- Sore throat
- Severe throat pain
- Acute exudative pharyngitis
- Acute membranous pharyngitis
- Pharyngeal ulcerations
- Cervical lymphadenopathy
- Development of a yellow white pseudomembrane
- Enlarged tonsils

Gastrointestinal Inoculation signs and symptoms may include
- Abdominal pain
- Nausea
- Vomiting
- Diarrhea
- Frank gastrointestinal bleeding from intestinal ulcerations
- Tender hepatomegaly

Differential Diagnosis of Oropharyngeal or Gastrointestinal tularemia

Condition	Features of condition that distinguish from oropharyngeal or gastrointestinal tularemia
Gastrointestinal anthrax	May be difficult to distinguish clinically
Diphtheria	No history of vaccination to diphtheria, diphtheria unlikely to have gastrointestinal involvement
Group A strep pharyngitis	Unlikely to have gastrointestinal involvement
Infectious mononucleosis	Unlikely to have gastrointestinal involvement

Clinical Laboratory Values
In severe cases patients may exhibit leukocytosis, lymphocytosis, elevated creatinine and BUN, elevated LFTs and elevated CK. Sterile pyuria may occur. Elevated C reactive protein and ESR are common.

Typhoidal (Septicemic) Tularemia

An acute, nonspecific febrile illness associated with *F. tularensis* that is **not** associated with prominent lymphadenopathy.

Incubation period

3-5 days (range 1-14 days).

Signs and Symptoms

- Fever with chills
- Pulse temperature dissociation often observed
- Coryza
- Myalgias
- Anorexia
- Nausea
- Vomiting
- Diarrhea (can be a major component of illness, generally watery and not bloody stool)
- Abdominal pain
- Cough
- Hepatomegaly
- Splenomegaly
- Rhabdomyolysis

Patients may develop a sepsis syndrome with hypotension, adult respiratory distress syndrome, renal failure, disseminated intravascular coagulation and shock.

Fifty percent of typhoidal cases may progress to develop pulmonary involvement. Rare complications include osteomyelitis, pericarditis, peritonitis, endocarditis and meningitis.

Differential Diagnosis of Typhoidal Tularemia

Condition	Features of condition that distinguish from typhoidal tularemia
Typhoid fever	Typically more gradual onset of disease
RMSF	Severe headache in prodrome rash occurs more frequently, anemia and leukopenia common
Ehrlichiosis	Rash in 50%, thrombocytopenia, anemia and leukopenia common
Brucellosis	History of animal contact or raw milk; may need labs to differentiate
Acquired toxoplasmosis	Usually mild, nonspecific illness, cervical lymphadenopathy present but less prominent than in tularemia
Infectious mononucleosis	Less severe illness; may need labs to differentiate
Miliary TB	Gradual onset of disease
Acute leukemia	Blasts on CBC

Clinical Laboratory Values
In severe illness patients may exhibit leukocytosis, lymphocytosis, elevated creatinine and BUN, elevated LFTs and elevated CK. Sterile pyuria may occur. Elevated C reactive protein and ESR are common.

Ulceroglandular Tularemia
Ulceroglandular tularemia is the most common naturally occurring form of the disease. While this form is thought less likely to be the predominant form of disease seen in a bioterrorist attack, patients exposed to contaminated food or water, or exposed to a surface contaminated by an aerosol attack may present with ulceroglandular disease. Furthermore, a terrorist or other criminal working with the agent could potentially present with cutaneous disease. Ulceroglandular tularemia is generally due to inoculation of the organism into the skin or mucous membranes

Incubation period
3-6 days (range 1-14 days).

Signs and Symptoms
A local papule develops at the inoculation site with progression to a pustule followed within several days by an ulcer. This non-healing cutaneous ulcer is typically erythematous, single and up to 3 cm in diameter with heaped up borders, sharply demarcated edges and yellow drainage. The ulcer gradually becomes necrotic in appearance with a black base while the local lymph nodes become enlarged and tender. Lymph nodes are usually tender and enlarged (mean 2 cm, up to 10 cm). Enlarged nodes may become fluctuant and drain spontaneously or persist for months to years. An ulcer may form without lymphadenopathy and vice versa. Cutaneous ulcer develops in 60% of cases and lymphadenopathy develops in 85% of patients. Lymphadenopathy without ulceration is thought to result from direct injection of the bacteria such as might occur after an arthropod bite.

Other signs and symptoms may include:
- Fever (present in 85% of patients)
- Chills
- Headache
- Cough
- Myalgia
- Chest pain
- Vomiting
- Arthralgia
- Sore throat
- Abdominal pain
- Diarrhea
- Dysuria
- Back pain
- Stiff neck

Differential Diagnosis of Ulceroglandular Tularemia

Condition	Features of condition that distinguish from Ulceroglandular Tularemia
Cat scratch disease	Difficult to distinguish clinically, especially in children
Sporotrichosis	Typically less lymphadenopathy than seen in tularemia; relevant exposure history to rose bushes, gardening
Plague	Plague typically more severe illness; history of flea bite or exposure; gram-negative diplococci with bipolar "safety pin" staining.
Mycobacterium marinum	Typically less lymphadenopathy than seen in tularemia; history of exposure to fish/seawater
Syphilis	Typically less lymphadenopathy than seen in tularemia; history of sexual contact
Anthrax	Typically less lymphadenopathy than seen in tularemia
Rat-bite fever	Typically less lymphadenopathy than seen in tularemia; relevant exposure history
Scrub typhus	Typically less lymphadenopathy than seen in tularemia
S. pyogenes skin infection	Typically less lymphadenopathy than seen in tularemia
S. aureus skin infection	Typically less lymphadenopathy than seen in tularemia
Lymphogranuloma venereum	Typically sexual exposure history, less severe illness.
Orf virus disease	Animal exposure (patient has had contact with sheep, goats or musk oxen); lesion associated with crusts and scabbing

Clinical Laboratory Values

Clinical laboratory values in disseminated disease are similar to those for typhoidal disease.

Oculoglandular tularemia

Oculoglandular tularemia, resulting from direct contamination of the eye, occurs in 1% of naturally acquired cases. Oculoglandular tularemia might occur in a bioterrorist setting either as a result of an aerosol exposure (although pulmonary and typhoidal symptoms would probably predominate), from direct contamination from contaminated water or after touching contaminated water or food and inadvertently introducing tularemia to the eye.

Incubation period

1-21 days.

Signs and Symptoms

Oculoglandular tularemia presents as a painful "red eye" with purulent exudation and prominent painful preauricular lymphadenopathy. Signs and symptoms may include:

- Pain
- Purulent granulomatous conjunctivitis
- Photophobia
- Intense ocular congestion
- Itching
- Lacrimation
- Edema of the ocular conjunctiva
- Mucopurulent discharge
- Loss of visual acuity

- Preauricular or cervical lymphadenopathy
- Chemosis
- Periorbital edema
- Small nodular or ulcerative lesions of the palpebral conjunctivae
- Corneal perforation
- Hypopyon
- Keratitis

Differential Diagnosis of Oculoglandular Tularemia

Condition	Features of condition that distinguish from Oculoglandular Tularemia
Cat scratch disease	Absence of painful preauricular lymphadenopathy
TB	Absence of painful preauricular lymphadenopathy
Sporotrichosis	Absence of painful preauricular lymphadenopathy
Syphilis	Absence of painful preauricular lymphadenopathy
Herpes zoster	Absence of painful preauricular lymphadenopathy

Clinical laboratory values
Clinical lab values in disseminated disease similar to those for typhoidal disease.

Laboratory Diagnosis
Routine laboratory work must be done in Biosafety Level (BSL)-2 facilities. However, handling of bacterial cultures once the organism is identified should be done in BSL-3 facilities. If tularemia is suspected, please call the Department of Public Health Acute Communicable Disease Control Program (Business Hours: (213) 240-7941 or After Hours: (213) 974-1234) to arrange for submission of specimens for confirmatory testing. Staff from the public health laboratory (PHL) is available for consultation at (562) 658-1300 or After Hours: (213) 974-1234.

The diagnosis of tularemia requires a high index of suspicion since the disease often presents with very nonspecific symptoms. The diagnosis can be made by recovery of the organism from blood, ulcers, conjunctival exudates, sputum, pleural fluid, lymph nodes, gastric washings and pharyngeal exudates. Since the organism is difficult to isolate and constitutes a potential danger to laboratory personnel, serologic evidence of infection in a patient with a compatible clinical syndrome is commonly used for diagnosis.

Staining
Direct examination of primary specimens such as biopsy material by Gram stain may be of little value, as *F. tularensis* is a small weakly staining pleomorphic gram-negative coccobacillus that cannot be readily distinguished from the background. A DFA test is available through the PHL. A positive DFA result is presumptive for a diagnosis of tularemia. Confirmation of the diagnosis requires culture or serologic evidence.

Culture
F. tularensis grows in commercial blood culture media as well as sulfhydryl containing media such as thioglycolate broth. The organisms require cysteine supplementation; therefore, *F. tularensis* may grow at first on sheep blood agar (SBA), but may not grow on subsequent subculture to standard SBA. The organism grows slowly on media containing cysteine (e.g.,

glucose cysteine blood agar, buffered charcoal yeast extract, modified Thayer-Martin or chocolate agar) and colonies may not be visible until after 48 hours at 37°C under 5% CO_2. They appear as 1 -2 mm gray-white to bluish-gray opaque colonies with smooth borders. The bacteria grow slowly; some strains may require up to a week to develop visible colonies, especially if the patient has been placed on bacteriostatic antibiotic therapy. **Notify the clinical laboratory in advance of submitting specimens for culture that may contain *F. tularensis,* since isolation of the organism can put laboratory workers at risk for infection.**

Isolates with Gram stain and culture characteristics that are weakly catalase positive, beta-lactamase positive, negative for oxidase, urease, and X and V factors provide presumptive evidence for *F. tularensis.* A positive DFA test on a culture isolate confirms the identification of *F. tularensis.* **The PHL must be contacted to co-ordinate transport of the isolate for confirmatory testing (Business Hours: (562) 658-1300 or After Hours: (213) 974-1234).**

Serology

Antibody detection assays include tube agglutination, microagglutination and ELISA. Significant antibodies do not appear until the end of the second week of illness, peaks at 4-5 weeks and can persist for more than a decade. A single titer of > 1:160 (by tube agglutination) or > 1:128 (by microagglutination) is a presumptive positive; a four-fold rise in titer is required for a definitive serologic diagnosis. ELISA and microagglutination tests may be more sensitive than tube agglutination. Antibodies may cross-react with *Brucella sp.* and Proteus 0X19. Serology testing is available through the PHL.

Handling Laboratory Specimens

Biosafety Level (BSL)- 2 practices containment equipment and facilities are recommended for all activities with materials potentially containing infectious organisms. Laboratory staff handling specimens from persons who might have tularemia must wear surgical gloves, protective gowns, and shoe covers if performing procedures with high splash potential or risk of aerosolization. Laboratory tests should be performed in BSL-2 cabinets and blood cultures should be maintained in a closed system. Every effort should be made to avoid splashing or creating an aerosol. Protective eye wear and masks should be worn if work cannot be done in a BSL-2 cabinet.

All biohazardous waste should be decontaminated by autoclaving. Contaminated equipment or instruments may be decontaminated with a hypochlorite solution, hydrogen peroxide, peracetic acid, 1% glutaraldehyde solution, formaldehyde, ethylene oxide, irradiation, or other OSHA approved solutions, or by autoclaving or boiling for 10 minutes.

Tularemia is the third most commonly reported laboratory-associated bacterial infection. Cases have occurred among clinical laboratorians working with bacterial cultures. Laboratory staff handling specimens from persons who are suspected of having tularemia must wear face masks with eye protection, surgical gloves, protective gowns and shoe covers - especially when working with pure bacterial cultures. Laboratory tests (such as serological examinations and staining of impression smears) should be performed in BSL-2 cabinets.

Treatment

The treatment recommendations in this section are adapted from the consensus recommendations of the Working Group on Civilian Biodefense, Tularemia as a Biological Weapon: Medical and Public Health Management, JAMA. 2001;285:2763-2773.

The treatment of choice for all forms of tularemia, except meningitis, is streptomycin; gentamicin is an acceptable alternative. For both drugs dosages must be adjusted for renal insufficiency. While gentamicin is safe during pregnancy streptomycin should be avoided due to its association with irreversible deafness in children exposed in utero.

Adults:

- Streptomycin, I g intramuscularly twice daily for 10 days.

Pregnant women:

- Gentamicin, 5 mg/kg/day intravenously or intramuscularly once daily (peak serum level of at least 5 ug/ml is desireable) for 10-14 days.

Pediatric dose:

- Streptomycin, 15 mg/kg intramuscularly twice daily (should not exceed 2 g/d) for 10 days.

Alternatives:

- Gentamicn: Adults and pregnant women: 5 mg/kg/day intravenously or intramuscularly
  once daily (peak serum level of at least 5 ug/ml is desirable) for 10-14 days.
- Gentamicin: Pediatric dose: 2.5 mg/kg intravenously or intramuscularly every 8 hours for 10 days.
- Doxycycline, 100 mg intravenously twice daily for at least 14 days. Pediatric dose: (Not generally recommended for children less than 9 years, pregnant or lactating women, however, potential risks must be weighed against benefits in treating serious infections.) If >8 years and > 45 kg, give adult dosage of doxycycline; if >8 years and <45 kg or $\leq$ 8 years, give 2.2 mg/kg twice a day.
- Chloramphenicol: Adults and Pediatrics: 15 mg/kg intravenously four times daily (not an FDA-approved indication).
- Ciprofloxacin: Adults and pregnant women: 400 mg intravenously twice daily. Pediatric dose 15mg/kg intravenously twice daily.

Doxycycline and chloramphenicol are bacteriostatic and associated with high relapse rates. These agents must be continued for a minimum of 14 days. Chloramphenicol should generally not be used due to the availability of effective alternatives with fewer serious side effects. Additional agents with favorable in vitro susceptibility tests but limited clinical data on efficacy include: fluoroquinolones (except cinoxacin), erythromycin (resistant strains of *F. tularensis* have been identified) and rifampin.

Penicillin and cephalosporins are not effective and should not be used to treat tularemia.

Meningitis

A rare complication of tularemia, meningitis requires special attention with regard to therapy as the penetration of streptomycin or gentamicin into the CSF is suboptimal. The treatment of meningeal infection should include combination therapy with chloramphenicol plus streptomycin or possibly a third-generation cephalosporin plus streptomycin (limited data available on efficacy).

Management of Exposed Persons

An exposed person is defined as a person who has been exposed to the release of a *F. tularensis* containing aerosol. Antibiotic prophylaxis should begin as soon as possible after exposure and is most effective if begun within 24 hours.

Adults:

- Doxycycline, 100mg orally twice daily for 14 days, or ciprofloxacin, 500 mg orally twice daily for 14 days.

Pediatric patients and pregnant women:

Although tetracyclines are not generally recommended for children under age 9 or for pregnant women, the risk of developing tularemia may outweigh other considerations.

- Doxycycline:
  - If >8 years and $\geq$ 45 kg, 100 mg orally twice daily
  - If >8 years and <45 kg or $\leq$ 8 years, 2.2 mg/kg orally twice daily

If antibiotic prophylaxis is not started within 24 hours of exposure, exposed persons should be instructed to begin a fever watch and seek medical care if temperature exceeds 101.3°F (38.5°C).

Table 7
Treatment of Patients With Tularemia in the Contained* and Mass Casualty Settings and for Postexposure Prophylaxis§

(adapted from consensus statement of the Working Group on Civilian Biodefense. JAMA. 2000;285:2763-2290)

Patient Category	Recommended Therapy
Contained Casualty Setting*	
Adults	***Preferred choices*** Streptomycin, 1 g IM twice daily Gentamicin, 5 mg/kg IM or IV once daily†
	Alternative choices Doxycycline, 100 mg IV twice daily Chloramphenicol, 15 mg/kg IV 4 times daily† Ciprofloxacin, 400 mg IV twice daily†
Children	***Preferred choices*** Streptomycin, 15 mg/kg IM twice daily (maximum daily dose, 2g) Gentamicin, 2.5 mg/kg IM or IV 3 times daily†
	Alternative choices Doxycycline > 8 years and ≥ 45 kg, 100 mg IV twice daily > 8 years and <45 kg, 2.2 mg/kg IV twice daily (maximum, 200 mg/d) ≤ 8 years, 2.2 mg/kg IV twice daily (maximum, 200 mg/d) Chloramphenicol, 15 mg/kg IV 4 times daily† Ciprofloxacin, 15 mg/kg IV twice daily†‡
Pregnant women	***Preferred choice*** Gentamicin, 5 mg/kg IM or IV once daily† Streptomycin, 1 g IM twice daily
	Alternative choices Doxycycline, 100 mg IV twice daily Ciprofloxacin, 400 mg IV twice daily†
Mass Casualty Setting and Postexposure Prophylaxis§	
Adults	***Preferred choices*** Doxycycline, 100 mg orally twice daily Ciprofloxacin, 500 mg orally twice daily†
Children	***Preferred choices*** Doxycycline > 8 years and ≥ 45 kg, 100 mg orally twice daily > 8 years and < 45 kg, 2.2 mg/kg orally twice daily (maximum, 200 mg/d) ≤ 8 years, 2.2 mg/kg orally twice daily (maximum, 200 mg/d) Ciprofloxacin, 15 mg/kg orally twice daily†‡
Pregnant women	***Preferred choices*** Ciprofloxacin, 500 mg orally twice daily† Doxycycline, 100 mg orally twice daily

* Treatment with streptomycin, gentamicin, or ciprofloxacin should be continued for 10 days; treatment with doxycycline or chloramphenicol should be continued for 14-21 days. Patients beginning treatment with IM or IV agents can switch to oral administration when clinically indicated.

§ One antibiotic, appropriate for patient age, should be chosen from among alternatives. The duration of all recommended therapies in this group is 14 days.

† Not a United States Food and Drug Administration-approved use.

‡ Ciprofloxacin should not exceed 1 g/d in children. Other fluoroquinolones can be substituted for ciprofloxacin. Children younger than 2 years should not receive chloramphenicol.

Infection Control

Tularemia is not transmissible from person-to-person. **Standard Precautions** should be followed for all patients. Respiratory isolation rooms are not required. Ulcers or wounds in patients with tularemia should be covered and Contact Precautions maintained, as *F. tularensis* can be isolated from such lesions for one month or longer.

Disposal of Infectious Waste

Use of tracking forms, containment, storage, packaging, treatment and disposal methods should be based upon the same rules as all other regulated medical wastes.

Autopsy and Handling of Corpses

All postmortem procedures are to be performed using Respiratory Precautions. Efforts should be made to avoid aerosolization. All persons performing or assisting in postmortem procedures must wear mandated PPE (personal protective equipment) as delineated by OSHA guidelines. Instruments should be autoclaved or sterilized with a 10% bleach solution or other solutions approved by OSHA. Surfaces contaminated during postmortem procedures should be decontaminated with an appropriate chemical germicide such as 10% bleach or 5% phenol (carbolic acid).

Reporting to the Health Department

Tularemia is a reportable condition in California.
Confirmed or suspected tularemia cases must be reported immediately to the:

Los Angeles County Department of Public Health

Business Hours (8am -5pm)	**213-240-7941**
After Hours (County Operator)	**213-974-1234**

Ask to Speak with the Public Health Physician On-Call

VIRAL HEMORRHAGIC FEVERS

ALL SUSPECTED CASES OF VIRAL HEMORRHAGIC FEVERS MUST BE REPORTED IMMEDIATELY TO THE DEPARTMENT OF PUBLIC HEALTH ACUTE COMMUNICABLE DISEASE CONTROL PROGRAM:

Monday - Friday (8am – 5pm)
(213) 240-7941

After Hours (County Operator)
(213) 974-1234

Ask to Speak with the Public Health Physician On-Call

Quick Reference Sheet: VIRAL HEMORRHAGIC FEVERS (VHF)

ALL SUSPECTED CASES OF VIRAL HEMORRHAGIC FEVERS MUST BE REPORTED IMMEDIATELY TO THE DEPARTMENT OF PUBLIC HEALTH ACUTE COMMUNICABLE DISEASE CONTROL PROGRAM

During Business Hours	213-240-7941
After Hours (County Operator)	213-974-1234

Epidemiology:

- VHF reside in animal hosts or arthropod vectors; humans are incidental hosts
- The natural reservoir of filoviruses (Ebola and Marburg) is unknown
- Low infectious dose and highly infectious by aerosol dissemination; ability to cause large outbreaks
- Person-to-person transmission occurs with filoviruses (Ebola, Marburg), arenaviruses (Lassa fever, New World arenaviruses) and Crimean-Congo virus
- Direct contact with infected blood and bodily fluids has accounted for the majority of cases of person-to-person transmission

Clinical:

- Incubation period ranges from 2-22 days
- Filoviruses, Rift Valley fever and flaviviruses present with an abrupt onset, while arenaviruses have a more insidious onset
- VHF initially exhibit a non-specific illness, with high fever, headache, malaise, arthralgias, myalgias, nausea, abdominal pain and nonbloody diarrhea
- Early signs include fever, hypotension, bradycardia, tachypnea, conjunctivitis, pharyngitis and cutaneous flushing or rash
- Later signs include progressive hemorrhagic diathesis, hematuria, hematemesis and melena
- Severe illness may lead to DIC, circulatory shock, nervous system dysfunction, coma, delirium and seizures

Diagnosis:

- Requires a high index of suspicion given non-specific presentation and no known risk factors
- Virus isolation requires BSL-4 containment facilities (CDC or USAMRIID)

Treatment:

- Supportive care is the mainstay of therapy
- Prompt initiation of ribavirin therapy while diagnostic confirmation is pending
- If an arenavirus or bunyavirus is confirmed continue ribavirin for a total of 10 days

Management of exposed persons:

- High risk and close contacts of patients diagnosed with VHF should record their temperature twice daily for 21 days postexposure and report any temperature > 101 °F (> 38.3°C) or other signs or symptoms of VHF
- Start ribavirin therapy in high risk or close contacts who report fever > 101 °F (> 38.3°C) or other signs or symptoms of VHF, while initiating diagnostic workup, treatment and infection control
- With the exception of yellow fever there is no vaccine for VHF

Patient Isolation:

- Contact and Airborne Precautions are required

Introduction and Epidemiology

Viral Hemorrhagic Fever (VHF) are a diverse group of organisms, each of which belong to one of four distinct families:

Filoviridae: Ebola and Marburg viruses
Arenaviridae: Lassa fever virus and a group of viruses referred to as the New World arenaviruses
Bunyaviridae: Crimean Congo hemorrhagic fever virus, Rift Valley fever virus and a group of viruses known as the 'agents of hemorrhagic fever with renal syndrome'
Flaviviridae: dengue, yellow fever, Omsk hemorrhagic fever and Kyasanur Forest disease virus

VHF are RNA viruses with lipid envelopes. They reside in animal hosts or arthropod vectors; humans are incidental hosts. These agents are all capable of causing clinical disease with fever and bleeding disorder classically referred to as "viral hemorrhagic fever (VHF)." None of these viruses occur naturally in the United States. Worldwide, human cases or outbreaks of VHF occur sporadically.

Significance as a Potential Bioterrorist Agent

- Could be released as an aerosol during a bioterrorist attack
- Significant morbidity and mortality
- Potential for person-to-person transmission
- Lack of therapy and vaccines, which may result in community outbreaks and nosocomial infections
- Former Soviet Union allegedly weaponized Marburg virus
- Aum Shinrikyo attempted to obtain samples of Ebola virus
- The United States weaponized both yellow fever and Rift Valley fever as part of its former bioweapons program

Clinical Manifestations

Clinical features vary according to virus.

Incubation period
Ranges from 2-22 days.

Signs and Symptoms
As with all bioterrorist disease it is not certain that symptoms would present in the same way as the naturally occurring form in the event of a bioweapon attack.

VHF initially exhibit a non-specific illness, lasting less than a week, with high fever, headache and systemic illness followed by flushing, maculopapular rash and conjunctival injection, progression to diffuse hemorrhagic disease and multiorgan system failure. Filoviruses, Rift Valley fever and flaviviruses present with abrupt onset while arenaviruses have a more insidious onset.

Early signs and symptoms include:

- High fever
- Hypotension
- Relative bradycardia
- Headache
- Malaise
- Arthralgias
- Myalgias (especially back pain)
- Lethargy
- Altered mental status
- Nausea
- Abdominal pain
- Watery diarrhea
- Tachypnea
- Conjunctivitis
- Periorbital edema
- Bleeding gums
- Pharyngitis
- Cervical lymphadenopathy
- Enanthem (may occur prior to rash)
- Cutaneous flushing or a skin rash (rash characteristics vary according to disease but often begin as a non pruritic diffuse maculopapular rash about day 5).

Later signs include:

- Progressive hemorrhagic diathesis (e.g., petechiae, mucous membrane and conjunctival hemorrhage)
- Epistaxis
- Hematemesis
- Hemoptysis
- Hematuria
- Melena
- Vaginal hemorrhage
- Desquamation may occur

Severe illness may lead to disseminated intravascular coagulation, circulatory shock, multiorgan system failure, nervous system dysfunction, coma, delirium and seizure disorder.

Death typically occurs 1-2 weeks following the onset of illness due to hemorrhage and hypovolemic shock. Mortality varies by disease, ranging from 10-90%. Mortality is near 100% in pregnancy.

Complications of illness may include:

- Prolonged fatigue
- Prolonged weakness
- Decreased appetite
- Weight loss
- Neurological complications such as transverse mellitus, hearing loss, visual loss and impaired coordination
- Pancreatitis

- Orchitis with testicular atrophy
- Myocarditis
- Arrthymias
- Hair loss
- Prolonged abdominal pain
- Psychotic changes
- Uveitis
- Parotitis
- Pericarditis

A detailed travel history and a high index of suspicion are essential in making the diagnosis of VHF in naturally occurring outbreaks. Absence of relevant exposure history would be highly suggestive of criminal terrorist activity.

Table 3. Clinical Characteristics of Hemorrhagic Fever Viruses Noted in Past Case Series or Outbreaks

Virus	Distinctive Clinical Features	Person-to-Person Transmission	Incubation Period, d	Mortality, %	Treatment
Ebola[25,42-44,47,86,99]	High fever and severe prostration. A diffuse maculopapular rash may occur by day 5 of illness. Bleeding and disseminated intravascular coagulation are common.	Yes	2-21	50-90*	Supportive
Marburg[40,41,87,102]	High fever, myalgias. Nonpruritic maculopapular rash of the face, neck, trunk, and arms may develop. Bleeding and disseminated intravascular coagulation are common.	Yes	2-14	23-70†	Supportive
Lassa fever[87,88-91,100,101,110]	Gradual onset of fever, nausea, abdominal pain, severe sore throat, cough, conjunctivitis, ulceration of buccal mucosa, exudative pharyngitis, and cervical lymphadenopathy. Late signs include severe swelling of head and neck; pleural and pericardial effusions. Hemorrhagic complications less common.	Yes	5-16	15-20	Ribavirin, supportive
New World Arenaviruses[84,92,126]	Gradual onset of fever, myalgias, nausea, abdominal pain, conjunctivitis, flushing of face and trunk, and generalized lymphadenopathy. May develop petechiae, bleeding, and central nervous system dysfunction (tremors of the tongue and upper extremities, myoclonic movements, dysarthria, and generalized seizures).	Yes	7-14	15-30	Ribavirin, supportive
Rift Valley fever[61,93-96]	Fever, headache, retro-orbital pain, photophobia, and jaundice. Less than 1% develop hemorrhagic fever or encephalitis. Retinitis affects approximately 10%, which may occur at time of acute febrile illness or up to 4 weeks later.	No	2-6	<1	Ribavirin, supportive
Yelow fever[58,97]	Fever, myalgias, facial flushing, and conjunctival injection. Patients either recover or enter a short remission followed by fever, relative bradycarcia, jaundice, renal failure, and hemorrhagic complications.	No	3-6	20	Supportive
Omsk hemorrhagic fever[59]‡	Fever, cough, conjunctivitis, papulovesicular eruption on the soft palate, marked hyperemia of the face and trunk (but no rash), generalized lymphadenopathy, and splenomegaly. Some patients may develop pneumonia and central nervous system dysfunction.	No	2-9	0.5-10	Supportive
Kyasanur Forest disease[59,98]	Similar to Omsk but biphasic illness: first phase lasts 6-11 days and is followed by an afebrile period of 9-21 days. Up to 50% of patients relapse and develop meningoencephalitis.	No	2-9	3-10	Supportive

*Reported Ebola data are for Sudan (50%) and Zaire (90%) subtypes. The Ivory Coast subtype has an indeterminate case-fatality rate, as there has been a single nonfatal human case. The Reston subtype causes subclinical infection in humans.
†Mortality ranges from 23% in the 1967 outbreak in Germany to 70% in the largest outbreak of 1999 in the Democratic Republic of the Congo.
‡Also Sergey Netesov, MD, written communication, February 27, 2002.

With permission from Borio L, Inglesby T, Peters CJ et al; "Hemorrhagic Fever Viruses as Biological Weapons." JAMA. 2002;287:2391 -2405.

Differential Diagnosis of Viral Hemorrhagic Fever

Condition	Features of condition that distinguish from VHF
Meningococcemia	Gram-negative diplococci in blood of CSF; shorter interval between onset of symptoms and rash; bacterial meningitis
Gram-negative sepsis	More rapid progression of illness; positive culture results
Influenza	Less severe; may have flushing but not hemorrhage
RMSF	Relevant exposure history; severe headache in prodrome; onset of rash occurs more rapidly after starting symptoms
Fulminant hepatitis	May need labs to differentiate if severe
Staphylococcal sepsis	More rapid onset; positive cultures
Endocarditis	Cardiac murmur; heart failure; embolic complications
Toxic shock syndrome	Fever, flushing and desquamation may occur; hemorrhage unlikely; may have history of vaginal tampon use and purulent vaginal discharge
Shigellosis	Hemorrhage rare unless HUS develops; anemia hemolytic and leukemoid reaction may occur
Salmonellosis	Typically more gradual onset of disease; less severe illness; culture results positive
Dengue	Travel history; hemorrhagic complications uncommon unless previously exposed to a different dengue serotype
Hantavirus pulmonary syndrome	Often circulating immunoblasts and myelocytes; GI symptoms; history of exposure to rodents
Hemorrhagic smallpox	Rapid onset of rash; rapidly fatal; may have underlying immunocompromise or pregnancy
Borreliosis	May be difficult to distinguish clinically; spirochetes present in blood and bone marrow
Trypanosomiasis	Chancre at initial site; hemorrhage not common; travel history
Plague (septicemic)	Plague has more rapid onset and illness severity with higher mortality; with plague exposure history or in a bioterrorist attack would expect pneumonic plague with cough productive of bloody, watery or purulent mucus and gram negative diplococci on sputum
Measles	Cough and coryza prominent; hemorrhage rare; no vaccination history
Malaria	Appropriate travel history
Psittacosis	Pneumonia, psittacosis patients may have exposure to birds; chest X-ray changes may be more severe than symptoms would suggest
ITP	Typically less severe; would not expect high fever or multiorgan system failure
TTP-HUS	Microangiopathic anemia; responds to plasmapheresis
Acute leukemia	Possible recent history of easy bleeding, fatigue, weight loss with malignancy; blasts on CBC

Clinical Laboratory Values

Typically there is thrombocytopenia, anemia, prolonged bleeding time, prolonged PT and PTT and elevated FDP. Decreased fibrinogen, leukopenia, leukocytosis in Lassa, hemoconcentration, elevated LFTS, elevated BUN and creatinine, proteinuria and hematuria occur. Atypical lymphocytes with Pelger Huet cells are characteristic. ESR is usually normal.

Laboratory Diagnosis

All specimens should be handled, at a minimum, in a class 2 biological safety cabinet following BSL-3 practices. Virus isolation requires BSL-4 containment facilities (CDC or USAMRIID).

If a VHF case is suspected, please immediately call the Department of Public Health Acute Communicable Disease Control Program (Business Hours: 213-240-7941 or After Hours: 213-974-1234) to arrange for submission of specimens for confirmatory testing.

Handling Laboratory Specimens

Biosafety Level (BSL)-3 practices containment equipment and facilities are recommended for all activities with materials potentially containing virus. Virus isolation requires BSL-4 containment facilities (CDC or USAMRIID). Laboratory staff handling specimens from persons who might have VHF must wear double gloves, impermeable gowns, leg and shoe covers, face shields and goggles.
All biohazardous waste should be decontaminated by autoclaving. Contaminated equipment or instruments may be decontaminated with a hypochlorite solution, hydrogen peroxide, peracetic acid, 1% glutaraldehyde solution, formaldehyde, ethylene oxide, irradiation, or other OSHA approved solutions, or by autoclaving or boiling for 10 minutes.

Accidental spills of potentially contaminated material should be decontaminated immediately by covering liberally with a registered hospital disinfectant solution or a 1:100 dilution of household bleach.

Treatment

The Working Group on Civilian Biodefense has developed consensus-based recommendations for measures to be taken by medical and public health professionals following the use of a VHF as a biological weapon against a civilian population (Hemorrhagic Fever Viruses as Biological Weapons: Medical and Public Health Management, JAMA. 2002;287:2391-2405). Treatment guidelines included in this section reflect these recommendations.

Supportive care is the mainstay of treatment and includes maintenance of fluid and electrolyte balance, hemodynamic monitoring, mechanical ventilation, renal dialysis and antiseizure therapy as indicated. Intramuscular injections, anticoagulant therapies, aspirin and nonsteroidal anti-inflammatory medications are contraindicated. There is no approved antiviral medication for the treatment of VHF. However, ribavirin has been shown, in vitro and in vivo, to have some activity against Arenaviridae and Bunyaviridae. Thus, for infections caused by arenaviruses and bunyaviruses, or cases with suspected VHF of unknown cause, ribavirin is recommended.

Adults:

Loading dose of ribavirin 30 mg/kg intravenously (maximum, 2 g), followed by 16 mg/kg intravenously (maximum, 1 g per dose) every 6 hours for four days, followed by 8 mg/kg intravenously (maximum, 500 mg per dose) every 8 hours for 6 days.

Pediatric patients and pregnant women:

While ribavirin is not approved by the FDA the benefits may outweigh the risks.

Vaccination

Except for yellow fever there is no licensed vaccine for VHF. The yellow fever vaccine is effective in protecting persons traveling to endemic areas. However, the vaccine would not be useful following a bioterrorist attack because yellow fever's incubation period is short and disease would likely develop before vaccinated persons could develop protective antibodies.

Management of Exposed Persons

An exposed person is defined as a person who is at high risk or a close contact. High risk persons are those who have had mucous membrane contact with a case or have a percutaneous injury involving contact with a patient's blood or bodily fluids. Close contacts are those who live with, touch (hug, shake hands), process laboratory specimens from or care for a patient with clinical evidence of VHF prior to initiation of infection control measures.

All high risk persons and close contacts should be placed under medical surveillance for 21 days postexposure. They should be instructed to record their temperature twice a day and report any temperature > 101°F (38.3°C). Ribavirin therapy should be started unless the agent is known to be a filovirus or a flavivirus. Since Rift Valley fever and flaviviruses may be transmitted in the laboratory setting, but not person-to-person, only laboratory workers would require medical surveillance given the identification of either of these agents.

Table 8:
Recommendations for Ribavirin Therapy in Patients with Clinically Evident Viral Hemorrhagic Fever of Unknown Etiology or Secondary to Arenaviruses or Bunyaviruses
(from JAMA. 2002;287:2391-2405)

	Contained Casualty Setting	Mass Casualty Setting†
Adults	Loading dose of 30 mg/kg IV (maximum, 2 g), followed by 16 mg/kg IV (maximum, 1 g per dose) every 6 hours for four days, followed by 8 mg/kg IV (maximum, 500 mg per dose) every 8 hours for 6 days	Loading dose of 2000 mg PO, followed by 1200 mg/d PO BID, if >75 kg, or 1000 mg/d PO in BID (400 mg in am and 600 mg in pm) if < 75 kg for 10 days‡
Pregnant women§	Same as for adults	Same as for adults
Children	Same as for adults, dosed according to weight	Loading dose of 30 mg/kg PO, followed by 15 mg/kg/d PO BID for 10 days

*Recommendations are not approved by the US Food and Drug Administration for any of these indications and should always be administered under an investigational new drug protocol. However, in a mass casualty setting, these requirements may need to be modified to permit timely administration of the drug.
†The threshold number of cases at which parenteral therapy becomes impossible depends on a variety of factors, including local healthcare resources.
‡Oral ribavirin is available in 200 mg capsules and cannot be broken.
§High death rate from infection appears likely to outweigh any fetal risk.

Infection Control

Filoviruses and arenaviruses are transmissible from person-to-person by direct contact with infected blood and bodily fluids. Therefore, **Contact Precautions** should be followed for all patients. There is a theoretical risk of airborne transmission. For this reason **Airborne Precautions** are also recommended. The Working Group on Civilian Biodefense has developed consensus-based recommendations for protective measures (referred to as VHF-specific barrier precautions) to be taken against nosocomial transmission of VHF. These precautions include:

- Strict hand hygiene
- Double gloves
- Impermeable gowns
- Face shields
- Eye protection
- Leg and shoe coverings

Decontamination

VHF-specific barriers should be worn when handling linen. Linens should be double bagged and washed without sorting in a regular hot water cycle with bleach. Alternatively, linens may be autoclaved or incinerated. Surfaces in patient's rooms and contaminated materials should be decontaminated with a registered hospital disinfectant solution or a 1:100 dilution of household bleach.

Autopsy and Handling of Corpses

All postmortem procedures are to be performed using VHF-Specific Barrier Precautions and Airborne Precautions. Due to the increased risk of VHF transmission, postmortems should be done only when absolutely necessary and after discussion with experts. Prompt burial or cremation of the deceased with minimal handling is recommended.

Reporting to the Health Department

All suspected cases of viral hemorrhagic fever must be reported immediately by phone to the:

Los Angeles County Department of Public Health

Business Hours (8am -5pm)	**213-240-7941**
After Hours (County Operator)	**213-974-1234**

Ask to Speak with the Public Health Physician On-Call

BRUCELLOSIS

ALL SUSPECTED CASES OF BRUCELLOSIS MUST BE REPORTED IMMEDIATELY TO THE DEPARTMENT OF PUBLIC HEALTH ACUTE COMMUNICABLE DISEASE CONTROL PROGRAM:

Monday - Friday (8am – 5pm)
(213) 240-7941

After Hours (County Operator)
(213) 974-1234

Ask to Speak with the Public Health Physician On-Call

Quick Reference Sheet: Brucellosis *(Brucella sp.)*

ALL SUSPECTED CASES OF BRUCELLOSIS MUST BE REPORTED IMMEDIATELY TO THE DEPARTMENT OF PUBLIC HEALTH ACUTE COMMUNICABLE DISEASE CONTROL PROGRAM

During Business Hours	213-240-7941
After Hours (County Operator)	213-974-1234

Epidemiology:

- *Brucella* is a zoonotic disease of wild and domestic animals
- *Brucella* species causing disease in humans are *B. abortus* (cattle), *B. melitensis,* (sheep and goats), *B. suis* (pigs) and rarely *B. canis* (dog). *Brucella* organisms can be found in a number of wild animals as well as domesticated animals including feral swine, caribou, foxes, antelope, elk, and American bison.
- Predominantly occurs as an occupational disease in those working with animals e.g. abattoir (slaughterhouse) workers, meat inspectors, farmers, veterinarians, shepherds, dairy industry professionals, and laboratorians.
- Endemic locations for disease - Brucellosis occurs naturally worldwide, but certain areas are hot zones for the disease including countries of the Mediterranean basin, Arabian Gulf, Indian subcontinent, and parts of Mexico, Central and South America.
- Rare in the United States (U.S.) with about 100 cases per year reported. Cases are mostly reported from CA, FL, TX, and VA (primarily *B. melitensis)* with the majority of these associated with ingestion of unpasteurized dairy products made outside the U.S.
- In Los Angeles County, about 4 to 11 cases per year of naturally acquired brucellosis have been reported since the year 2000.
- Transmission to humans can occur by:
    - Direct inoculation through cuts and skin abrasions or via the conjunctiva especially from handling animal carcasses, placentas, or contact with animal vaginal secretions (e.g. veterinarians, ranchers, slaughterhouse workers, shepherds)
    - Inhalation of infected aerosols (e.g. slaughterhouse workers, laboratorians)
    - Ingestion of contaminated food such as raw milk or cheeses made from unpasteurized milk
- Is generally not spread from person-to-person. Rare cases reported of congenital brucellosis and sexual transmission; infected mothers may transmit *Brucella* to their infants through breast feeding.
- Outbreaks can occur in those who consumed raw milk and unpasteurized cheese and in laboratory workers.

Clinical:

- Clinical diagnosis is a challenge due to the protean clinical features
- Is an illness characterized by acute or insidious onset of fever (spiking or "undulant" pattern), night sweats, undue fatigue, anorexia, weight loss, headache, and arthralgia. Cough and chest pain are rare.
- Incubation period: varies from 1 week to several months; most people become ill within 3-4 weeks of exposure.
- Physical exam is usually normal; may also find lymphadenopathy, splenomegaly, and/or hepatomegaly (10-30%)
- The most common sites for localization are: osteoarticular (especially sacroilitis), genitourinary (especially epididymoorchitis), neurobrucellosis (usually presenting as meningitis), endocarditis (most are left-sided), and hepatic abscess.

Laboratory Diagnosis:

- Isolation of *Brucella* by culture from blood, or other sites, especially bone marrow or liver biopsy specimens; may require 30-40 days
- Cultures are not always positive; blood cultures are positive in 15-70% percent of cases
- A variety of other specimens may provide positive cultures. These include areas of localized disease, pleural fluid or tissue, and occasionally cerebrospinal fluid
- The ordering clinician should instruct the laboratory if brucellosis is suspected
- Culture of *Brucella* from blood, bone marrow, or joint fluid should utilize an automated blood culture system, a Lysis-centrifugation system, or biphasic system
- *Brucella are* non-motile Gram-negative coccobacilli that are oxidase, catalase, and urease positive
- Fourfold rise in the microagglutination titer in paired sera or a single microagglutination titer of >1:160
- ELISA IgM, IgG, and IgA, allowing for better interpretation, especially in cases of brucellosis relapse. ELISA of CSF titers is also helpful in diagnosing neurobrucellosis. Because levels should decrease with effective treatment, ELISA is also helpful in follow-up
- PCR of blood or fluid, and tissue samples (in patients with focal complications) is available through LRN laboratories

Treatment:

Adults

- Doxycycline 100mg PO twice daily for six weeks plus streptomycin 1 gram (15 mg/kg) IM daily for the first 14 to 21 days. If streptomycin is not available, gentamicin (5 mg/kg/day IV in three divided doses x 5-7 days) may be a suitable alternative.

Alternatives

- Doxycycline 100mg PO twice daily plus rifampin 600 to 900mg PO (15mg/Kg) once daily for six weeks.
- Quinolone (ofloxacin or ciprofloxacin) plus rifampin OR trimethoprim - sulfamethoxazole (TMP - SMX) plus rifampin may represent suitable alternatives.

Pregnant Women

Two regimens have been suggested for the therapy of brucellosis in pregnancy.

- Rifampin 900 mg once daily for six weeks
- Rifampin 900 mg once daily plus trimethoprim-sulfamethoxazole (5 mg/kg of the trimethoprim component twice daily) for four weeks

Pediatric dose:

Avoid tetracyclines in children <8 years old.

- Trimethoprim-sulfamethoxazole (TMP-SMX) (10 to 12 mg/kg per day of the trimethoprim component, max 480 mg/day and 50 to 60 mg/kg per day, max 2.4 g/day of the sulfa component in two divided doses) plus rifampin (15 to 20 mg/kg per day of rifampin up to a maximum of 600 mg PO daily in two divided doses) for six weeks.
- In children > 8 years old, doxycycline 2-4 mg/kg up to 200 mg/day, in 2 divided doses plus rifampin 15-20 mg/kg up to 600-900 mg/day.

Management of Exposed Persons:

- No controlled studies exist to assess the value of administering post-exposure prophylaxis (PEP) to persons at risk but anecdotal evidence suggests that PEP may reduce the risk of developing clinical disease
- Doxycycline 100 mg po BID plus rifampin 600 mg po QD x 3 weeks may be considered after a high-risk exposure such as exposure in a biological weapon context, laboratory exposure, or a percutaneous membrane exposure.

- For pregnant women - trimethoprim-sulfamethoxazole 160/800 mg po BID x 3 weeks.
- Increased surveillance among exposed may be warranted, such as fever checks. Consult with Acute Communicable Disease Control.

Infection Control:

- Standard precautions - brucellosis is not spread from person-to-person
- Avoid generation of secondary aerosols
- Contact precautions are indicated for handling body fluids.

Introduction and Epidemiology

Brucellosis (also known as undulant fever, Malta fever, Gibraltar fever, Cyprus fever) is a zoonotic infection of domesticated and wild animals caused by an organism of the genus *Brucella.* It occurs naturally worldwide in Europe, Africa, Middle East, Central Asia, Central & South America and Mexico. Approximately less than 0.5 cases per 100,000 are reported in the U.S. annually. In the U.S. most cases are reported from CA, FL, TX, and VA (primarily *B. melitensis)* with the majority of these associated with ingestion of unpasteurized dairy products made outside the U.S. (e.g. "queso fresco" imported from Mexico).

Various *Brucella* species affect goats, sheep, deer, cattle, dogs and elk. Brucellosis is an infectious disease of the reproductive system of livestock and depending on the species affected, is associated with infertility, abortion, retained fetal membranes, orchitis and infection of the male sex glands.

Animals may transmit *Brucella* organisms to humans and other animals during septic abortion, at the time of slaughter, and in their milk. Humans can acquire brucellosis by direct inoculation through cuts and skin abrasions or conjunctiva exposure, especially from handling animal carcasses, placentas, or contact with animal vaginal secretions (e.g. veterinarians, shepherds, ranchers, slaughterhouse workers), inhalation of infected aerosols (e.g. slaughterhouse workers, laboratorians), or ingestion of contaminated food such as raw milk, or cheeses made from unpasteurized milk. Brucellosis is generally not transmitted from person to person. There have been rare cases reported of congenital brucellosis and sexual transmission; infected mothers may transmit *Brucella* to their infants through breast feeding. The ease of transmission by aerosol suggests the *Brucella* species may be useful as a biological agent.

Brucella species are small, non-motile, Gram-negative coccobacilli. The species most commonly associated with human infection includes *B. melitensis, B. suis, B. abortus,* and *B. canis. Brucella melitensis* in sheep and goats represents by far the most important source of brucellosis in humans. Humans are primarily infected by the handling of animals and the consumption of raw milk and milk products.

Brucella suis occurs in most areas in which pigs are kept; infections occur in people handling pigs on farms and during slaughtering. Bovine brucellosis caused by *B. abortus* tend be sporadic and are often stemmed from occupational exposure, veterinarians are at risk from care of cattle and from accidental inoculation with live vaccine. Cases of *B. canis* infection in humans have primarily occurred only in dog handlers (e.g. trainers or breeders who may have extensive daily contact).

Table 1: Selected characteristics of *Brucella* infections in livestock and humans

Brucella Species	Human virulence*	Primary Reservoir	Secondary Reservoir	Geographic Distribution	Human Exposure Activity
B. melitensis	++++	Goat, sheep, cattle	Dog, human	Latin America, Asia, Mediterranean	Raw dairy foods, animal husbandry, laboratory
B. abortus	++ to +++	Cattle, bison, cervids (deer, elk, moose, etc.), yaks, camels	Goat, sheep, dog, Human	Worldwide	Raw dairy foods, animal husbandry, laboratory
B. suis	+	Pig, hares, caribou, reindeer, wild rodents, cattle	Dog, human, Cattle	SE Asia, Scattered and Midwest US, S. America	Pork slaughter, processing, feral pig hunting, laboratory
B. canis	+	Dog, coyote		Scattered	Dog breeding and whelping operations
B. ovis		Sheep			Has not been identified to cause human disease
B. neotomae		Rodents			Has not been identified to cause human disease
B. pinnipediae and B. cetaceae	+ (only 3 reports to date of human infection)	Minke whales, dolphins, porpoises (pinnipediae), seals (cetaceae)	Possibly transmitted to domestic animals and wildlife		Pathogen icity for humans of the different *Brucella* species found in cetaceans and pinnipeds still has to be clearly established

*Virulence is graded on a scale from no virulence (-) to the highest degree of virulence (++++)

From: Pappas, G, Akritidis, N, Bosilkovski, M, Tsianos, E. Brucellosis. N Engl J Med 2005; 352:2325.
McDonald WL, Jamaludin R, Mackereth G, et al. Characterization of a *Brucella* sp. Strain as a Marine-Mammal Type despite Isolation from a Patient with Spinal Osteomyelitis in New Zealand. 2006; 44: 4363-4370.
Sohn AH, Probert WS, Glaser CA, et al. Human Neurobrucellosis with Intracerebral Granuloma Caused by a Marine Mammal *Brucella* spp. Emerg Infect Dis 2003; 9: 485-488.

Significance as a Potential Bioterrorist Agent

- The U.S. military developed *B. suis* as a biological weapon in the 1950's, but terminated the program in 1967.
- *Brucella* could be released as an aerosol or used to contaminate food or milk
- The most likely form of intentional release would be via infectious aerosols; however food-borne exposure is also possible. Any large-scale outbreak of brucellosis would suggest deliberate release *of Brucella* organisms.
- The CDC considers brucellosis a lesser threat than agents such as anthrax and smallpox; its incubation period is rather long, many infections are asymptomatic, and the mortality is low.
- Bioterrorism might also be suggested by clusters of brucellosis cases without a travel history to endemic areas, without relevant food-borne or occupational exposures, or where the cases are linked in time and place (e.g. geographically related cases following a wind direction pattern).
- *Brucella* is susceptible to heat, sunlight, and commonly used disinfectants but can survive in the environment months under certain specific conditions, becoming a continuing threat to both humans and animals.
- No human vaccine is available

Clinical Manifestations & Complications

Brucella sp. are facultative intracellular pathogens that survive and multiply within the phagocytic cells of the host. After entering the human body and being taken up by local tissue lymphocytes, brucellae are transferred through regional lymph nodes into the circulation and are subsequently seeded throughout the body, with tropism for the reticuloendothelial system.

Incubation period
Varies from 1 week to several months; most people become ill within 3-4 weeks of exposure.

The symptoms of brucellosis are non-specific. Patients usually complain of fever, sweats, malaise, anorexia and back pain. Malodorous perspiration, mild lymphadenopathy, hepatomegaly, and splenomegaly may also be present. Brucellosis is a well documented cause of fever of unknown origin with varied and non-specific symptoms and it is a systemic infection that can involve any organ or organ system. Patients may present with an acute, febrile illness, a chronic infection or a localized inflammatory process. Brucellosis should be suspected when patients present with acute or insidious onset of fevers, night sweats, fatigue, gastrointestinal symptoms, anorexia, weight loss, headache, arthralgias, splenomegaly, and/or hepatomegaly.

Signs and Symptoms

Table 2: Clinical presentation of human brucellosis*

Features	Percentage of cases
Signs and symptoms	
Fever	91
Constitutive symptoms (e.g.	26
Hepatomegaly	17
Splenomegaly	16
Lymphadenopathy	7
Complications	
Peripheral arthritis	22 (8 in hips, 7 in knees, 4 in elbows, 4 in wrists, 4 in other locations)†
Sacroiliitis	3
Spondylitis	19 (15 lumbar, 3 dorsal, 1 cervical)
Central nervous system disorders	3
Epididymoorchitis	5.7§
Vomiting and diarrhea	3
Respiratory disorders	6
Rashes	3
Cardiovascular disorders	0
Laboratory findings	
Hematologic	49 (40 relative lymphocytosis, 5 isolated thrombocytopenia, 2 isolated
Transaminasemia	24
Positive blood cultures	16
Rate of relapse	4

From: Pappas, G, Akritidis, N, Bosilkovski, M, Tsianos, E. Brucellosis. N Engl J Med 2005; 352:2325.
* Data are from the most recent 100 patients who received the diagnosis of brucellosis at the University Hospital of Ioannina and whose cases were followed for at least a year.
†Some of the patients had polyarthritis.
§Data are for 70 male patients.

Virtually any organ system can be affected, most common sites are:

- Osteoarticular (most common complication), especially sacroiliitis — 20 to 30 percent
- Genitourinary, especially epididymoorchitis — 2 to 40 percent of males
- Neurobrucellosis, usually presenting as meningitis — 1 to 2 percent less common neurologic complications include papilledema, optic neuropathy, radiculopathy, stroke, and intracerebral hemorrhage
- Endocarditis — 1 percent; most cases of endocarditis are left-sided, and about two-thirds occur on previously damaged valves; is the principal cause of mortality in the course of brucellosis
- Hepatic abscess — 1 percent

Other less common complications include splenic, thyroid, or epidural abscess, pneumonitis, pleural effusion or empyema, and uveitis. A few cases of *Brucella* infection involving prosthetic devices, such as pacemaker wires or prosthetic joints, have been reported. Respiratory complications of brucellosis are considered rare.

The case fatality rate is very low in untreated patients (less than 2%) and it is usually due to *B. melitensis* endocarditis or meningitis. Systemic symptoms may last for weeks or months, however most patients recover within a year, even without antibiotic treatment.

Imaging studies may help to identify localized infection but does not provide a definitive diagnosis.

Clinical Laboratory Values

Routine laboratory studies are non-specific. Leukocyte count is usually normal but may be low; anemia, neutropenia, and thrombocytopenia may also occur. AST and ALT may be mildly elevated.

Laboratory Diagnosis

The diagnosis of brucellosis is primarily dependent on clinical suspicion along with the taking of an adequate history of exposure including animal contact history, travel to enzootic areas, and ingestion of high-risk foods such as unpasteurized dairy products (including from goats). The diagnosis is made definitively when brucellae are recovered from blood, bone marrow or other tissues. Blood cultures are positive in 15%-70% of cases. Other clinical samples can be tested depending on the distribution of infection (synovial fluid, pleural fluid, CSF, biopsies of the liver and lymph nodes). Clinicians should be sure to inform the laboratory of suspected brucellosis.

In the absence of culture confirmation, a presumptive diagnosis can be made by a rise in titer of specific antibodies in serum. A variety of tests have been used for the serologic diagnosis of brucellosis one of which is the microagglutination test (MAT). No single titer is always diagnostic, however, most cases of active infection have a single titer of 1:160 or higher. Drawbacks of the MAT include the inability to diagnose *B. canis* infection, cross-reaction with other Gram-negative organisms, and lack of seroconversion in some cases. When interpreting serum agglutination test results, the possibility of cross reactions of *Brucella* antibodies with those against other Gram-negative bacteria, such as *Yersinia enterocolitica* serotype 0:9, *Francisella tularensis,* and *Vibrio cholerae,* should be considered. Also, in previously published reports *Brucella* was misidentified as micrococcus or a coryneform bacillus, and *Moraxella phenylpyruvica.* PCR testing is available for blood and tissue through the LRN laboratories.

Laboratory criteria for diagnosis are a) isolation of *Brucella* from a clinical specimen, or b) fourfold or greater rise in *Brucella* agglutination titre between acute- and convalescent-phase serum specimens obtained > 2 weeks apart and studied at the same laboratory, or c) demonstration by immunofluorescence of *Brucella* sp. in a clinical specimen.

Handling Laboratory Specimens

Inform laboratories if suspecting *Brucella* as it is a BSL-3 pathogen. Cultures should also be held for a minimum of 4 weeks before being declared "no growth".

Treatment

Generally accepted principles of brucellosis treatment are that the antibiotics used must penetrate macrophages, and that monotherapy has a higher rate of relapse compared with combined therapy. No treatment regimen is 100% effective; 10% of patients relapse after treatment.

Adults

- Doxycycline 100mg PO twice daily for six weeks plus streptomycin 1 gram (15 mg/kg) IM daily for the first 14 to 21 days. If streptomycin is not available, gentamicin (5 mg/kg/day IV in three divided doses x 5-7 days) may be a suitable alternative.

Alternatives

- Doxycycline 100mg PO twice daily plus rifampin 600 to 900mg PO (15mg/Kg) once daily for six weeks.
- Quinolone (ofloxacin or ciprofloxacin) plus rifampin OR
  trimethoprim - sulfamethoxazole (TMP - SMX) plus rifampin may represent suitable alternatives.

More prolonged regimens may be required for patients with complications such as hepatitis, splenitis, meningoencephalitis, endocarditis, or osteomyelitis. Treatment regimens and duration of therapy may need to be adjusted based on specific complications of the disease (e.g. neurobrucellosis has generally been treated with 3 agents).

Pregnant Women

Two regimens have been suggested for the therapy of brucellosis in pregnancy.

- Rifampin 900 mg PO once daily for six weeks
- Rifampin 900 mg PO once daily plus trimethoprim-sulfamethoxazole (5 mg/kg of the trimethoprim component twice daily) for four weeks

With the sulfa containing regimen, attention needs to be given to the possibility of kernicterus in the infant when therapy is given during the last week prior to delivery

Pediatric dose:

Avoid tetracyclines in children <8 years old.

- Trimethoprim-sulfamethoxazole (TMP-SMX) (10 to 12 mg/kg per day of the trimethoprim component, max 480 mg/day and 50 to 60 mg/kg per day, max 2.4 g/day of the sulfa component in two divided doses) plus rifampin (15 to 20 mg/kg per day of rifampin up to a maximum of 600 mg PO daily in two divided doses) for six weeks.
- In children > 8 years old, doxycycline 2-4 mg/kg BID up to 200 mg/day plus rifampin 15-20 mg/kg up to 600-900 mg/day.

Management of Exposed Persons

Doxycycline 100 mg PO BID plus rifampin 600 mg PO QD x 3 weeks may be considered after a high-risk exposure such as exposure in a biological weapon context, laboratory exposure, or a percutaneous membrane exposure. For pregnant women - trimethoprim-sulfamethoxazole 160/800 mg PO BID x 3 weeks.

In the event of an outbreak, the Los Angeles County Department of Public Health will provide updated situational guidelines for prophylaxis.

Laboratory exposures should be reported to Acute Communicable Disease Control to receive advice on prophylaxis and monitoring; increased surveillance among exposed may be warranted, such as fever checks.

Vaccination

There are no vaccines for human use.

Handling Laboratory Specimens

Biosafety level 3 precautions should be utilized in the laboratory when handling suspected Brucella specimen cultures due to potential aerosol exposure.

Infection Control

Standard precautions are adequate for managing brucellosis patients, as the disease is generally not transmissible from person-to-person. In addition, contact precautions are indicated for handling body fluids.

Disposal of Infectious Waste

Use of tracking forms, containment, storage, packaging, treatment and disposal methods should be based upon the same rules as all other regulated medical wastes.

Autopsy and Handling of Corpses

All postmortem procedures are to be performed using Standard Precautions. All persons performing or assisting in postmortem procedures must wear mandated personal protective equipment (PPE) as delineated by OSHA guidelines. Surfaces contaminated during postmortem procedures should be decontaminated with an appropriate chemical germicide such as iodine, 10% hypochlorite or 5% phenol (carbolic acid). Cremation is preferable

Reporting to the Health Department

All suspected cases of brucellosis must be reported immediately to the:

Los Angeles County Department of Public Health

Business Hours (8am -5pm)	**213-240-7941**
After Hours (County Operator)	**213-974-1234**

Ask to Speak with the Public Health Physician On-Call

GLANDERS AND MELIOIDOSIS

ALL SUSPECTED CASES OF BURKHOLDERIA MALLEI (GLANDERS) AND BURKHOLDERIA PSEUDOMALLEI (MELIOIDOSIS) MUST BE REPORTED IMMEDIATELY TO THE DEPARTMENT OF PUBLIC HEALTH ACUTE COMMUNICABLE DISEASE CONTROL PROGRAM:

Monday - Friday (8am – 5pm)
(213) 240-7941

After Hours (County Operator)
(213) 974-1234

Ask to Speak with the Public Health Physician On-Call

Quick Reference: Glanders and Melioidosis

ALL SUSPECTED CASES OF GLANDERS and MELIOIDOSIS MUST BE REPORTED IMMEDIATELY TO THE DEPARTMENT OF PUBLIC HEALTH ACUTE COMMUNICABLE DISEASE CONTROL PROGRAM

During Business Hours	213-240-7941
After Hours (County Operator)	213-974-1234

Epidemiology:

- Glanders: Zoonosis primarily of horses, mules, and donkeys. Disease in humans typically in individuals with frequent contact with infected animals.
- Melioidosis: Widely distributed in water and soil in tropical and subtropical regions. Spread to humans usually through direct contact with contaminated source.
- Both are caused by gram negative bacilli: Glanders *(Burkholderia mallei)* and Melioidosis *(Burkholderia pseudomallei)*
- Glanders: No natural cases in the Western hemisphere since 1945: **a case of glanders in the United States is evidence for bioterrorism until proven otherwise**
- **Melioidosis: Is endemic in Southeast Asia and northern Australia**

Clinical:

- Both with similar clinical symptoms but varying incubation periods
- Glanders: incubation period 1 -5 days.
- Melioidosis: 1 -21 days or extended incubation of months to years can occur
- Clinical forms:
  - Localized - cutaneous
  - Pulmonary Septicemia
  - Chronic

Laboratory Diagnosis:

- BSL 3
- Potentially dangerous in lab - high risk of aerosolization
- *B. mallei* Non motile, gram negative bacillus
- B. pseudomallei motile, gram negative bacillus
- blood cultures usually negative for *B. mallei* but urine and blood cultures often positive with *B. pseuodomallei*
- serology
- PCR available in some labs and can distinguish glanders from melioidosis

Treatment:

- Little data in humans for glanders
- Generally felt that empiric antibiotics for melioidosis would also work for glanders
- For severe disease: ceftazidime, imipenem, or meropenem
- Also consider addition of Trimethoprim-sulfamethoxazole.

Management of Exposed Persons:

- Little data available, post-exposure prophylaxis with TMP/SMX or doxycycline, optimal duration unknown
- No vaccine available

Infection Control:

- Standard precautions
- Person to person transmission unlikely but may occur through improper handling of infectious materials.

Introduction and Epidemiology

Glanders and Melioidosis are caused by non-motile gram negative bacilli, *Burkholderia mallei* and *Burkholderia pseudomallei,* respectively.

Glanders is a zoonotic illness that primarily affects horses, although donkeys, mules, goats, cats, and dogs can also be infected. Pigs and cattle appear to be immune. Historically, glanders infection was primarily associated with exposure to horses. Glanders has not occurred naturally in the United States since 1945, and the last natural human case in the U.S. occurred in 1938. One case occurred in a lab worker in 2000. **Glanders in the United States is highly suspicious for a bioterrorist event.** There continue to be sporadic cases in Asia, Africa, the Middle East, and South America.

There are several clinical forms of glanders, localized - cutaneous, pneumonic, systemic or septicemic, and chronic. Clinically, glanders is similar to melioidosis. Naturally, glanders was generally transmitted from animals to humans by invasion of nasal, oral, and conjunctival mucous membranes; by inhalation into the lungs; or through lacerated or abraded skin. Cutaneous infection can lead to systemic or septicemic infection if untreated.

Melioidosis is widely distributed in soil and water in the tropics and is endemic in Southeast Asia and northern Austrialia. The greatest concentration of cases reported are in Vietnam, Cambodia, Laos, Thailand, Malaysia, Myanmar (Burma), and northern Australia. Additionally, it is seen in the South Pacific, Africa, India, and the Middle East. Sporadic cases have occurred elsewhere (Africa, Central and South America, etc.) Most individuals who develop symptomatic disease due to natural exposure have predisposing medical conditions (diabetes, alcoholism, cirrhosis, renal disease, immunosuppressive medications). Patients can remain asymptomatic after initial exposure and can remain quiescent for decades, presenting with active melioidosis up to 29 years later.

In Southeast Asia, the organism has been repeatedly isolated from agriculture fields, with infection occurring primarily during the rainy season. Humans and animals are believed to acquire the infection by inhalation of dust, ingestion of contaminated water, and contact with contaminated soil especially through skin abrasions, and for military troops, by contamination of war wounds

An intentional high-dose release of aerosolized organisms would most likely be clinically indistinguishable between glanders and melioidosis and would manifest likely as pneumonia or sepsis.

Significance as a Potential Bioterrorist Agent

- Glanders
  - Used in WWI by Germany as an agent against allied horses (Khan A. S., Ashford D)
  - Used in WWII by Japan on animals and experimentally in humans
  - Studied but not weaponized by United States, (Khan A. S., Ashford D)

- Soviets allegedly developed an antibiotic-resistant strain of glanders stable as aerosols and persistent in the environment
- Can cause severe illness with high fatality in pneumonic forms
- Can infect via aerosol
- Very few organisms are required to cause disease by an aerosol route
- High mortality rates
- No vaccine available
- Little data on treatment options available
- Prolonged antibiotic therapy needed for prophylaxis and/or treatment

- Melioidosis
  - Potential for efficient aerosol spread
  - No available vaccine or reliable therapy
  - Studied by US as potential bioweapon but never weaponized
  - Reported that former Soviet Union was experimenting with it as a bioweapon agent

Clinical Manifestations

Pulmonary

Presents as an acute, febrile, necrotizing pneumonia with or without sepsis, with necrosis of tracheobronchial tree

Incubation period

Glanders: 10-14 days
Melioidosis: more difficult to determine, 1-21 days or could be extended months to years

Signs and Symptoms

- fever
- malaise
- myalgias
- headache
- excessive tearing of eyes
- light sensitivity
- diarrhea
- pleuritic chest pain
- cervical adenopathy
- splenomegaly
- generalized popular-pustular rash
- pleural effusion

- ecthyma gangrenosum-like lesions and cutaneous abscesses (which may ulcerate)
- X-RAY findings: bilateral bronchopneumonia, miliary nodules, segmental or lobar
  infiltrates, and cavitating lesions

Glanders: Pneumonia may progress rapidly with development of osteomyelitis, meningitis, and brain, liver, or splenic abscesses. With septicemia clinical course can be rapid with death occurring after 7 to 10 days. Most clinical data in the US occurred prior to development of antibiotics and mortality was 95%. There is little data on human glanders, with modern antibiotics and supportive therapy, mortality may be reduced.

Melioidosis: Severe disease and fatalities due to naturally occurring exposures are uncommon in those without defined risk factors.

In the event of an intentional release, inoculating dose, mode of acquisition, host factors, and virulence properties would factor into clinical manifestations and prognosis for illness due to glanders and melioidosis.

Differential Diagnosis of Pulmonary Glanders and Melioidosis

Condition	Features of Condition that Distinguishes from glanders
Mycoplasma pneumonia	Marked patchy infiltrates, + cold agglutinins
Legionnaire's disease	May have high fever with relative bradycardia, diarrhea, infiltrates
Psittacosis	History of exposure to birds, pneumonitis
Plague	
Tularemia	less fulminant disease
Invasive group A streptococcal pneumonia	
Q fever	Serologic evidence, less severe disease
Histoplasmosis	Long standing X-ray findings, chronic onset
Coccidioidomycosis	Residence or travel to southwestern U.S.
Anthrax	Hemorrhagic mediastinitis
Inhalation of staphylococcal enterotoxin B (as a bioterrorist agent)	No prodrome present

Localized - Cutaneous

Glanders: In addition to inhalational exposure, glanders may be acquired through a break in the skin and lead to either an acute or chronic infection. With exposure through a break in the skin, a localized infection will occur after 1-5 days with ulceration and lymphadenopathy. The infection then may either lead to sepsis with widespread hematogenous abscesses and a rapidly progressive course (see above), or can develop a chronic skin infection historically known as farcy, which consists of subcutaneous ulcers, lymphatic thickening, lymphatic nodules, and often fever, rigors and malaise.

Melioidosis: Local nodule or abscess formation but not as common as with glanders. Can cause pneumonia through hematogenous spread from percutaneous inoculation.

INCUBATION PERIOD

Glanders: 1-5 days
Melioidosis: difficult to determine

Differential Diagnosis of cutaneous glanders and melioidosis

Condition	Features of Condition that Distinguish from Glanders
Insect bite	History of insect bite, often painful
Brown recluse spider bite	History of insect bite (lesion becomes painful, and may manifest the "red, white and blue sign")
Ulceroglandular tularemia	More tender than pruritic; local edema typically less than in anthrax
Scrub typhus	Generalized macular-papular or papular-vesicular rash; papular base is discernible under the vesicle or eschar; history of residence or travel to endemic areas
Rickettsial spotted fevers	Generalized macular-papular or papular-vesicular rash; papular base is discernible under the vesicle or eschar; history of residence or travel to endemic areas
Ecthyma gangrenosum	Usually associated with frank cellulitis or with known immunosuppression
Plague	Sudden onset of painful lymphadenopathy; skin lesions are rare in U.S. cases
Orf virus disease	Animal exposure; contact with sheep, goats, or musk oxen; lesion associated with crusts and scabbing
Staphylococcal lymphadenopathy	Lesion purulent with palpable lymph nodes; primary wound is associated with red, linear streaks toward regional lymph node
Cutaneous leishmaniasis	Travel to or residence in endemic area; eschar is absent
Cat scratch disease	Contact with kittens or cats with fleas; primary lesion is a papule or vesicle, tender lesion and lymphadenopathy

Septicemia

Septicemia can occur with or without pneumonia and can affect multiple organ systems including liver, spleen, prostate, and kidney. Mortality rate is 90%.

Chronic

The chronic form can present with multiple abscesses or re-activation pneumonia.

Naturally occurring glanders most likely presents as cutaneous or chronic, however cutaneous infection can lead to systemic or septicemic infection if untreated. **It should be noted that glanders does not occur naturally in the United States, and ANY case of glanders is evidence for bioterrorism until proven otherwise.** If glanders were used as a weapon, it would be most effective as an aerosol and thus would present primarily in the pulmonic or systemic forms.

Most naturally occurring cases of melioidosis is often subclinical or local skin or pulmonary forms but clinical manifestations can be diverse if bacteremic spread occurs to other organs.

Laboratory Diagnosis

BSL-3 practices, containment equipment and facilities are recommended for procedures on clinical materials suspected as being positive f or glanders; BSL-2 practices containment equipment and facilities are recommended for procedures on clinical materials suspected as being positive for melioidosis. If melioidosis or glanders is suspected, please call the Department of Public Health Acute Communicable Disease Control Program (Business Hours: (213) 240-7941 or After Hours: (213) 974-1234) to arrange for submission of specimens for confirmatory testing. Staff from the public health laboratory is available for consultation at (213) 250-8619 or After Hours: (213) 974-1234.

Microbiology

B. pseudo mallei may be readily cultivated on MacConkey agar and may require up to 72 hrs of incubation. *B. mallei* strains are variable in the ability to grow on MacConkey agar.

Gram Stain

- Gram stain and culture of blood, sputum, urine, and skin lesions
  - Blood cultures usually are negative for glanders but cultures often positive for *B. pseudomallei*
  - Gram stain and culture of sputum, urine, and skin lesions can be performed Gram stain may reveal small gram-negative bacilli, which stain irregularly with methylene blue.

- Characteristic bipolar staining with "safety pin" appearance
- Meat nutrient agar or the addition of 1-5% glucose may accelerate growth of bacteria.

Serology

- **Agglutination tests:** Agglutination tests for glanders may be positive after 7-10 days, but a high background titer found in normal sera from patients in an endemic area makes interpretation difficult without paired sera.

Complement fixation tests

- Complement fixation tests are more specific and are considered positive for glanders if the titer is equal to or greater than 1:20.
- A 4-fold increase in the titer for melioidosis is considered positive.

Autopsy Findings

Cultures of autopsy nodules in septicemic cases will usually establish the presence of *B. mallei.*

Handling Laboratory Specimens

BSL-3 practices, containment equipment and facilities are recommended for procedures on clinical materials suspected as being positive for glanders.

Laboratory staff handling specimens from persons who might have glanders must wear surgical gloves, protective gowns and shoe covers.

Accidental spills of potentially contaminated material should be decontaminated immediately by covering liberally with a disinfectant solution 0.5% hypochlorite (10% household bleach) or 10% formalin), **left to soak for 30 minutes,** and wiped up with absorbent material soaked in disinfectant. All biohazardous waste should be decontaminated by autoclaving. Contaminated equipment or instruments may be decontaminated with a hypochlorite solution, hydrogen peroxide, iodine, peracetic acid, 1% glutaraldehyde solution, formaldehyde, ethylene oxide, irradiation, or other OSHA approved solutions, or by autoclaving or boiling for 20 minutes.

Treatment

Clinical experience with treatment for glanders is limited as disease waned before modern antibiotic era but generally thought that empiric antibiotics for melioidosis will also work for glanders pending susceptibility results.

Treatment will vary depending on type and severity of clinical presentation.
Although no consensus exists, localized disease can be treated with oral antibiotics trimethoprim-sulfamethoxazole (TMP-SMX), doxycycline, or amoxicillin/clavulanate for 60-150 days.

For severe disease, treatment with either high dose ceftazidime (1 gram Q 3 hours or 2 grams q 6 hours IV) or imipenem or meropenem (1 gram Q 8 hours IV) for at least 2 weeks is recommended. The addition of TMP-SMX may be added to ceftazidime or a carbapenem. Granulocyte colony stimulating factor (G-CSF) was used in addition to empiric antibiotics for septic shock in northern Australia and data suggested increased survival but further studies are needed to determine its specific role in treatment.

Emergence of resistance of *B. pseudomallei* during therapy has been documented.

Eradication therapy is considered necessary to prevent relapse of melioidosis to continue for 3 months with high-dose TMP-SMX.

Vaccination and Duration of Therapy

There is no vaccine currently available.

Management of Exposed Persons

In the event of a bioterrorist release of glanders or melioidosis, it may be difficult to define who has been exposed. Once the site of the attack is determined, all persons at the site of the release or downwind from the release (assuming aerosol dispersal) would be considered potentially exposed.

Inhalational exposures

Prophylaxis with TMP/SMX or doxycycline is of unproven benefit.

Management of Laboratory Exposure to Burkholderia pseudomallei and mallei

If a hospital laboratory worker has been exposed to Burkholderia, please call the Department of Public Health Acute Communicable Disease Control at 213-240-7941 for recommended follow-up.

Laboratory workers that have worked with cultures of the organism are at risk of developing disease. Laboratories that have handled the specimen should conduct an exposure risk assessment on their lab employee.

CDC recommends symptom watch for 21 days as well as baseline and follow-up serologies on employees with lab exposure (regardless of high or low).

The following Emerging Infectious Disease article by Peacock et al.,can be used as guidance on the Management of Accidental Laboratory Exposure to *Burkholderia pseudomallei* and *B. mallei*: http://wwwnc.cdc.gov/eid/article/14/7/07-1501_article.htm

Infection Control

Standard precautions are indicated. Melioidosis can spread from person to person by contact with the blood and body fluids of an infected person

Disposal of Infectious Waste

Use of tracking forms, containment, storage, packaging, treatment and disposal methods should be based upon the same rules as all other regulated medical wastes.

Autopsy and Handling of Corpses

All postmortem procedures should be performed using Standard Precautions. All persons performing or assisting in postmortem procedures must wear mandated personal protective equipment (PPE) as delineated by OSHA guidelines. Surfaces contaminated during postmortem procedures should be decontaminated with an appropriate chemical germicide such as iodine, 10% hypochlorite or 5% phenol (carbolic acid).

Reporting to the Health Department

Any case of glanders in the United States is highly suspicious for bioterrorism. Any suspicion of glanders should be reported immediately by phone to the:
Los Angeles County Department of Public Health

An individual or group of individuals presenting with melioidosis without a clear exposure history (travel or residing in endemic areas - Thailand, northern Australia, travels to tropical/sup-tropical regions) may be the first clue of a bioterrorist attack. A suspicious case or outbreak does require immediate reporting to the:

Los Angeles County Department of Public Health

Business Hours (8am -5pm)	**213-240-7941**
After Hours (County Operator)	**213-974-1234**

Ask to Speak with the Public Health Physician On-Call

Q FEVER

ALL SUSPECTED CASES OF Q FEVER MUST BE REPORTED IMMEDIATELY TO THE DEPARTMENT OF PUBLIC HEALTH ACUTE COMMUNICABLE DISEASE CONTROL PROGRAM:

Monday - Friday (8am – 5pm)
(213) 240-7941

After Hours (County Operator)
(213) 974-1234

Ask to Speak with the Public Health Physician On-Call

Quick Reference: Q Fever *(Coxiella)*

ALL CASES OF Q FEVER IN WHICH TERRORISM IS SUSPECTED
MUST BE REPORTED IMMEDIATELY TO THE
DEPARTMENT OF PUBLIC HEALTH
ACUTE COMMUNICABLE DISEASE CONTROL PROGRAM

During Business Hours	213-240-7941
After Hours (County Operator)	213-974-1234

Epidemiology:

- Animal infection widespread
- Rickettsial agent highly resistant to drying, chemicals and heat
- Acute and Chronic forms

Clinical:

Acute Q Fever

- Incubation period ranges from 3 to 30 days, typically 10 to 16, probably dose dependent
- Presentation can vary; asymptomatic, febrile illness with headache, pneumonia, hepatitis
- High index of suspicion needed with confirmatory testing to diagnose
- Mortality rates low (1 -2%)

Chronic Q Fever

- Infrequent (<1 % of infected persons)
- Primarily presents as culture negative endocarditis

Laboratory Diagnosis:

- Dangerous to culture in lab, highly infectious
- BSL- 3
- Diagnosis primarily by serology, IFA (immunoflourescence antibody) or immunohistochemical staining of tissues
- PCR testing for clinical specimens is available through the LRN Laboratories

Treatment:

- Most effective when initiated within first 3 days of illness
- Doxycycline 100 mg PO BID for 14-21 days
- Quinolones second line
- Chronic Q fever treatment difficult, years of combination therapy

Management of Exposed Persons:

- Decontamination
- Vaccine unlicensed in U.S., unlikely to be of use in terrorism situation
- Doxycycline or tetracycline for 5 days, beginning 8-12 days AFTER exposure.
- Follow up with initiation of therapy for symptomatic patients

Infection Control:

- Standard precautions

Introduction and Epidemiology

Q fever is a disease caused by the bacterial agent *Coxiella burnetii.* Coxiella burnetii is an obligate intracellular pleomorphic gram negative coccobacillus. The bacterium also has a spore-like form that is highly resistant in the environment, and can survive for months in the environment or in cold storage. This form is also highly resistant to desiccation and can travel long distances by wind. *Coxiella burnetii* is found worldwide (except for New Zealand), and distributed throughout the US and Canada.

The normal animal hosts for *Coxiella burnetii are* numerous and widespread. Q fever is a zoonosis and its usual hosts are cattle, sheep, goats, although it can also infect cats, dogs, birds, wildlife, rodents, and ticks. *Coxiella burnetii* can be shed in urine, feces and milk, and high concentrations of the bacteria are found in mammary tissues and in birth products. Abortion or birth can generate aerosols that are able to spread by wind over long distances. Humans usually acquire Q fever through aerosolized *Coxiella burnetii.* Human outbreaks are usually associated with farms, slaughterhouses, agricultural fairs, or research facilities through exposure to parturient animals. Exposure to parturient cats has also resulted in cases. People may also be infected through ingestion of contaminated dairy products although volunteer studies of ingestion of contaminated, unpasteurized milk are contradictory. It has been suggested that inhalation is more likely to lead to pneumonia presentation, and ingestion is more likely to lead to hepatitis syndromes. Other, rarer means of infection include crushing an infected tick between fingers, transmission through fomites such as contaminated clothing (from an occupational^ exposed person) or exposure to contaminated pigeon droppings.

Clinically, infection with *Coxiella burnetii* is most frequently (60%) asymptomatic. When symptomatic, Q fever presents as both acute and chronic forms. Acute forms include a non specific febrile illness with high fever and severe headache, pneumonia, hepatitis, myocarditis, pericarditis and occasionally neurological symptoms. Chronic Q fever occurs in approximately 1 % of patients and forms can include endocarditis and osteomyelitis among other presentations. It is thought that the development of chronic Q fever is likely due to immunocompromise or other host factors rather than the particular bacterial strain itself. Patients with prosthetic or abnormal heart valves are at particular risk (perhaps up to 40%) of developing chronic Q fever endocarditis.

The designation of the name Q fever (for Query) was made by Derrick describing an outbreak of febrile illness in an abattoir in Queensland, Australia in 1935 because the etiology of the new illness was unknown. Burnet first isolated the organism in 1938 and *Coxiella burnetii* was then also found thereafter in the United States by Davis and Cox in wood ticks. The agent was later identified by Burnet and Freeman. *Coxiella burnetii* is capable of forming small cell variants, which are metabolically inactive spore like forms with a thickened cell wall. These spore-like forms can survive for extended periods of time outside of a living cell, and are highly resistant to drying and other extreme environmental conditions. In fact, these spores can retain infectivity after being blown for miles by wind, after cold storage or fixation in formalin, in paraffinized tissue, or even after some gas sterilization procedures. Q fever is endemic throughout the world except for New Zealand. The natural reservoir includes sheep, goats, cattle, and a variety of other animals. Seroprevalence studies show highly variable results, some studies show seroprevalence in individuals with occupational risk factors as high as 7.8%, compared to 0.8%

for persons without risk factors. Animal seroprevalence also varies widely, some studies show seroprevalence among US dairy cattle to be as low as 0.9% or high as 72%, goats from 3.2% to 56%, sheep from 5.7% to 24%, antibodies have also been seen in dogs, cats, horses, and a variety of other wildlife species. There were 1168 cases of Q fever reported in the US between 1948 and 1977, (58.4 cases/ year) with the majority (785) from California. From 1978 to 1986 there were 228 cases reported (28.5/year) Los Angeles County reported a total of 7 cases from 1997 to 2003. Q fever has been a nationally notifiable disease since 1999, but is most likely highly underreported.

Person to person transmission is unlikely to play a significant role. There have been several isolated reports of obstetricians contracting Q fever after delivering an infected pregnant woman.

Clinicians should consider the diagnosis of Q fever in an individual with pneumonia, fever, headache, cough (typically dry) with or without hepatitis. Clinicians should consider the possibility of bioterrorism in any single patient with Q fever without a history of exposure to sheep, goats or cattle. By law in California, any case of Q fever must be reported within 1 day by mail, telephone or fax. However, any suspicious outbreak or possible bioterrorist incident is legally required to be reported by phone immediately.

An individual or group of individuals presenting with Q fever pneumonia without a clear exposure history (e.g. occupational risk or exposure to parturient animals) may be the first clue of a bioterrorist attack. Although for isolated cases of Q fever, California law requires notification of health authorities within one day, rather than immediately, a suspicious case or outbreak does require immediate reporting. Therefore, a single, suspect case, or suspected outbreak of Q fever must be immediately reported to the Department of Public Health Acute Communicable Disease Control Unit (213) 240-7941.

Significance as a Potential Bioterrorist Agent

- Weaponized by the US, Japan, Soviet Union, allegedly Aum Shinrikyo
- United States experimented with use of Q fever as weapon until 1971
- Aum Shinrikyo allegedly investigated use of Q fever as well in the mid 1990s
- It is unknown if Iraq experimented with Q fever; although there were several cases in US soldiers during the Persian Gulf War, these are thought to be most likely due to endemic disease
- Spore like forms of the Q fever agent are environmentally tough and can resist heat, cold, drying and other extreme conditions
- *Coxiella burnetii* is easily available in the environment
- Q fever is easily spread by aerosol
- Q fever has a low infective dose (as few as 10 organisms)
- It is estimated that an aerosol attack using 50 kg of *Coxiella burnetii* would cause as many as 100,000 casualties
- There is a limited supply of vaccine (not licensed in the U.S.) and individuals must undergo serological testing prior to vaccination.
- Q fever is most likely to be used as an agent of mass panic as most cases are asymptomatic, and symptomatic cases, while debilitating, often resolve spontaneously and are rarely fatal

Clinical Manifestations

If Q fever were used as a biological weapon, it would most likely be disseminated as an aerosol, and this the most likely presentation of a biological attack would be large numbers of ill individuals presenting with pneumonia, with or without hepatitis, as well as perhaps some individuals with hepatitis alone, many with non specific respiratory illness, and likely a smaller number with the more atypical presentations of myocarditis, pericarditis and meningitis. Importantly, the majority of those exposed will seroconvert, but remain asymptomatic. Complications of acute Q fever infection can include chronic Q fever, (see below) prolonged weight loss, or Q fever chronic fatigue syndrome.

Acute Q Fever

Although the majority of Q fever infections are asymptomatic, non-specific febrile illness, pneumonia, and hepatitis are common presentations of acute Q fever infection. Patients typically present with abrupt onset of high fever (>104F) severe headache, non productive cough, and other symptoms possibly including chills, sweats, disorientation and/or confusion, myalgias, malaise, sore throat, nausea, vomiting, diarrhea, abdominal pain and chest pain. Up to 50% of symptomatic patients will develop pneumonia, and up to 40% will develop hepatitis; some patients will develop both pneumonia and hepatitis. Rarely, meningitis, myocarditis, pericarditis, meningoencephalitis, and other neurological manifestation including peripheral and cranial neuropathies, seizures, cerebellar signs, and the Miller-Fisher syndrome can also occur. There is conjecture that the route of infection affects the clinical presentation such that ingestion is more likely to present with hepatitis, and inhalation with pneumonia, and there is great geographical variation in the proportion of types of syndromes resulting from Q fever.

Incubation period

The incubation period for acute Q fever varies widely from as few as 3 days to as long as 30 days, (average 10-16 days) and appears to be dose dependent. The infectious dose may be as small as a single organism, but higher doses appear to be associated with shorter incubation periods.

Signs and Symptoms

- high fever (>104F)
- severe headache
- non productive cough > productive cough
- pneumonia
- elevated liver enzymes
- hepatitis
- meningitis
- hepatosplenomegaly
- anorexia
- weight loss
- rash
- inspiratory crackles on physical exams
- pulse temperature dissociation
- X-RAY findings often include alveolar infiltrate, sometimes with lower lobe

predominance, rounded opacities in greater than 50% of cases, pleural effusions 3 to 35% of cases. CXR may be normal in up to 10% of patients.

- Non-contrast CT findings include lobar, segmental, or patchy airspace involvement, pleural effusion and mild lymphadenopathy can be seen, and occasionally necrotizing pneumonia in immunocompromised patients.

The majority of acute Q fever infections resolve spontaneously, (although more rapidly with early antibiotic treatment) Mortality is typically less than 2%.

Differential Diagnosis of Acute Q Fever

Condition	Features of Condition that Distinguishes from Q fever
Mycoplasma pneumonia	Marked patchy infiltrates, + cold agglutinins, need serology to determine
Legionnaire's disease	May have high fever with relative bradycardia, diarrhea, infiltrates, need serology to determine
Psittacosis	History of exposure to birds, pneumonitis, need serology to determine
Plague	More severe rapidly progressive clinical course, more productive cough, watery or bloody mucous, gram negative diplococci in sputum
Tularemia	Laboratory testing
Anthrax	Mediastinal widening, gram positive organisms in blood, severe course and rapidly fatal
Histoplasmosis	Long standing X-ray findings, chronic onset
Coccidioidomycosis	Residence or travel to southwestern U.S.
Inhalation of staphylococcal enterotoxin B (as a bioterrorist agent)	No prodrome present

Clinical Laboratory Values

Patients with acute Q fever may present with the following abnormalities

- Elevated liver enzymes, in as many as 85% of cases (although LFTs may be normal in cases with primarily pneumonic symptoms)
- Erythrocyte sedimentation rate > 20 (43-88%)
- Thrombocytopenia (12%) or Thrombocytosis (40%)
- Elevated creatinine phosphokinase level (20%)
- Microscopic hematuria (50%)
- Hyponatremia (up to 28%)
- Elevated WBC (25%) (normal WBC common)
- + anti-phospholipid antibodies (in hepatitis patients with prolonged fever)
- + anti-smooth muscle antibodies (in hepatitis patients with prolonged fever)

Chronic Q Fever

Chronic Q fever develops in a small percentage of patients exposed to Coxiella burnetii. Patients may either develop chronic Q fever after insufficient or no therapy for symptomatic acute Q fever, or may develop chronic Q fever without ever displaying symptoms of acute infection.

Chronic Q fever may present as

- Culture negative endocarditis
- Vascular infection
- Osteoarticular arthritis
- Q fever during pregnancy
- Chronic hepatitis
- Chronic pericarditis

Culture negative endocarditis is the most frequent form of chronic Q fever (60-70%). Risk factors include having a prosthetic or abnormal valve, immunocompromise, transplant patients, malignancy, or chronic renal insufficiency. As many as 50% of patients with abnormal valves may develop chronic Q fever endocarditis. Mortality is up to 65% of patients with Q fever endocarditis.

Incubation period

Ranges from 1 to 20 years after initial exposure.

Signs and Symptoms

- Fever (68%)
- Heart failure (67%)
- Hepatosplenomegaly (>50%)
- Clubbing (37%)
- Purpuric rash (20%)
- Embolization (21%)

Mortality in one study was as high as 37%, although fatality should be less than 10% if appropriately treated, relapse greater than 50% if not treated adequately

Clinical Laboratory Values

Clinical laboratory values in patients with Q fever endocarditis include

- Elevated or depressed white blood cell count
- Elevated transaminases
- Anemia
- Elevated erythrocyte sedimentation rate
- Increased creatinine
- Increased gamma globulin fraction
- + ANA
- + rheumatoid factor
- + smooth muscle antibodies
- circulating immune complexes

Q Fever During Pregnancy

Incubation period

Pregnant women can either develop acute Q fever, or can have disease reactivated after a remote exposure.

Signs and Symptoms

- Premature birth >25%
- Spontaneous abortion >20%
- Placentitis
- Fever
- Flu like illness
- Severe thrombocytopenia
- Atypical pneumonia
- Asymptomatic

Laboratory Diagnosis

Routine laboratory work must be done in Biosafety Level (BSL)-2 facilities. Culture is not recommended, and handling of clinical materials or culture should be done in BSL-3 facilities. If Q Fever is suspected, please call the Department of Public Health Acute Communicable Disease Control Program (Business Hours: (213) 240-7941 or After Hours: (213) 974-1234) to arrange for submission of specimens for confirmatory testing. Staff from the public health laboratory are available for consultation at (562) 658-1300 or After Hours: (213) 974-1234.

The diagnosis of Q fever requires a high index of suspicion since the disease often presents with very nonspecific symptoms. The diagnosis is generally made serologically. Since isolating the organism is difficult to culture and constitutes a potential danger to laboratory personnel, serologic evidence of infection in a patient with a compatible clinical syndrome is commonly used for diagnosis. Culture is not recommended

Staining

Direct examination of primary specimens such as biopsy material by Gram stain may be of little value. Immunohistochemical staining may be helpful.

Culture

Coxiella burnetii does not grow in standard laboratory media. Furthermore, culture of the organism is dangerous due to its high infectivity in the lab and is not recommended.

Serology

Several assays are available; including indirect fluorescence antibody (IFA), microagglutination, and complement fixation. IFA is recommended as it is the most widely available and sensitive. Antibody levels are typically first detectable during the second week of illness. In acute Q fever, phase II antibody levels exceed phase I, the reverse is true for chronic Q fever. Differentiation between IgM and IgG is also helpful, as IgM antibody levels to phase I and IgG to phase II are typically elevated in acute infection, whereas IgA and IgG to phase II are elevated in chronic infection such as endocarditis. Seroconversion is usually 7-15 days after onset of clinical symptoms. Approximately 90% of patients have detectable antibodies by 3rd week.

PCR

Polymerase chain reaction (PCR) is also available and can be used for diagnosis.

Handling Laboratory Specimens

BSL- 3 practices, containment equipment and facilities are recommended for inoculation, incubation and harvesting of cell culture, and procedures on infected tissues, for clinical materials suspected as being positive for Coxiella Burnetii. Blood cultures are not recommended.

BSL- 2 practices and procedures can be used for serological examinations and staining of tissue impression smears.

Pathological and Autopsy Findings

Pathological manifestations of Q fever depend on the syndrome, but most commonly may include the following

- Pulmonary
  - Gross consolidation
  - Microscopic interstitial pneumonia
  - Alveolar exudates
- Hepatic
  - Granulomatous hepatitis
  - Fatty change
- Cardiac
  - In chronic Q fever endocarditis, aortic, mitral and prosthetic valve involvement are most common
  - Vegetations are typically small with non specific findings on histology
- Other organ involvement (neurologic, bone marrow, osteomyelitis, placentitis, endometritis, vascular aneurysm involvement may also occur.

Treatment of Acute Q Fever

The key to successful treatment is prompt initiation of appropriate antimicrobial therapy at the first suspicion of Q fever. Antibiotics are most effective if started within 3 days of illness. Antibiotic therapy should be restarted if symptoms recur.

In adults (Including immunocompromised)

- Doxycycline 100mg bid x 14-21 days
- Tetracycline 500 mg qid x 14-21 days
- Second line: Ofloxacin 200 mg tid 14-21 days

In children (including immunocompromised)

- Initial therapy:
- 8 years and older:
  - if > 45 kg: Doxycycline 100 mg IV/PO BID
  - if < 45 kg: Doxycycline 2.2mg/kg IV/PO BID
- under 8 years:
  - Co -trimoxazole 4mg/kg IV/PO BID
  - Chloramphenicol* 25mg/kg PO BID
  - Second line:erythromycin 500mg QID

*oral formulation only available outside the U.S.

- Newborns up to age 2 months
  - Ciprofloxacin 10-20mg/kg PO BID do not exceed 1 gram/day

Pregnant women
- Co-trimoxazole 1 DS tablet PO BID
- at term, (greater risk of kernicteris) ciprofloxacin 500 mg PO BID
- Second line: erythromycin 500mg qid

Immunocompromised individuals:
IV drug users and HIV infected individuals appear to be at higher risk of developing symptoms after exposure to Q fever, however, there appears to be no clinical difference in illness or increased risk of development of chronic Q fever.

Patient with abnormal or prosthetic valves are at high risk of developing chronic Q fever endocarditis and should be treated carefully with consideration for a longer course of antibiotics with combination drug treatment, and followed up closely.

Patients with meningitis should be treated with quinolones.

Treatment of Chronic Q fever

Individuals with chronic Q fever or Q fever endocarditis require lengthy (at least several years) combination therapy and often require valve replacement. Infectious disease consultation should be obtained.

Duration of Therapy

At least 18 months of doxycycline 100 mg bid and chloroquine 200 mg tid
Or at least 3 years doxycycline 100mg bid and ofloxacin 200 mg tid

Vaccination

There is a vaccine available, licensed in Australia, and used primarily for those at occupational risk. Prior to vaccination, serological testing must be performed, as those individuals with antibodies to Coxiella burnetii from a prior symptomatic or asymptomatic infection often develop severe post vaccination reactions. Immune response is typically demonstrated in 5 weeks. No vaccine is currently licensed in the United States. For these reasons, vaccination would probably not play a significant role in treatment or prophylaxis during a bioterrorist attack.

Management of Exposed Persons

In the event of a bioterrorist release of ***Coxiella burnetii,*** it may be difficult to define who has been exposed. Once the site of the attack is determined, all persons at the site of the release or downwind from the release (assuming aerosol dispersal) would be considered potentially exposed. Exposure may also occur due to fomites or contaminated clothing.

Decisions regarding post-exposure prophylaxis will be made in consultation with public health. **Contacts (e.g., household contacts, friends, coworkers) do not require post-exposure prophylaxis unless they were exposed to the aerosol or other source of contamination at the site of attack.** It is important to establish that both the patient and the

patient's household members understand that Q fever is not contagious. Neither exposed nor infected patients present any infectious risk.

Elevated fear and anxiety within the community will result in unexposed individuals seeking medical treatment. These individuals will present with vague somatic symptoms which in some cases may mimic symptoms of infection.

There will most likely be a significant number of anxious persons who were not actually exposed. These persons should still be considered victims. Most will exhibit anxiety, some will exhibit somatic symptoms that they will attribute to exposure and/or infection referred to as disaster somatization reaction (DSR). These symptoms range from general anxiety to mimicking symptoms of infection. Mental health referral should be made AFTER appropriate medical triage.

Prophylaxis of Exposed Individuals

Vaccine may be effective in post exposure prophylaxis, however it is not currently licensed in the United States. In addition, use of vaccine would likely be unhelpful in a mass casualty incident, as serologic testing is required before administration of vaccine.

Doxycycline or tetracycline orally for five days have been suggested as agents for post-exposure prophylaxis. However, the timing of prophylaxis is important also, as if it is started too early, it may be ineffective.

Post-exposure prophylaxis: Antibiotic prophylaxis is very effective and will prevent clinical disease **if administered 8-12 days AFTER exposure** (doxycycline 100 mg PO every 12 hours or tetracycline 500 mg PO every 6 hours) for 5 days. **Chemoprophylaxis given within 1-7 days of exposure is not effective and may only prolong the onset of disease.**

In adults (Including immunocompromised)

- Doxycycline 100mg bid
- Tetracycline 500 mg qid
- Second line: ofloxacin

In children (including immunocompromised)

Initial therapy:

- 8 years and older:
  - if > 45 kg: Doxycycline 100mg PO BID for 5 days
  - if <45 kg: 2.2mg/kg PO BID for 5 days
- under 8 years:
  - Co -trimoxazole 4mg/kg PO BID for 5 days
  - chloramphenicol* 25mg/kg PO BID for 5 days

Newborns up to age 2 months:

- Ciprofloxacin 10-20mg/kg PO BID for 5 days, (do not exceed 1 gram/day)

*oral formulation only available outside the U.S.

Pregnant women

- Co-trimoxazole 1 DS tablet PO BID for 5 days
- at term, (greater risk of kernicteris) ciprofloxacin 500 mg PO BID

Infection Control

There are no data to suggest that person-to-person transmission of acute or chronic Q fever occurs (with the possible exception of delivering the fetus of an infected pregnant woman). **Standard Precautions** are indicated for hospitalized patients with all forms of suspected or confirmed Q fever infection. High-efficiency particulate air filtration masks are not indicated. Patients do not require isolation rooms. Articles contaminated with infective material including bandages should be discarded, bagged and labeled before being sent for decontamination and reprocessing.

Contaminated surfaces should be cleaned with a hospital-approved disinfectant such as hypochlorite.

(Airborne precautions, if feasible, may be reasonable during labor and delivery of a pregnant woman known to be infected with Q fever.)

Disposal of Infectious Waste

Use of tracking forms, containment, storage, packaging, treatment and disposal methods should be based upon the same rules as all other regulated medical wastes.

Autopsy and Handling of Corpses

All postmortem procedures should be performed using Standard Precautions.
All persons performing or assisting in postmortem procedures must wear mandated personal protective equipment (PPE) as delineated by OSHA guidelines. Surfaces contaminated during postmortem procedures should be decontaminated with an appropriate chemical germicide such as iodine, 10% hypochlorite or 5% phenol (carbolic acid).

Reporting to the Health Department

An individual or group of individuals presenting with Q fever pneumonia without a clear exposure history (e.g. occupational risk or exposure to parturient animals) may be the first clue of a bioterrorist attack.
Although for isolated cases of Q fever, California law requires notification of health authorities within one day, rather than immediately. A suspicious case or outbreak does require immediate reporting. Therefore, a single, suspect case, or suspected outbreak of Q fever must be immediately reported to the:

Los Angeles County Department of Public Health

Business Hours (8am -5pm)	**213-240-7941**
After Hours (County Operator)	**213-974-1234**

Ask to Speak with the Public Health Physician On-Call

RICIN

ALL SUSPECTED CASES OF RICIN MUST BE REPORTED IMMEDIATELY TO THE DEPARTMENT OF PUBLIC HEALTH ACUTE COMMUNICABLE DISEASE CONTROL PROGRAM:

Monday - Friday (8am – 5pm)
(213) 240-7941

After Hours (County Operator)
(213) 974-1234

Ask to Speak with the Public Health Physician On-Call

Quick Reference Sheet: Ricin Poisoning

ALL SUSPECTED CASES OF RICIN POISONING MUST BE REPORTED IMMEDIATELY TO THE DEPARTMENT OF PUBLIC HEALTH ACUTE COMMUNICABLE DISEASE CONTROL PROGRAM

During Business Hours	213-240-7941
After Hours (County Operator)	213-974-1234

Epidemiology:

- Ricin is a potent protein toxin derived from the beans of the castor plant (Ricinus communis)
- Castor beans are widely available; the toxin is easily extracted and stable
- Possible routes of exposure include: respiratory, gastrointestinal and parenteral

Clinical:

- Incubation period varies depending on type of exposure and dose; ranges from minutes to 18 hours
- Inhalation of ricin presents with fever, weakness, cough, dyspnea and arthralgia; pulmonary edema develops within 18-24 hours; death occurs within 36-72 hours
- Ingestion of ricin presents with severe gastroenteritis that may progress to severe fluid and electrolyte imbalance, peripheral vascular collapse and death
- Injection of ricin presents with severe local necrosis of muscle and regional lymph nodes followed by multiorgan failure and death

Diagnosis:

- Diagnosis depends on a high index of suspicion
- Geographical clustering of patients presenting with similar symptoms
- *Two types of laboratory testing are available for suspected ricin exposures:*

  Environmental. *Detection of ricin in environmental samples, as determined by CDC (for suspected exposures from the environment) or FDA (for suspected exposures from food or medication). Ricin can be detected qualitatively by time-resolved fluoroimmunoassay (TRFIA) and polymerase chain reaction (PCR) in environmental specimens (e.g., filters, swabs, or wipes).*

  Biologic*. CDC can assess selected specimens on a provisional basis for urinary ricinine, an alkaloid in the castor bean plant. Urinary ricinine testing is the only clinical test for ricin exposure available at CDC.*

Treatment:

- Supportive care is the mainstay of therapy including IV fluid and electrolyte replacement
- Respiratory support may be necessary
- Gastric decontamination with superactivated charcoal

Prophylaxis:

- Currently there is no available prophylaxis

Infection Control:

- Standard precautions - ricin is not transmitted from person-to-person

Introduction and Epidemiology

Ricin is a potent protein toxin found in the beans of the castor plant (Ricinus communis). The toxin is easily extracted from the castor bean or from the "waste mash" generated from the production of castor oil. The toxin is highly potent, although toxicity by weight is slightly less than botulinum toxin or Staphylococcal enterotoxin B. Ricin poisoning occurs after accidental or deliberate ingestion of castor beans. Cases of ricin poisoning are rarely reported; in 1998, 245 cases of ingestion of beans were reported to poison control centers in the United States. Of those cases 31% had minor symptoms and 65% had no symptoms. Veterinary cases, accidental ingestion by children of the castor bean, intentional ingestion of beans in suicide attempts and deliberate poisoning as a form of homicide have been reported in the literature. The bean has a tough outer coat, and if swallowed but not chewed, can pass through the gastrointestinal tract without absorption of the toxin.

Ricin is made up of two hemagglutinins and two toxins. The toxins have an A and B chain, these are polypeptides joined by a covalent bond. The B chain binds to the cell wall and allows penetration of the toxin into the cell. The A chain binds to a specific component from ribosomal RNA causing inactivation of the affected ribosome resulting in the inhibition of protein synthesis and, eventually cell death.

Research is ongoing for medical uses of the ricin toxin. For instance, it may be coupled to a monoclonal antibody and used to destroy certain cell lines such as cancer cells. Ricin may also have application in autoimmune diseases.

As a weapon, ricin could be disseminated by aerosol, injection, being dissolved in a solvent such as DMSO for dermal exposure or contamination of food or water. Aerosolization of the agent is technically difficult and would be unlikely to cause a large-scale effect. However, aerosolization would result in severe pulmonary symptoms with high morbidity and mortality. Cases of injection have occurred as a form of assassination. Dermal exposure, while theoretically possible, is thought to be unlikely because the amount needed to achieve toxicity is more than would occur in imaginable delivery scenarios. Of most concern is contamination of food and water. The amount of toxin required to contaminate a municipal water source would be quite large but small-scale contamination of food or water is a potential threat.

Significance as a Potential Bioterrorist Agent

- Ricin is listed as a **category B** potential bioterrorist agent.
- Ricin is easily produced, inexpensive, highly toxic and stable
- Ricin toxin could be released as an aerosol or used to contaminate food or water supplies.
- Ricin has been weaponized by the former Soviet Union.
- Quantities of ricin were found in Al Qaeda caves in Afghanistan.
- Castor beans and equipment for crushing the beans were found in an apartment in London in January 2003.
- Ricin toxin containing envelope was found in 2003 at a US Postal facility, no human cases were associated with it.
- In February 2008, a man was hospitalized in critical condition. He was thought to be exposed to ricin vials found in his Las Vegas motel room.

- Injection of ricin toxin was used by the KGB as a method of assassination
- Lack of specific therapy and vaccines.

Clinical Manifestations

Clinical manifestations of ricin poisoning from a bioterrorist attack would depend on the route of exposure and dosage received.

Aerosol exposure

Incubation period
Ranges from 4 to 24 hours depending on the dose inhaled.

Signs and Symptoms
Inhalation exposure will present as a rapid onset of fever, weakness, chest pain, and dyspnea, with either spontaneous resolution of symptoms or progression within 18 to 24 hours to respiratory failure and death, depending on size of inoculum.

Signs and Symptoms may include:
- Acute onset of fever
- Weakness
- Chest tightness or pain
- Cough
- Dyspnea
- Nausea
- Bloody diarrhea
- Arthralgias
- Diaphoresis
- Dermal reaction or hypersensitivity
- Conjunctival irritation
- Optic nerve damage
- Pulmonary edema
- ARDS
- Seizures and CNS findings have been reported
- Death within 36-72 hours of exposure

In animal studies, large doses of aerosolized ricin have been shown to cause necrotizing tracheitis, bronchitis, bronchiolitis, interstitial pneumonia and alveolar edema.

Physical exam findings include respiratory distress, pulmonary edema and cyanosis. Urticarial and allergic upper airway reaction may occur. The LD50 for aerosol exposure of ricin is 3 mcg/kg.

Differential Diagnosis of Ricin Inhalation

Condition	Features of Condition that Distinguish from Ricin Ingestion
Staphylococcal enterotoxin B	Less often progresses to life-threatening illness
Septicemia	Responds to antibiotic therapy
Pneumonic plague	Gram-negative diplococci on sputum
Phosgene exposure	Odor of newly mown hay; history of exertion
Q fever	Responds to antibiotics

Clinical Laboratory Values

No specific findings on routine laboratory values; may see neutrophilic leukocytosis, DIC, azotemia or hypoxemia.

Gastrointestinal exposure

Incubation period

Varies depending on the amount of ricin toxin ingested. Generally, symptoms begin within several hours after ingestion but have been known to begin within 15 minutes of ingestion.

Signs and Symptoms

Ingestion of ricin toxin will present rapidly as severe gastroenteritis with volume depletion and hypotension. With large doses, multiorgan system involvement may occur with death resulting from hypovolemic shock.

Signs and Symptoms may include:

- Abdominal pain
- Vomiting
- Bloody diarrhea
- Fluid and electrolyte depletion
- Gastrointestinal bleeding
- Hemolysis
- Hypotension
- Hypoglycemia
- Hepatic, pancreatic, splenic and renal necrosis

DIC and multiorgan failure have been reported in animal studies.

The lethal dose for an adult has been reported to be as low as 1 mg which is the amount of toxin typically found in one bean. If a lethal dose has been ingested, death occurs in 3-5 days from hypovolemic shock. Physical exam findings are consistent with gastroenteritis and volume depletion.

Differential Diagnosis of Ricin Ingestion

Condition	Features of Condition that Distinguish from Ricin Ingestion
Salmonella	Stool culture positive
Shigella	Stool culture positive
Cholera	Diarrhea more likely to be "rice water stools" than bloody

Clinical Laboratory Values

There are no specific findings on routine laboratory values; neutrophilic leukocytosis, DIC or azotemia may be seen.

Parenteral Exposure

Parenteral exposure is not anticipated in a bioterrorist attack. Symptoms, which may occur within 5 hours, are similar to that of gastrointestinal exposure with the addition of severe local necrosis of the muscles and regional lymph nodes at the injection site.

Laboratory Diagnosis

If a ricin poisoning case is suspected, please immediately call the Department of Public Health Acute Communicable Disease Control Program (Business Hours: 213-240-7941 or After Hours: 213-974-1234) to arrange for submission of specimens for confirmatory testing.

The diagnosis of ricin is primarily clinical or epidemiological and requires a high index of suspicion.

Two types of laboratory testing are available for suspected ricin exposures:

1. **Environmental.** Detection of ricin in environmental samples, as determined by CDC (for suspected exposures from the environment) or FDA (for suspected exposures from food or medication). Ricin can be detected qualitatively by time-resolved fluoroimmunoassay (TRFIA) and polymerase chain reaction (PCR) in environmental specimens (e.g., filters, swabs, or wipes).

2. **Biologic**. CDC can assess selected specimens on a provisional basis for urinary ricinine, an alkaloid in the castor bean plant. Urinary ricinine testing is the only clinical test for ricin exposure available at CDC.

These tests are available, or can be arranged at the CDC through the Los Angeles County Public Health Laboratory (562) 658-1300 or After Hours (213) 974-1234.

Handling Laboratory Specimens

Biosafety Level (BSL)-2 practices containment equipment and facilities are recommended for all activities with materials potentially containing toxin. Clinical laboratories should not attempt to test environmental samples, these should be forwarded to the nearest LRN laboratory for evaluation. **The dust of the castor bean plant and crushed castor beans contain glucoproteins that are particularly allergenic. Laboratory staff handling specimens from persons who might have ricin poisoning must wear surgical gloves, protective gowns and shoe covers if performing procedures with high splash potential or risk of aerosolization. Laboratory tests should be performed in BSL-2 cabinets and blood cultures should be maintained in a closed system. Every effort should be made to avoid splashing or creatingan aerosol. Protective eye wear and masks should be worn if work cannot be done in a BSL-2 cabinet.**

Accidental spills of potentially contaminated material should be decontaminated by covering liberally with a hypochlorite solution (0.1% sodium hypochlorite), which inactivates ricin.

All biohazardous waste should be decontaminated by autoclaving. Contaminated equipment or instruments may be decontaminated with a hypochlorite solution, or other OSHA approved solution or by autoclaving or boiling for 10 minutes.

Treatment

Treatment is symptomatic and supportive. There is no specific antidote, vaccine or treatment available.

For aerosol exposure, treatment is primarily standard critical care support of pulmonary edema and ARDS, including diuresis, airway protection or mechanical ventilation with PEEP. Antibiotics are generally not helpful.

For gastrointestinal exposure, H2 blockers and decontamination with superactivated charcoal may be helpful. Intravenous fluid and electrolyte replacement is critical. Late cytotoxic effects may occur 2-5 days after exposure, even in asymptomatic persons. Therefore, monitor serum chemistries for a minimum of five days to rule out organ damage.

For parenteral exposure consider excision of the injection site immediately. Update tetanus immunity status.

Consultation with public health and a toxicologist is recommended.

Management of Exposed Persons

There is currently no available postexposure prophylaxis.

Persons thought exposed to ricin should be referred to a hospital. Symptomatic persons and persons thought to have ingested ricin should be admitted for observation. Persons thought to have ingested ricin who remain asymptomatic 8 hours postexposure can be discharged. Persons thought exposed by aerosol should be observed for 24 hours (admission should be considered), even if asymptomatic. Persons who remain asymptomatic for 24 hours may be taken off observation. Asymptomatic patients discharged home should be advised to return immediately if symptoms develop.

Infection Control

Ricin poisoning is not transmitted from person-to-person. All staff should observe Standard Precautions when caring for patients with suspected or confirmed ricin poisoning. Patients do not require isolation rooms. Secondary aerosols are not expected to be a danger to healthcare providers.

Decontamination

Patients' clothing and personal effects should be removed. Decontaminate exposed skin by washing with soap and water. Hypochlorite solutions (0.1 % sodium hypochlorite) can inactivate ricin on environmental surfaces. Persons' clothing should be placed in clear, labeled, sealed bags to prevent further contamination. If eyes are exposed, remove contact lenses and irrigate thoroughly with running water or saline for 15 minutes.

Persons exposed only via ingestion do not require whole body decontamination.

Autopsy and Handling of Corpses

All postmortem procedures are to be performed using Standard Precautions. All persons performing or assisting in postmortem procedures must wear mandated PPE (personal protective equipment) as delineated by OSHA guidelines. Instruments should be autoclaved or sterilized with solutions approved by OSHA. Surfaces contaminated during postmortem procedures should be decontaminated with a hypochlorite solution (0.1% hypochlorite).

Reporting to the Health Department

. All suspected cases of Ricin poisoning must be reported immediately by phone to the:

Los Angeles County Department of Public Health

Business Hours (8am -5pm) **213-240-7941**
After Hours (County Operator) **213-974-1234**

Ask to Speak with the Public Health Physician On-Call

LOS ANGELES COUNTY PUBLIC HEALTH LABORATORY
Bioterrorism Emergency Response Unit

Detection & Identification by molecular and conventional methods:

1. *Bacillus anthracis*
2. *Yersinia pestis*
3. *Francisella tularensis*
4. *Burkholderia pseudomallei and Burkholderia mallei*
5. *Clostridium botulinum*
6. Ricin
7. Vessicular rash (Rule out Smallpox)
8. Avian Flu - H5N1
9. Serology - *Brucella, Francisella, and Yersinia*

Reporting to the Health Department

If any of the above organisms or conditions is suspected,
please contact and report to the Public Health Physician On-Call
Los Angeles County Department of Public Health

Monday – Friday (8am -5pm)	**213-240-7941**
After Hours (County Operator)	**213-974-1234**

The Public Health Laboratory is also available for the technical assistance;
ask to speak to the staff member On-Call

Los Angeles County Public Health Laboratory

Monday – Friday (8am -5pm)	**562-568-1300**
After Hours (County Operator)	**213-974-1234**

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SECTION II

CHEMICAL TERRORISM

INFORMATION and TREATMENT GUIDELINES for HOSPITALS and CLINICIANS

INTRODUCTION

Background

Hospitals represent a vital disaster resource to local communities. After a terrorist attack, victims, either on their own or by emergency vehicles, will go to emergency departments regardless of the level of preparedness of the medical facility. It is essential that hospitals develop an awareness and operational level of understanding regarding the consequences of a chemical agent terrorist attack.

Historical Perspective

The first successful use of a chemical warfare weapon of mass destruction (WMD) occurred during World War I (WWI) at Ypres, Belgium, in April 1915. In that attack, the Germans released 168 tons of chlorine. The allies claimed that 5,000 troops were killed, but the actual number may have beeninflated number propaganda purposes.

In July 1917, the Germans first used sulfur mustard, again in Ypres, Belgium. This persistent agent (it does not evaporate readily and stays on terrain for a long time) caused many casualties as it damaged eyes, airways, and skin, but most survived. Sulfur mustard was successful as a weapon because of its persistency in the battlefield, its delayed clinical effects, and its ability to cause casualties.

Chemical agents caused over one million casualties in WW I, but killed fewer than 5 percent of these casualties, excluding those from Russia. After World War II (WWII), Egypt allegedly used chemicals in Yemen, and Iraq used them against Iran and the Iraqi Kurds.

On June 27, 1994, the AumShinrikyo, a well-funded Japanese religious cult, initiated the use of chemical warfare terrorism in Japan. The nerve agent GB, or sarin, was manufactured in a secret facility in Japan and was first released in Matsumoto, Japan with about 280 casualties and 7 deaths. Nine months later, on March 20, 1995, sarin was released in five separate subway cars in downtown Tokyo. There were 12 deaths, hundreds injured (a few dozen seriously), and 5,500 who sought medical care. Over 80 percent of those found their own transportation to the medical facilities. One hundred thirty-five of the first responders were injured. Hence, knowledge about the effects of chemical agents, how to protect oneself, and how to decontaminate and treat victims is essential.

Terrorist Threat

Chemicals make an ideal weapon for the terrorist. The effects can be immediate or delayed, the chemicals can be delivered by a variety of routes, the cost is low, the chemicals are available, and they are easily transported. In addition, most countries are poorly prepared to deal with a terrorist chemical attack.

Transport of phosgene, cyanide, anhydrous ammonia, and chlorine is a daily event in most large cities. Rail cars, which can contain up to 30,000 gallons of chemical, are susceptible to a terrorist use. A terrorist wanting to cause panic and fear could use teargas, which is available in many stores. Dual use of industrial chemicals as agents for a terrorist attack is a concern.

Disaster Somatization Reaction

There will likely be a large number of anxious patients who have been determined not to have been exposed. This population of patients should still be considered victims. Most will be exhibiting anxiety, some will exhibit somatic symptoms that they will attribute to exposure and/or infection, referred to here as disaster somatization reaction (DSR). These symptoms can range from symptoms of general anxiety, to mimicking symptoms of true exposure. Mental health referral should be made AFTER appropriate medical triage. Mental health can elicit additional pertinent history which may result in rapid identification of patients in need of medical re-evaluation. Mental health treatment should include reassurance and possible treatment with anxiolytic medications.

Current Preparedness

Not all first responders are universally trained to recognize a chemical incident or injuries that may be due to a chemical exposure. Thus, first responders (police, fire, EMS) may become secondary victims. Chemical cross-contamination of ambulances and hospitals due to this lack of preparedness could cripple the capacity of the local pre-hospital and hospital system. One patient exposed to a hazardous chemical can contaminate a transport vehicle and temporarily close a hospital emergency department (ED). Convergent casualties, those who leave the incident site without pre hospital care and then seek hospital care, who are chemically contaminated pose a serious threat to the hospital and staff.

For communities to be prepared, law enforcement, fire, EMS, and hospital personnel must develop policies and procedures to address:

- The safe identification, decontamination, treatment, and transport of the chemically contaminated victim.
- The procurement of adequate caches of antidotes that are readily available to quickly and accurately treat the victims of a chemical agent attack.
- The purchase of appropriate PPE and decontamination equipment, with frequent training in the use of this gear to protect the safety of the first responder and hospital personnel.

Over the past 10 years, significant efforts have been made to provide hospitals with personal protective equipment (PPE) and training on decontamination procedures. However, since decontamination events are very infrequent, hospitals are challenged in maintaining competency and will require assistance in any large chemical event.

CHEMICAL WARFARE AGENTS

Chemical warfare agents are hazardous chemicals that have been designed for use by the military to irritate, incapacitate, injure, or kill. Some have local effects on the eyes, skin, or airways (riot control agents, chlorine), some have only systemic effects (hydrogen cyanide), and some have both (nerve agents and vesicants).

The types of chemical agents to be discussed are listed below.

Agent	Name
Nerve Agents	**Tabun, Sarin, Soman, Cyclosarin, VX**
Vesicants (Blister Agents)	**Mustard, Lewisite**
Blood Agents	**Cyanide, Hydrogen Cyanide, Cyanogen**
Pulmonary Intoxicants	**Phosgene, Chlorine, Ammonia**
Riot Control Agents	**Mace7, Pepper Spray**
Incapacitating Agents	**BZ (Incapacitating agents, chemical agents that might cause psychological effects, might be used, but these will not be discussed)**

Some of the chemical warfare agents are said to have characteristic odors. However, these are not adequate warning signs for the purpose of protecting oneself against adverse health effects associated with exposure.

NERVE AGENTS

The nerve agents are tabun (GA), sarin (GB), soman (GD), cyclosarin (GF), and VX. Nerve agents are among the most toxic of all the weaponized military agents. These agents can cause sudden loss of consciousness, seizures, apnea, and death. Sarin (GB), one of the more common nerve agents, may be inhaled as a vapor, or cause toxic effects by contact with the skin in liquid form. VX is mainly a liquid at most ambient temperatures. These chemicals are easily absorbed through the skin, eyes, and lungs.

The diagnosis of a nerve agent poisoned casualty must be made clinically on the basis of the presenting signs and symptoms **sudden loss of consciousness, seizures, apnea, and death.** There is little or no time for laboratory confirmation. Nerve agents inhibit cholinesterase, an enzyme present in nerve tissues and in blood. There is a laboratory blood test to determine cholinesterase activity; however, measurement of cholinesterase activity is impractical during the diagnosis and management of nerve agent poisoning.

Characteristics

The nerve agents belong to a class of chemicals called organophosphates, and have a physiological effect similar to that of many insecticides commonly found commercially, such as malathion, diazinon, and chlorpyrifos. Impairment of cholinesterase activity may be severe.

Included among the nerve agents are chemicals called carbamates, which include some medicinal antidotes (such as physostigmine and pyridostigmine) and some insecticides (Sevin7, Raid, etc.). Carbamates cause clinical effects similarto the nerve agents developed for military use, but they are significantlyless potent on cholinesterase activity,

Nerve agents are stored and transported in the liquid state. The G-agents such as sarin (GB), soman (GD), and tabun (GA) are volatile liquids at normal temperatures although, the most volatile, sarin, evaporates at about the same rate as water. In liquid form, the G-agents can be absorbed through the skin and eyes; vapor is absorbed by inhalation and through the eyes, but not through the skin unless the concentration of vapors is extremely high. The G-agent liquids are more effective in penetrating skin when the chemical is trapped between the skin and clothes. GB rapidly evaporates and is considered to be a "non-persistent agent," meaning that it does not remain on terrain or equipment very long. VX is a persistent agent due to its low volatility. Though liquid at normal temperatures, VX has the consistency of motor oil, and seldom presents a vapor hazard, unless exploded or subjected to high temperature. VX is much more toxic (100 to 150 times) than sarin when on the skin, because sarin evaporates from the skin surface while VX does not.

Mechanism of Action

Nerves communicate with muscles, glands, and other nerves by releasing chemicals (neurotransmitters) at their connection sites (synapses). One of the most common neurotransmitters is acetylcholine (ACh), which is released and collects at the receptor site stimulating the end organ to respond and produce a variety of effects: muscle contractions, gland secretions, and nerve-to-nerve conduction. These are known as cholinergic nerves and synapses.

When a nerve impulse reaches the synapse, ACh is released from the nerve ending and diffuses across the synaptic cleft to bind with receptor sites on the next nerve, muscle, or gland, to stimulate a response.

To help regulate stimulation of the nerve, muscle, or gland, ACh is rapidly broken down by the enzyme acetylcholinesterase (AChE) located in the postsynaptic receptor region, producing choline, acetic acid, and the regenerated enzyme. Thus, a check and balance system prevents the accumulation of ACh and the resultant over-stimulation of nerves, muscles, and glands.

The term "nerve agent" refers to chemical that produces biological effects by inhibiting the enzyme AChE, thus allowing the neurotransmitter ACh to accumulate. As a result of inhibition of AChE, the neurotransmitter ACh accumulates and over-stimulates the receptors of the cholinergic nerves and causes hyperactivity of the cholinergic nerves, muscles, and glands.

Cholinergic synapses have two types of receptors: muscarinic receptors, nicotinic receptors, or a combination (central nervous system and cardiovascular system). Organs with muscarinic receptors include smooth muscles and exocrine glands; those with nicotinic sites include skeletal muscles and pre-ganglionic fibers.

Muscarinic receptors

Over-stimulation at muscarinic sites will increase glandular secretions. The victim may experience increased saliva, tearing, runny nose, thick secretions in the airways, and sweating; remembered by the acronym DUMBBBELS: **D**efecation, **U**rination, **M**iosis, **B**radycardia, **B**ronchoconstriction, **B**ronchorrhea, **E**mesis, **L**acrimation, **S**alivation.

Nicotinic receptors

Over-stimulation of nicotinic receptors causes skeletal muscle fasciculation, twitching, cramping, weakness, and finally paralysis. There is also stimulation of the pre-ganglionic fibers, which may contribute to transient initial hypertension and tachycardia in some victims. **The combination of pinpoint pupils, muscle fasciculations and respiratory distress is reliable clinical evidence of organophosphate (nerve agent) poisoning, however, these symptoms may not appear simultaneously.**

Cardiovascular

Cardiovascular effects may includebradydysrhythmias and hypotension. Tachydysrhythmias(sinus tachycardia, ventricular tachycardia, and ventricular fibrillation), hypertension, and heart blocks may occur transiently in some victims. Cardiac effects may improve quickly after antidote administration in some victims.

Central Nervous System
Acute severe effects may include: loss of consciousness, seizures, and centrally-mediated apnea. Effects from mild exposure may include: nervousness, fatigue, minor memory disturbances, agitation, and other minor psychological symptoms. The latter, whether caused by a severe or mild exposure, might linger for 4 to 6 weeks after exposure before resolving.

Cause of Death
The cause of death in nerve agent exposure is respiratory failure due to: bronchospasm and thick secretions in the airways; weakness of respiratory muscles to flaccid paralysis; and inhibition of the respiratory center in the CNS.

Clinical Effects

Vapor
After exposure to a small amount of vapor from a volatile nerve agent like GB, the most common effects are miosis - often with pain in the eye or head, complaints of dim or blurred vision or conjunctival injection, rhinorrhea, and some degree of bronchoconstriction and bronchosecretions with associated complaints of a tight chest and/ or shortness of breath.

After exposure to a moderate amount of vapor, besides the signs and symptoms noted above, the victim will show signs of multiple system involvement - especially increasing respiratory distress and nausea, vomiting and diarrhea.

After exposure to a large amount of vapor, the victim will almost immediately lose consciousness, and seizures will begin within 1 to 2 minutes. After several minutes of seizing, apnea and flaccid paralysis will occur.

Effects begin within a minute or so after vapor exposure and generally do not worsen significantly once the contamination is removed. Peak effects usually occur within the first 5 minutes following exposure.

If the exposure has been small and a victim is removed from the area of the exposure, shortness of breath may improve. In this situation, the removal of clothing is often adequate decontamination.

Liquid
Persistent agents like VX present more of a liquid contact hazard. The onset of effects following exposure can be delayed from 10 minutes to 18 hours after contact with the agent, depending on the dose. With military grade purity the LD 50 for VX is 10 mg, a droplet the size of the head of a pin. Fortunately, terrorists are unlikely to achieve such purity (the sarin at the Tokyo incident was a 20-40 % solution).

- Mild dose - A very fine droplet on the skin will cause fasciculations and diaphoresis under the droplet site. There will be no pinpoint pupils.
- Moderate dose - With a larger droplet multiple system effects will occur including gastrointestinal (GI), nausea, vomiting, and diarrhea. Generally, there will be no pinpoint pupils.
- High dose - A droplet the size of the LD50 on the skin will cause sudden loss of consciousness, seizures, flaccid paralysis, and apnea within minutes.

Medical Management

Self-protection

The process of treating nerve agent casualties may be divided into several components. The first and most important concept is to protect oneself. Although liquid contaminated casualties are unlikely to present directly to the hospital ED prior to decontamination by emergency responders, hospital staff should always protect themselves by assuming the presence of liquid contamination, unless a clear vapor-only exposure history is obtained. Whenever possible, areas of liquid contamination should be decontaminated prior to patient handling to minimize spread of contamination and cross-contamination of other providers.

Decontamination

In the immediate aftermath of the sarin nerve agent attack in Tokyo, over 650 patients presented to St. Luke's Hospital within several hours after the release of sarin. With high numbers of vapor-exposed patients presenting to a medical facility under these conditions, minimum decontamination should include removal of patients' clothing and jewelry. This will hopefully prevent secondary chemical exposure of hospital personnel due to vapor off-gassing. If the patient has been exposed to liquid nerve agent (such as spraying or an explosion), survivors will require complete decontamination of skin and hair with water, soap and water, and water rinse at the scene prior to evacuation. Young children should avoid aggressive shower decontamination, secondary to hypothermia risk.

Patients arriving at the ED with an unclear exposure history who are symptomatic from nerve agent exposure should be fully decontaminated as above before entering treatment areas.

Airway and ventilation

Establishment of a patent airway is essential for the survival of the severely exposed patient. Severely intoxicated patients will die if aggressive airway management is not readily addressed. With large numbers of victims, rapid scene and resource assessment will influence triage decisions regarding interventional therapy. Because of the intense bronchoconstriction and secretions associated with nerve agent exposure, effective ventilation may be initially difficult because of high airway resistance (50 to 70 cm H_2O). Adequate atropinization will help to reverse these muscarinic effects; therefore, atropine should be administered immediately with findings of bronchoconstricition and/or significant airway secretions. Endotracheal intubation, followed by positive pressure ventilation with a bag-valve mask, should be performed as soon as possible. Periodic suctioning of secretions may help to improve ventilation and air exchange.

Antidote administration

Three medications are commonly used to treat the signs and symptoms of nerve agent intoxication: atropine sulfate, pralidoxime chloride, and benzodiazepines, such as diazepam, midazolam and lorazapam. The general indications for use of these antidotes will be presented first, followed by a discussion of their use in the treatment of mild, moderate, or severe nerve agent intoxication.

Atropine

Atropine blocks muscarinic receptors. Accumulation of acetylcholine in the synapse from nerve agent exposure, and cholinergic over-stimulation, may require high doses of atropine to counter-act these effects. Atropine can be administered intravenously (IV), or intramuscularly (IM). Note this

has been shown to be almost completely ineffective per AHA cardiac arrest studies. Parenteral atropine will counter-act muscarinic effects such as rhinorrhea, salivation, sweating, bronchoconstriction, bronchorrhea, nausea, vomiting, and diarrhea.

The IV route of atropine administration is preferred but can be also given intramuscularly (IM), but only until IV access is established. Children may receive atropine via an intraosseous line.

The initial parenteral dose of atropine is 2 to 6 mg in the adult, with subsequent doses titrated to the severity of the nerve agent signs and symptoms. Treatment for chemical nerve agent exposure might require 40 mg or more of atropine. Patients poisoned with insecticides may require these large doses; over 1,000 mg of atropine have been used. There is no established limit to maximum dosage nor to dosing interval in the case of nerve agent exposure. When atropine therapy exceeds the amount necessary to reverse the effect of the cholinergic hyperstimulation, it may cause toxicity manifested by dry mouth, flushing, and diminished sweating, but this would be unexpected in a patient poisoned by an organophosphate (OP) compound. Side effects in unexposed people (not poisoned by OP compounds) include mydriasis, blurred vision, tachycardia, and diminished secretions. The latter (i.e., loss of sweating) may be of concern in a hot environment. Glycopyrrolate is a poor substitute and should not be used if atropine is readily available.

Atropine dosing is guided by the patient's clinical presentation and should be given until secretions are dry or drying and ventilation becomes less labored. When shortness of breath, increased airway resistance, and secretions have abated and the patient is breathing easier, he or she has received enough atropine. Heart rate and pupillary size, ordinarily reliable parameters of atropine dosing, are not useful for clinical monitoring after nerve agent exposure.

Atropine will not reverse nicotinic effects such as fasciculations, twitching, or muscle weakness. Miosis or ciliary body spasm may not be reversed by parenteral atropine; relief of intractable pain in or around the eye is rare, and may respond to the installation of one percent homatropine topically.

Pralidoxime chloride (2-PAMCl)

This is an antidote that can specifically break the bond between the nerve agent and the enzyme AChE and thus remove the agent. This will free the enzyme, making it once again available to break down ACh. Clinically, this will decrease muscle twitching, improve muscle strength, and allow the patient to breathe easier; however, it has little effect on the muscarinic effects described previously. The bond between the enzyme and the nerve agent can "age," that is, the enzyme and agent become irreversibly bound. This means that if the antidote is not administered within 4 to 6 hours after sarin exposure (the aging time for the sarin-enzyme complex) or within 60 hours after VX exposure (the aging time for the VX-enzyme complex), the bond becomes permanent. Usually, there is plenty of time to treat patients with 2-PAMCl after exposure to nerve agents with the exception of GD. The soman-enzyme complex ages in about 2 minutes. Since pralidoxime takes time to take effect, atropine administration is the first priority.

DuoDote®

DuoDote® is an auto-injector that includes atropine and pralidoxime chloride (2-PAMCl) and is indicated for the treatment of poisoning by organophosphoursous nerve agents. The

DuoDote® auto-injector contains 2.1 milligrams (mg) of atropine and 600 mg of Pralidoxime and is administered IM by pressing the end of the device onto the thigh. A spring pushes the needle into the muscle and causes the medication to be injected.

Los Angeles County first responder EMS units have caches of these for field use. The DuoDote® is for adult use however, in emergent situations where only adult doses are readily available administration of at least one DuoDote®.

Benzodiazepines
Seizures and agitation are treated with benzodiazepines such as diazepam, midazolam or lorazapam. These medications can be used IV or via adiazapmanauto-injector which contains 10 mg of diazepam. Some authorities recommend treating all severely exposed patients with one of the benzodiazepines whether they are convulsing or not. If three DuoDotes® are required initially, because of the victim's clinical presentation, a benzodiazepine should be administered immediately thereafter. These should be given liberally.

Treatment

Latent effects
Victims who present to the ED alleging exposure to nerve agents should be considered potentially exposed, triaged for anxiety and other injuries, and observed for up to 1 hour if a vapor exposure is alleged, or up to 18 hours if a liquid exposure is possible (or if the exposure history is uncertain).Young children, and sometimes adults, may develop significant dehydration from fluid losses from increased sweating, requiring aggressive resuscitation with intravenous fluids.

Mild effects
If there are mild effects from liquid exposure (localized sweating and fasciculations at the site of liquid contact), give 600 mg 2-PAMCl IM (DuoDote® Auto-injector) or 1 gram (gm) 2-PAMCl IV slowly over 20 to 30 minutes. The presence of miosis and rhinorrhea requires observation only. If the victim is suffering from airway effects (shortness of breath, chest tightness, and profuse airway secretions) that are not improving, then treat with 2 mg of atropine IM or IV, or with the DuoDote® auto-injector. Supplemental oxygenation will be needed only in those patients with pulmonary or cardiac disease. IM atropine dosing can be repeated at 5 to 10 minute intervals as needed.

Note: Patients with pinpoint pupils may have severe light sensitivity and pain, but only require reassurance since these symptoms will resolve. At the hospital, these patients should be given a topical eye medication (homatropine) only for relief of severe pain in the eye(s) or head, because the drug causes blurred vision.

Moderate vapor exposure
Be more aggressive with moderate vapor exposures.
Symptoms include those for mild exposures with more severe respiratory distress and may be accompanied by muscular weakness and possibly GI effects (vomiting and diarrhea). Initial dose for these patients is 1 or 2 DuoDote® auto-injectors containing a total of 2.1 mg atropine and 600 mg 2-PAMCl. Treatment may also be given IV, with 2 to 4 mg Atropine given IV push, and 1 gram of 2-PAMCl given by IV infusion slowly.

This dosing can be followed by repeat doses of 2 mg of Atropine at 5 to 10 minute intervals as needed, and 600 mg of 2-PAMCl for a total of 1,800 mg 2-PAMCl or the administration of up to three DuoDote® autoinjectors.

Antidotes can also be given IV, with Atropine given in 2 mg increments at 5 to 10 minute intervals, and 2-PAMCl given by infusion, 1 gm over 20 to 30 minutes, for a total of 3 doses at hourly intervals.

Moderate liquid exposure

Symptoms will include increasing respiratory distress and nausea, vomiting and diarrhea. For moderate toxicity several hours after liquid exposure, 2 mg of atropine and 600 mg 2-PAMCl should be given initially. Repeated doses of atropine and 2-PAMCl may be necessary. Oxygen may be needed in those with cardiac or pulmonary disease who have severe breathing difficulty.

Severe vapor or liquid exposure

Severe exposure symptoms will include all the above, plus: unconsciousness, seizures, apnea, or severe effects in two or more systems (excluding the eyes). Give 3 DuoDote® auto-injectors and a benzodiazepine and manage the airway. Repeat atropine at 5-10 minute intervals as necessary and 2-PAMCl in one hour.

Treatment for Nerve Agent Exposure

Exposure	Clinical	Treatment
Latent	None	None, observe for 1 hour with vapor and for 18 hours if liquid or unknown exposure
Mild	Miosis with dim and/or blurred vision, rhinorrhea, shortness of breath	Miosis and rhinorrhea, observation only. Shortness of breath: one DuoDote® auto-injector or Atropine 2 mg IM/IV and 2-PAMCl 600 mg IM or 1 gm IV.
Moderate	Above, but more severe; or vomiting and diarrhea	One DuoDote® auto-injector t or Atropine 2mg IM/IV and 2-PAMCl 600 mg IM or 1 gm IV. Repeat 2 mg Atropine at 5-10 minute intervals until agent effects diminish.
Severe	Above plus unconsciousness, Flaccid paralysis, respiratory distress, cyanosis, seizures or severe effects in two or more organ systems	Oxygen, bag mask, intubate after three DuoDote® auto-injectors or Atropine 6 mg IM and 2-PAMCl 1800 mg IM or 1 gm 2-PAMCl IV repeated twice at hourly intervals. Repeat 2 mg Atropine at 3-5 minute intervals until atropinized. Benzodiazepine for seizures.

Age-Related Antidote Administration

Atropine

Certain members of the population may be more sensitive to Atropine. These include infants, young children, and the elderly. Pediatric experts have divided the age groups for IM administration of Atropine. These doses may be repeated as clinically indicated.

Category/Age	Dose
Infant - 0 to 2 years	0.5 mg single dose
Child - 2 to 10 years	1.0 mg single dose
Adolescent - young adult	2.0 mg single dose
Elderly - frail or medically compromised adult	1 mg and repeat as necessary
If Atropine is to be given IV, then the dose for infants through young adults is 0.02 mg/kg.	

The use of a 0.5 mg or 1.0 mg Atropenautoinjector can be used for treating pediatric patients. The most significant adverse effect of high dose Atropine in the younger patient is the inhibition of sweating, raising the risk for hyperthermia in rare cases.

Pralidoxime chloride

(no data available for 2-PAMCI use in children exposed to nerve agents) Dose may be adjusted in the elderly; frail, hypertensive, or with renal disease, using one-half the usual adult dose of 2-PAMCl (7.5 mg/kg IV). If hypertension becomes significant during the administration of the 2-PAMCl, treat with IV phentolamine as follows: Adults - 5mg IV, Pediatrics - 1 mg IV

Category/Weight	IV 2PAMCLdose	Weight	IM dose
Infant $\leq$ 70 kg	15 mg/kg repeated twice at hourly intervals	< 20 kg	15 mg/kg
Above 70kg	1 gm repeated twice at hourly intervals PRN	> 20 kg	600 mg autoinjector

Diazepam Recommended Pediatric Dose	
Infants > 30 days to < 5	0.2 to 0.5 mg/kg IV slowly every 2 to 5 minutes to maximum dose of 5 mg
Children > 5 years	1 mg IV every 2 to 5 minutes to maximum dose of 10 mg

Midazolam Recommended Pediatric Dose	
Infants > 30 days to < 5	0.1 mg/kg IV slowly every 2 to 5 minutes to maximum dose of 5 mg
Children > 5 years	0.1 mg/kg IV every 2 to 5 minutes to maximum dose of 10 mg

Lorazapam Recommended Pediatric Dose	
Infants > 30 days to < 5	0.1 mg/kg IV slowly every 2 to 5 minutes to maximum dose of 4 mg
Children > 5 years	1 mg IV every 2 to 5 minutes to maximum dose of 10 mg

BLISTER AGENTS OR VESICANTS

Vesicants cause blistering. They may be plant, animal, chemical, or sunlight. Those discussed are the chemical warfare vesicants, namely sulfur mustard and Lewisite. A close relative of sulfur mustard, nitrogen mustard was the first cancer chemotherapeutic agent.

Sulfur Mustard

Sulfur mustard is a vapor inhalation and liquid contact hazard. Mustard causes injury to the eyes, skin, airways, and some internal organs. This chemical warfare agent has a delayed action, and exposure to it may result in blisters on the skin, temporary blindness, and respiratory distress. More extensive injury can result in death due to respiratory failure from airways injury, sepsis as a result of bone marrow damage, decrease in white blood cells, and impairment of the immune system. There is no specific therapy.

Characteristics

Mustard is an oily liquid yellow to brown in color. Its name comes from its odor of garlic or mustard, but odor should not be relied upon for detection. Mustard is a persistent agent and not volatile at temperate conditions, however at temperatures above 100 °F it is a definite vapor hazard. Mustard has a relatively high freezing point and is often mixed with similar agents such as Lewisite to lower the freezing point. Because of its oily and persistent nature, mustard poses a definite concern for cross contamination.

Mechanism of action

Mustard is absorbed and causes chemical cellular damage within 1 to 2 minutes, but clinical effects do not begin for hours. There is no immediate pain, there is no immediate skin discoloration, and there is no immediate eye irritation. However, hours later, the victim realizes that he or she has been exposed and presents to the ED for evaluation and treatment. The onset time for clinical effects ranges from 2 to 24 hours, but the most common interval is 4 to 8 hours.

Despite years of research, the exact mechanism by which mustard damages cells is unknown. Mustard alkylates DNA, and binds to proteins and other cellular components. The end result is DNA damage and cellular death. The injury is very similar to that produced by radiation, and mustard is a radiomimetic agent. Topically, three organ systems directly affected by mustard are the eyes, skin, and respiratory tract.

Clinical Effects

Ophthalmic

There is a spectrum of eye involvement. The eye lesion, after a small exposure to mustard, may consist only of mild conjunctivitis. A larger exposure will produce a more severe conjunctivitis, lid inflammation and edema, blepharospasm, and corneal roughening. These casualties will be unable to open their eyes and will be temporarily without sight. A larger exposure, particularly if by liquid, may produce corneal opacification, corneal ulceration, or corneal perforation. Miosis is sometimes observed after mustard exposure and is thought to be due to cholinergic effects.

Integumentary
Skin effects begin hours after exposure with erythema accompanied by burning and itching. This is followed by the development of small vesicles, which later coalesce to form blisters. The size and depth of the lesion depends on the amount of exposure and whether exposure was by vapor or liquid. Coagulation necrosis extending into the dermis may develop under blisters caused by liquid.

Pulmonary
Mustard damages the mucosa or lining of the airways. This damage begins in the upper airways and descends in a dose-dependent manner to the smallest bronchiole. After a small exposure or initially after a large exposure, there may be epistaxis, sinus discomfort, and a mild to moderate pharyngitis with a hacking cough. After a moderate to large exposure, there may be laryngitis with voice loss and a productive cough. If the exposure is large, the agent reaches the smallest airways to cause dyspnea and productive cough, as the mustard will damage not only the mucosa, but the underlying musculature as well. At this stage, there may be hemorrhagic pulmonary edema around the bronchioles, but otherwise, pulmonary edema is rare.

Gastrointestinal
Gastrointestinal effects within the first 24 hours following exposure include nausea and vomiting. These effects are thought to be in part due to cholinergic stimulation. There may be some added effects of mustard on the GI tract from the swallowed tracheal secretions. Gastrointestinal effects seen after 3 to 5 days are thought to be due to tissue destruction in the abdomen.

Hematopoietic or Blood Forming System
Absorption of significant amounts of mustard produces damage to and death of the stem or precursor cells of the bone marrow. If this occurs, the white blood cell count, after an initial increase because of the toxic exposure, starts decreasing on about the third or fourth day after exposure and continues downward until recovery begins. If the amount of mustard absorbed is quite large, there is no recovery and the cell count will reach zero. Survival usually does not occur when this happens. The absence of these cells increases susceptibility to infection and contributes to death. The red blood cells and platelets also decline following the white blood cells.

Medical Management

Decontamination
Decontamination should consist of physical removal of any residual agent by whatever means available. The casualties should remove all clothing, rings, and jewelry. Skin and hair decontamination should be performed with soap and water. Decontamination must be done as quickly as possible since cellular damage occurs in as little as two minutes. Decontamination of the casualty at the ED 30 minutes or more after contact with mustard will not change the clinical course of the patient's illness, but is effective in preventing cross-contamination of providers.

Treatment
Treatment is largely supportive since there is no antidote for the effects of sulfur mustard.

Skin

Soothing creams or lotions might be effective for irritation and itching. Large blisters should be unroofed and denuded areas irrigated several times a day followed by a topical antibiotic (Silvadene, etc.) to prevent skin bacterial superinfection. Oral pain medications will likely be necessary. Fluid requirements should be assessed, less fluid replacement is necessary than with thermal burns. Care must be taken not to over hydrate the patient (burn formula resuscitation is not recommended). Rarely will burns be full thickness requiring skin grafting.

Eyes

Again, mustard fixes to tissues within the first several minutes after exposure. Gentle irrigation with saline or water during this time period will be helpful. Aggressive attempts to pry apart severely painful, blepharospastic eyelids to accomplish an irrigation 30 minutes or more after exposure is of dubious value, since the damage has been done and the agent has evaporated or has been absorbed. With severe eye injuries, homatropine or other mydriatics should be applied topically to prevent synechiae formation. Topical antibiotics should be applied several times a day and petroleum jelly should be applied to lid edges to prevent them from adhering. Topical ophthalmic analgesics may be used to facilitate initial examination. However, oral pain medication is preferred to topical analgesics, since topical agents may damage the cornea and delay healing. Many ophthalmologists feel that the application of topical steroids within the first 24 hours, but not after, might be of benefit. Early involvement of an ophthalmologist is advised, and visual acuity should be obtained before treatment measures are instituted.

Pulmonary

Upper or minor airway symptoms (sore throat, non-productive cough, hoarseness) may be relieved by steam inhalation and cough suppressants. The initial chemical pneumonitis should be treated in the usual manner; however, antibiotics should not be used until an organism is demonstrated, which usually occurs between the third and fifth day post-exposure. A patient with severe airway effects will benefit from oxygen and assisted ventilation, particularly positive end expiratory pressure (PEEP) or continuous positive airway pressure (CPAP). Intubation should be performed if there are signs of severe upper airway involvement, and should be done early, before laryngeal spasm or edema makes it difficult. Bronchodilators may be needed; if they fail to relieve bronchospasm, steroids may be tried. Otherwise, steroids are of questionable benefit.

Lewisite

Characteristics

Lewisite is a vesicant that has been stockpiled militarily, but there have been few human exposures to the chemical.

Clinical Effects

Lewisite is rapidly absorbed by the eyes, skin, and lungs and produces blisters similar to sulfur mustard. In contrast to sulfur mustard, however, lewisite is highly irritating on initial exposure. It also produces visible lesions more quickly. Unlike mustard, it does not damage the bone marrow. Lewisite is an arsenical compound, thus a heavy metal poison.

Integumentary

Lewisite causes greater skin damage than sulfur mustard. A gray area of dead skin can progress to blisters and severe tissue necrosis and sloughing.

Pulmonary

Since lewisite causes immediate irritation to the nose and sinuses, an effort by the victim to evacuate the area of contamination may prevent more severe lung damage. Pseudomembraneformation is common.

Cardiovascular

Lewisite causes increased capillary permeability, leading to volume depletion, hypotension, hepatic and renal injury.

Medical Management

Decontamination

Casualties should remove all clothing and jewelry. Decontamination of skin and hair with soap and water will remove most of the chemical, if performed quickly after contamination.

Treatment

The antidote is dimercaprol, also known as British anti-Lewisite (BAL**). BAL can be administered IM to reduce the systemic effects of the vesicant. Because it is administered parenterally, BAL has no effect on Lewisite damage to the skin and eyes; however, it may be reconstituted as an extemporaneously prepared lotion for topical administration.

***BAL is also used for some other heavy metal poisonings.*

Cyanide

Cyanide is a chemical that is widely utilized, manufactured, and transported in the U.S. Over 300,000 tons of cyanide are produced annually. It is used in printing, agriculture, photography, and in the manufacture of paper and plastics. It is also a combustion product of burning synthetic materials. Rail cars with 30,000-gallon tanks of cyanide represent potential transportation and terrorist threats. A large amount of cyanide is needed to cause death on the battlefield; therefore, it is not a very good military weapon. Terrorist use in confined spaces such as a subway care, shopping center, convention center or high-rise building would be far more effective.

Characteristics

Cyanide is stored and utilized in the liquid or solid state. It may have an odor of bitter almonds, but the ability to smell the cyanide exists in only 40 percent of the population.

Three types of cyanide may be encountered: hydrogen cyanide (AC), cyanogen chloride (CK), and cyanide salts. The term cyanide refers to the anion, CN-, or to its acidic form, hydrocyanic acid (HCN). Cyanogen (CN2) is formed by the oxidation of cyanide anions. However, the term cyanogen has also come to mean a substance that forms cyanide upon metabolism and produces the biological effects of free cyanide. Cyanogen chloride is a pungent, heavier-than-air vapor, which can cause irritation of the eyes, nose, and throat. This is in distinct contrast to hydrogen cyanide, which has no irritant properties.

Cyanide salts (for example, NaCN) are compounds that dissociate into the cyanide anion (CN-) and a cation (Na+). Salts are most dangerous following ingestion; onset of action is slower and more prolonged. Cyanide salts generate hydrogen cyanide gas on contact with a strong acid (e.g., sulfuric acid).

Mechanism of Action

Cyanide exists normally in human tissues and is usually metabolized by sulfur in the presence of a hepatic enzyme, rhodanese, into thiocyanante, which is excreted in the urine.

Under normal conditions, the cyanide anion is attracted to iron in the ferric state (Fe+++). In the mitochondrion of the human cell, cytochrome A3 in the cytochrome oxidase complex contains Fe+++. Cyanide is bound to cytochrome A3 and thus inhibits the effect of cytochrome oxidase. This enzyme complex is responsible for the utilization of oxygen within the cell. In the presence of cyanide, even though there is plenty of dissolved oxygen in the blood, the cells cannot use the available oxygen. As a result, cells must utilize anaerobic metabolism, or the creation of energy without the benefit of oxygen, which causes severe lactic acidosis. When cells cannot get enough energy, they die. Cells in the brain and heart are affected initially.

Acute cyanide poisoning occurs after inhaling the agent, but may also occur after drinking solutions of cyanide (it is sometimes used with suicidal intent) or by skin contact with large amounts of liquid cyanide.

Clinical Effects

After inhalation of a low concentration, the patient may become anxious, will often be dyspneic and tachypneic, and typically develops a headache with dizziness and vomiting. Skin color may initially be flushed but may also be normal or cyanotic. A cherry-red skin color is characteristic of cyanide, but this is not always observed.

In about 15 seconds after inhaling a large amount of cyanide, victims become anxious and start breathing rapidly. Thirty seconds after exposure, the patient may begin to convulse. In 3 to 5 minutes, breathing ceases. Asystole, or cessation of heart activity, occurs in 6 to 10 minutes, followed by death. The patient may have normal sized or dilated pupils. Death can occur within 8 minutes of exposure.

Laboratory

A normal oxygen saturation is often noted when using a pulse oximeter, despite the fact that the patient may be in severe distress, because oxygen is not being used by tissues. There is high arterial oxygen content to venous blood because oxygen is not extracted from arterial blood by the cells; venous blood gas sampling may reveal an unusually high oxygen tension. Metabolic (lactic) acidosis may result from impairment of aerobic cellular respiration in the tissues. Cyanide toxicity can be measured at the hospital by checking serum cyanide concentrations. These values may, however, only be available after a delay of several hours and of little value in the initial management of acute severe poisoning.

Medical Management

Patients who have inhaled significant doses of cyanide must be rapidly treated with appropriate antidotes to prevent brain damage. Cyanide is attracted to iron (Fe+++) in a form of hemoglobin called methemoglobin. In fact, cyanide will preferentially leave the cytochrome oxidase enzyme in the cell and bind to circulating methemoglobin.

There are two available cyanide treatment kits, one of which contains amyl nitrite and sodium nitrite; these drugs work to, increase blood concentrations of methemoglobinand are antidotal. Adding sodium thiosulfate completes the detoxification process. There is also a kit containing hydorxocobalamin (CYANOKIT®), which binds cyanide to the Cobalt molecule found in hydroxocobalamin.

Patients should be treated with IV saline for hydration; sodium bicarbonate and intubation with hyperventilation should be used for the metabolic acidosis. Oxygenation should be maintained with high-flow oxygen by mask or by endotracheal tube. Monitor and treat significant arrhythmias.

The Cyanide Antidote Kit

This kit (formerly known as the Lily Cyanide Kit) contains amyl nitrite, sodium nitrite, and sodium thiosulfate.

Amyl nitrite

Amyl nitrite is available in perles, more commonly referred to as ampules, which are broken and placed in either a gauze bandage, or in the bag-mask, and inhaled for 15 seconds, then taken away for 15 seconds (although, if the patient is breathing, he probably does not need the antidote). This is the initial step in antidote therapy. Amyl nitrite forms methemoglobin and reduces the elevated total peripheral resistance caused by the acidosis and cyanide. This should be used only until the IV drugs can be given. Inhalation of amyl nitrite will cause orthostatic hypotension. However, if the patient can stand, he or she does not need the antidote.

Sodium nitrite

Sodium nitrite is a strong methemoglobin former that is available for IV use in a dose of 300 mg in 10 cc. This dose is injected over 2 to 4 minutes and has the potential side effect of orthostatic hypotension. Normal saline infusion and supine posture can help to correct the hypotension. However, if patients can stand, they do not need the sodium nitrite. The pediatric dosage is 0.2 cc/kg, not to exceed 10 cc.

Sodium thiosulfate

This compound is a co-factor for the enzyme rhodanese for detoxification (to change cyanide to a form that can be excreted by the kidneys). The drug is administered in a 50cc ampule (12.5 gm) over 5 minutes by IV.

CYANOKIT® (Hydroxocobalamin)

Meridian Medical Technologies manufactures this product, which is available as 2.5 or 5 gram vials.

Hydroxocobalamin

Hydroxocobalamin is also known as Vitamin B12, and forms an irreversible bound to cyanide in the formation of cyanocobalamin. This is non-toxic and typically excreted in the urine. The drug is administered as a 5 gram dose, diluted with 200cc's of normal saline and instilled intravenously over 15 minutes. This dosage may be repeated.

Treatment

General:

Remove from the area of exposure and remove clothing

Mild exposure:

If conscious and breathing, give O_2 and IV fluids. Observe and monitor no antidotes are necessary.

Severe exposure:

If unconscious, whether breathing or not, give O_2, and bag-mask ventilate with 100 percent O_2. Cardiac monitor. Oxygen saturation may or may not be normal. Administer the components of the CYANOKIT® or the multi-drug Cyanide Kit.

CYANOKIT®

5 grams hydroxocobalamin diluted in 200 mls of 0.9% Sodium Chloride solution and administered as an intravenous infusion over 15 minutes is indicated for the treatment of known or suspected cyanide poisoning. If clinical suspicion of cyanide poisoning is high, CYANOKIT® should be administered without delay. A second dose may be administered if symptoms persist.

OR

Cyanide Kit

Amyl nitrite:

Crush into a 4 x 4 piece of gauze and place over face or in a bag mask Inhaled for 15 seconds, then taken away for 15 seconds (although a spontaneously breathing victim probably does not need the antidote).Add another ampule every few minutes. *Give only until IV drugs are available.*

Sodium nitrite:

When IV established, give 300 mg (10 cc ampule) over 5 minutes for adults. For children, use 0.22 to 0.33 ml/kg of the 3 percent solution. Watch for orthostatic hypotension (however, if patient can stand, they do not need this).

Sodium thiosulfate:

Give 12.5 gm (50 cc) IV (administered after sodium nitrite). For children, use 1.65 ml/kg of the 25 percent solution.

Treatment for Cyanide Exposure				
Patient	**Mild (conscious)**	**Severe (unconscious)**	**Other Treatment**	**Precautions**
Pediatric	If patient is conscious and has no other signs or symptoms, antidotes may not be necessary	Sodium nitrite[1]: 0.12 - 0.33 ml/kg, not to exceed 10 ml of 3% solution[2] slow IV over no less than 5 minutes, or slower if hypotension develops and Sodium thiosulfate: 1.65 ml/kg of 25% solution IV over 10 - 20 minutes	For sodium nitrite induced orthostatic hypotension, normal saline infusion and supine position are recommended. If still apneic after antidote administration, consider sodium bicarbonate for severe acidosis.	Victims whose clothing or skin is contaminated with hydrogen cyanide liquid or solution can secondarily contaminate response and hospital personnel by direct contact or through off-gassing vapors. Avoid dermal contact with cyanide-contaminated victims or with gastric contents of victims who may have ingested cyanide-containing materials. Victims exposed to hydrogen cyanide gas only, do not pose a contamination risk to rescuers or health care providers. If the patient is a victim of recent smoke inhalation (may have high carboxyhemoglobin levels) administer the sodium thiosulfate only.
Adult	If patient is conscious and has no other signs or symptoms, antidotes may not be necessary	Sodium nitrite[1]: 10 - 20 ml of 3% solution[2] slow IV over no less than 5 minutes, or slower if hypotension develops and Sodium thiosulfate: 50 ml of 25% solution IV over 10 - 20 minutes OR CYANOKIT (hydroxocobalamin) 5 grams reconstituted in 200 ml of 0.9% Sodium Chloride administered as an intravenous infusion over 15 minutes		

[1]If sodium nitrite is unavailable, administer amyl nitrite by inhalation from crushable ampules.
[2]Available in Cyanide Antidote Kit, formerly Lilly Cyanide Kit.

PULMONARY INTOXICANTS

Pulmonary intoxicants cause severe life-threatening lung injury after inhalation. These effects are generally delayed several hours after exposure. Treatment is usually supportive and may require advanced intensive care techniques including intubation, use of a mechanical ventilation and PEEP. Pulmonary intoxicants included with this group are phosgene and chlorine.

Phosgene

Phosgene is widely used today in the manufacturing of dyes, coal tar, pesticides, and Pharmaceuticals. It was widely used in WWI until mustard was introduced on the battlefield.

The Bhopal, India disaster of 1984, at a Union Carbide plant, involved the release of 50,000 pounds of methylisocyanate. This chemical is composed of phosgene and methylamine. There were 150,000 people affected, 10,000 severely injured, and 3,300 killed. The effects of the release were thought to be due to a combination of isocyanate and phosgene.

Characteristics

Phosgene has a characteristic odor of freshly mown hay and is four times heavier than air. It is a gas above 47 °F, and is principally a hazard by inhalation.

Mechanism of Action and Clinical Effects

Phosgene dissolves slowly in water to form carbon dioxide and hydrochloric acid (HCl). In contact with the moist mucosa the HCl causes a transient irritation of the eyes, nose, sinuses, and throat. It can also irritate the upper airway and bronchi, causing a dry cough. However, the primary damage from phosgene is from the carbonyl group, which destroys the alveolar capillary membrane. (Perflouroisobutylene, PFIB, the combustion product of burning Teflon, found in many military vehicles, has a similar action as phosgene, but is more toxic.)

Phosgene penetrates poorly into the airways due to its poor water solubility. There is a symptom-free period of 2 to 24 hours. Over the first several hours, the carbonyl group from the phosgene attacks the surface of the alveolar capillaries. Eventually, this causes the leakage of serum from the capillaries in the lung into the alveoli and interstitial space. The fluid fills the tissues, causing severe hypoxia and apnea. As the fluid leaks into the alveoli, massive amounts of fluid (up to 1 liter per hour) pour out of the circulation. The patient develops a severe non-cardiogenic pulmonary edema.

Medical Management and Treatment

The leakage of fluid in the lungs causes volume depletion. Although the patient may clinically look like traditional heart failure, DO NOT USE DIURETICS or NITROGLYCERIN. These patients are volume depleted. Treat hypotension with fluids. These patients may require intubation and the use of PEEP.

In the hospital, the initial examination of a patient, symptomatic or not, should include - (as a minimum): auscultation, chest x-ray, and arterial blood gases. If the victim develops severe dyspnea due to upper airway irritation, early intubation should be considered to manage oxygen delivery and to prevent laryngeal spasm. The airway should be suctioned frequently to remove secretions. According to some authorities, antibiotic use should be guided by Gram stain and culture results. Another source recommends prophylactic antibiotics, as autopsy studies show uniform evidence of pneumonia and bronchitis.

Ventilator management, PEEP, and oxygen administration might require consultation with a pulmonologist. Fluid hydration may be necessary to treat the hypotension, bradycardia, or impending renal failure. Diuretics such as Lasix are contraindicated because of the hypotension and the noncardiac nature of the pulmonary edema. Standard bronchodilators will usually control bronchospasm, but if not, steroids may be needed for this purpose. Routine steroid use is controversial, but steroids seemed to offer some efficacy after the Bhopal tragedy. Once the patient recovers, there should be little residual pulmonary effect.

Chlorine

Chlorine is a significant irritant to the eyes and respiratory tract. It is widely used in the manufacture of chemicals, plastics, and paper and is commonly used in swimming pools and laboratories. Industrial exposures have produced large numbers of injuries.

Characteristics

Chlorine is a greenish-yellow gas that has a characteristic pungent odor that is irritating to the nasal mucosa. It is transported as a liquid and is less alkaline than ammonia.

Mechanism of Action and Clinical Effects

Chlorine injures cells by reacting with water, producing hydrochloric acid (irritating) and free oxygen radicals (attack cells). It is toxic to any body surface including the eyes, skin, respiratory tract, and GI tract. Chlorine gas is 30 times more irritating to the respiratory mucosa than HCl.

In seconds after the exposure, there are symptoms of irritation to the eyes, nose, and throat. This is followed by irritation of the respiratory tract with coughing, shortness of breath, wheezing, chest pain,

and sputum production. Initial respiratory distress is followed in 12 to 24 hours by non-cardiogenic pulmonary edema. Sudden death is usually due to severe hypoxia and cardiac arrest.

Medical Management and Treatment

Move exposed victims away from the source of exposure. If the victim has no complaints, probably no treatment will be necessary.

Toxicity to skin and eyes should be treated with copious flushing with water. Irritation of the respiratory tract is treated with oxygen, cool mist to moisten the damaged mucosa, and bronchodilators to resolve bronchospasm.

Intubation, mechanical ventilation, and assessment of hydration may be required. Bronchoscopy may be useful to remove mucosal plugs.

Ammonia

Characteristics

Ammonia is a colorless, highly water-soluble, alkaline gas that has a pungent odor. It is widely used industrially in the U.S. with over 500,000 workers potentially exposed annually. It is used as an agricultural fertilizer and is used in the manufacture of explosives, dyes, and plastics.

Mechanism of Action

Ammonia is rapidly absorbed by mucosal surfaces and causes damage to the eyes, oral cavity, throat, and lungs. When mixed with water, it forms a corrosive agent, ammonium hydroxide (NH_4OH) that causes considerable damage in the form of liquefaction necrosis. Due to its high water solubility, ammonia penetrates rapidly into tissue. Household ammonia generally has a pH less than 12 and generally causes limited damage to eyes or mucosa. Anhydrous ammonia is an industrial chemical that has a very high pH and is extremely corrosive and can cause severe damage to the eyes, lungs, and skin.

Clinical Effects

Ophthalmic

Initially, ammonia causes burning, tearing, and severe pain. It has a tremendous capacity to penetrate the eye, causing corneal opacification and lens damage leading to cataract formation.

Pulmonary
Mild exposure causes cough, shortness of breath, chest pain, wheezing, and laryngitis. Higher exposure can cause hypoxia, chemical pneumonia (pneumonitis), and hemorrhage. This will gradually improve over 72 hours. If the patient survives the first 24 hours, recovery is probable.

Integumentary
Pain, blister formation, and possibly deep burns similar to frostbite can occur.

Gastrointestinal
If ammonia is ingested, severe mouth pain, cough, abdominal pain, nausea, and vomiting can occur. Severe edema of lips and mouth is seen. The patient should be examined to make certain that laryngeal irritation does not cause airway obstruction. Esophageal stricture and perforation is common.

Medical Management

After the patient has been removed from the area of exposure, decontamination should be started immediately in the field.

General Management

Remove all clothing and wash skin and hair with soap and large amounts of water for 15 to 20 minutes.

Cover burns with a sterile dressing.

The eyes should be irrigated continuously with water. A Morgan lens device and topical analgesics will enable continuous eye irrigation therapy. Both of these items should be considered part of an antidote/equipment cache. Slit lamp exam after fluorescein staining will reveal the ocular injury.

Damage to the lungs is common after inhaling anhydrous ammonia, often resulting in non-cardiogenic pulmonary edema. Since the victims may quickly develop shortness of breath and laryngeal swelling, early intubation should be considered to protect the airway.

Riot Control Agents

Irritating agents and lacrimators are chemicals that stimulate lacrimal glands to produce tears. Riot control agents and tear gas are synonyms for a group of aerosol-dispersed chemicals that produce eye, nose, mouth, skin, and respiratory tract irritation. This class of chemical agents causes involuntary eye closing due to irritation. For police, this is an effective weapon as it can disable an assailant. It is widely used in the civilian arena for self-protection. The deleterious effect is usually transient, about 30 minutes after exposure.

Riot Control Agents include:

- **CN (Mace7)**
- **OC (oleoresin capsicum or pepper spray)**
- **Adamsite**
- **CS (tear gas)**

Characteristics

Riot control agents are solids. They are sometimes dispersed in a solution that is aerosolized and can be dispersed from grenade or bomb.

Some police SWAT teams have small grenades that contain rubber pellets and/or CS. CN (the active ingredient in Mace7) has caused several deaths from pulmonary injury. CS is less toxic.

Capsicum, or pepper spray, is derived from the oleoresin capsicum in certain peppers. It is also used as an over-the-counter topical pain medication.

Adamsite is an irritating and vomiting agent that acts very similarly to CN and CS. The onset of its effects is delayed for minutes, compared to seconds for CN and CS. In addition, adamsitedoes not cause skin irritation.

Clinical Effects

Pain, burning, and irritations of exposed mucous membranes comprise the clinical picture.

Ophthalmic

Blepharospasm, or spasm of the muscle that causes eyelid closure, causes very transient blindness due to the closed eyelids. Vision, however, is not impaired once the eyes are opened. They cause tearing, conjunctival injection, and redness.

Pulmonary

Upper airway (mouth, nose)
Can cause nasal discharge, sneezing and burning.

Lower airway (lungs, bronchi)
Can cause coughing, shortness of breath, and chest tightness. Bronchospasm and wheezing can occur for hours after the exposure.

Integumentary
All can cause burning and redness, and it is claimed that O. capsicum has fewer tendencies to cause dermatitis. After exposure to large amounts of CS and CN, the onset of a more severe dermatitis with erythema and blisters may be delayed for 4 to 6 hours after exposure. These more severe effects occur under high temperature conditions with high humidity and large amounts of agent contacting the skin.

Cardiovascular
Increased blood pressure and heart rate are probably a response to anxiety.

Medical Management

The effects of the riot control agents will rarely last longer than 30 minutes, although the skin redness or erythema may last longer. In fact, in non- terrorist situations, most people will not seek medical care. Less than 1 percent will have eye, airway, or skin complaints severe enough to be medically assessed. A higher percentage might seek care because of anxiety and panic.

There is no antidote available for these agents. Treatment is supportive and directed towards alleviating symptoms which are not usually severe.

Ophthalmic
Should be irrigated copiously with water or saline. Remove contact lenses. Utilize slit lamp exam to make certain that all solid particle foreign bodies are removed. Follow-up with ophthalmologist is recommended.

Pulmonary
Treat wheezing with bronchodilators or steroids if standard bronchodilators fail. Oxygen therapy if indicated. Most symptoms should be maximal within an hour or two.

Integumentary
Most skin exposures require little more than reassurance. With prolonged pain, decontaminate with soap and water or a solution containing a carbonate and/or a bicarbonate. Do NOT use bleach. The delayed onset dermatitis should be managed with frequent irrigation and soothing ointments or creams.

TRIAGE OF CHEMICAL AGENT CASUALTIES

	Nerve Agent	Mustard	Pulmonary Intoxicants
Immediate	Unconscious or convulsing casualties, or those with major disorders of two or more body systems are triaged as immediate. Immediate treatment should include antidote administration and positive pressure ventilation to preserve airways. Rapid intervention will result in an improved outcome.	Patients with moderate to severe pulmonary signs and symptoms are classified as immediate.	Patients who require immediate attention are those who develop non-cardiogenic pulmonary edema within 6 hours after exposure to a pulmonary intoxicant such as phosgene
Delayed	Nerve agent casualties are categorized as delayed if their initial symptoms are improving. Antidote treatment of these patients depends on the amount of antidote available. If supplies are limited, then immediate patients will be treated first. The delayed category is also used for patients recovering from exposure after treatment who are conscious and have improved respiratory status. These patients may need additional treatment and need to be observed for several hours.	Most mustard casualties are triaged as delayed, including those with burns covering 5 to 50 percent of their body surface area (BSA) or with eye involvement.	Delayed casualties are those who develop cough and dyspnea more than 6 hours after exposure. These casualties should be admitted and observed for the development of latent pulmonary edema.
Minimal	The minimal nerve agent casualty is walking and talking and indicates intact breathing and circulation. These patients may be able to assist with other patients and/or decontamination.	Casualties with burns of less than 5 percent BSA are minimal.	
Expectant	The patient who has been apneic for more than 5 minutes and has no pulse or blood pressure is categorized as expectant.	The expectant casualty is the victim with burns greater than 50 percent BSA or no respiration or pulse.	Expectant casualties are those who develop non-card iogenic pulmonary edema within 6 hours of exposure, in circumstances where, due to limited resources, ICU support is not readily available (i.e. mass casualty circumstance)

CHEMICAL AGENT DETECTION

Recognition of a chemical attack is initially based on clinical criteria. This assessment can be augmented by chemical detection. The current technology for the detection of a chemical agent release is limited. Each of the various types of detectors currently available has specific qualifying factors.

In general, chemical agent detection equipment can help to determine the need for and level of PPE required to protect first responders and hospital personnel. It can be used to certify that the victim has been adequately decontaminated to prevent cross-contamination, and as an early warning device to notify authorities and the community of a chemical agent release. Chemical detectors do not, however, replace the need for an adequately supervised decontamination process.

KEY POINTS

To safely respond to a chemical terrorist attack, local communities must develop resources, protocols, and policies that will enable a safe and appropriate response. Patients exposed to hazardous chemicals require evacuation, life-saving intervention e.g., ABCs, antidote therapy if available, and decontamination. First responders and hospital staff must be trained and equipped to safely function in a chemically contaminated environment.

Decontamination

Proper decontamination is the most important first step in treating a patient exposed to chemical agents. Immediate removal of the patient's clothing can remove up to 90 percent of the contaminant. Removed clothing should be bagged, sealed and retained as possible evidence and for proper treatment and/or disposal. After the clothing is removed, the patient's skin and eyes may need to be decontaminated. In most cases, decontamination of skin can be accomplished by gentle and thorough washing with soap and water. For eyes, flush with plenty of water or normal saline solution. Whenever possible, water run-off from decontamination should be contained.

It is important not to abrade the skin during washing and rinsing. This is especially true after exposure to blistering/vesicant agents which bind to skin. These agents may leave the skin compromised and susceptible to further damage. For pulmonary agents do not generally pose a secondary contamination risk to hospital personnel, secondary to their high volatility; therefore, clothing removal and a quick rinse may be adequate. For incapacitating agents, clothing removal and a rinse in water alone may be adequate.

Victims contaminated with hydrogen cyanide liquid can secondarily contaminate response personnel by direct contact or through off-gassing vapors. Avoid dermal contact with cyanide-contaminated victims or with the gastric contents of victims who may have ingested cyanide-containing materials. Victims exposed to hydrogen cyanide gas do not pose a contamination risk to rescuers.

Personal protective equipment

Respiratory Protection

Protection from both vapors and particulates may be required when dealing with chemical agent releases. Surgical and N-95 masks will NOT protect against inhalation of vapors. Powered air-purifying respirators (PAPR) are recommended for hospital staff performing decontamination procedures.

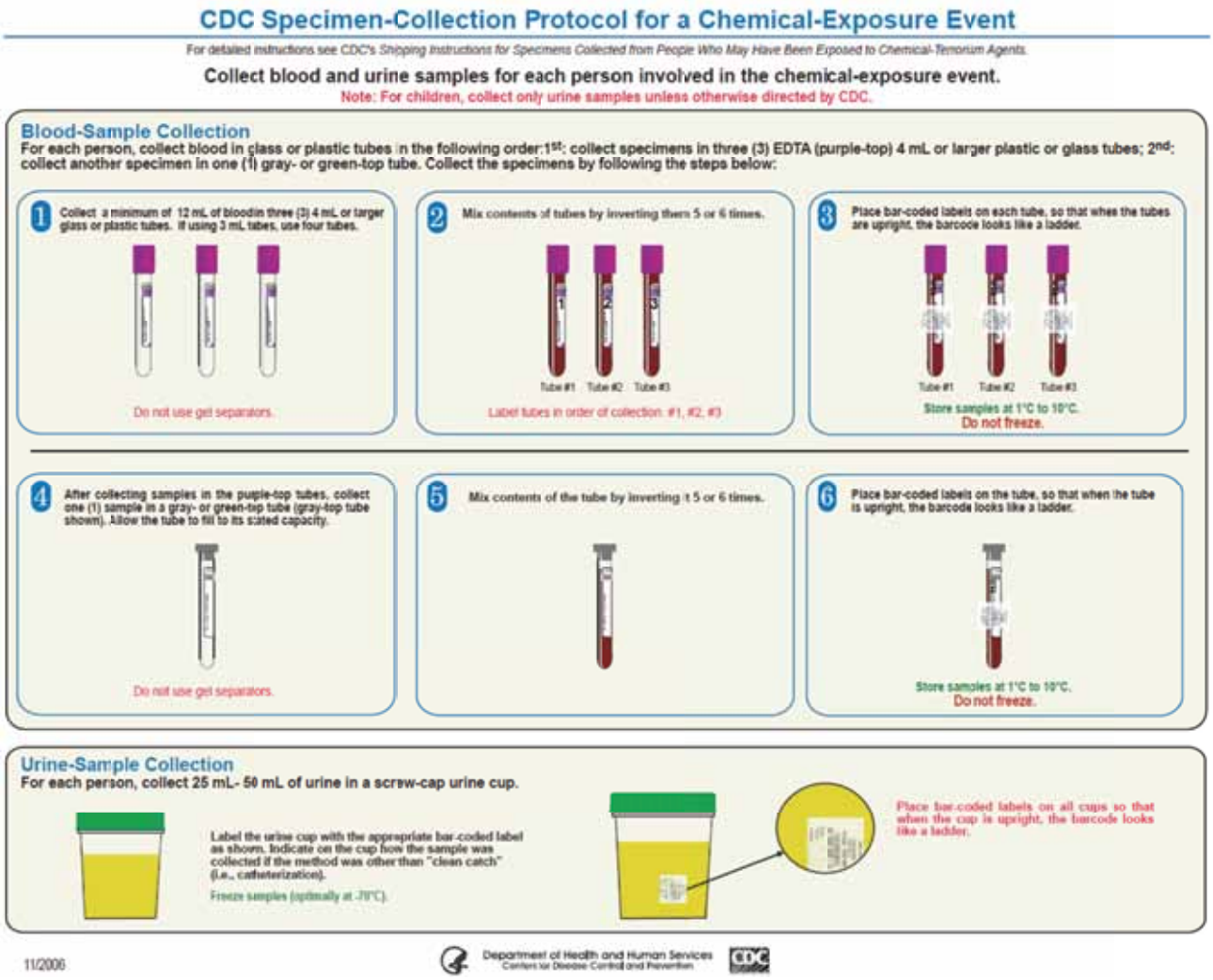
Dermal Protection

Latex examination gloves provide little protection from most chemical agents and can cause allergies. Chemical resistant suits, nitrile, butyl or neoprene gloves and boots provide splash protection and need to be worn when performing decontamination.

Antidote Therapy for Chemical Weapons Attacks

Chemical	Antidote	Decontamination (Including removal of clothing)	Other
Nerve Agent	Atropine, 2-PAMCl	Soap and Water	Diazepam (Valium)
Sulfur Mustard	None, Supportive	Soap and Water	Delayed onset, delayed bullae, pulmonary care
Lewisite	BAL, Supportive	Soap and Water	Acute onset, treat acidosis, volume depletion, pseudomembranes
Cyanide	Methemoglobin, Amyl Nitrite, Sodium Nitrite, Sodium Thiosulfate or Hydroxocobalamin	Soap and Water	Bicarbonate, O_2, fluids, treat acidosis, Sudden loss of consciousness
Phosgene	None, Supportive	Soap and Water	IVF, monitor volume, O_2, early intubation, steroids, watch for pulmonary edema
PFIB	None, Supportive		Monitor, O_2, watch for pulmonary edema
Ammonia	None, Supportive	Irrigate eyes - water only Soap and Water	Milk, bronchodilators, Silvadene, GI endoscopy, watch for mediastinitis, liquefaction
Chlorine	None, Supportive	Irrigate eyes - water only Soap and Water	Bronchodilators, steroids, intubation, bronchoscopy
CN (Mace)	None	Irrigate eyes - water only Soap and Water	Remove foreign body from eye, watch for bronchospasm
CS (Tear gas)	None	Irrigate eyes - water only Soap and Water	
Oleoresin capsicum	None	Irrigate eyes - water only Soap and Water	From chili pepper, dermatitis, eye injury

Specimen Collection Protocol for a Chemical Exposure Event



View above protocol at: **http://publichealth.lacounty.gov/lab/docs/chemspecimencollection.pdf**

Other LA County Department of Public Health Laboratory Resources:
Laboratory Response and Information and Forms
http://publichealth.lacounty.gov/lab/labct.htm

Chemical Exposure Resources for Medical Facilities
http://publichealth.lacounty.gov/lab/labct.htm

California Poison Control System – Tel. (800) 222-1222

For urgent inquiries or assistance during non-business hours, call the LA County Operator at (213) 974-1234 and ask for the LRN On-Call Person.
E-Mail: LAC-LRNC@ph.lacounty.gov

TO REPORT A POSSIBLE CHEMICAL TERRORIST INCIDENT, CALL THE DEPARTMENT OFPUBLIC HEALTH EMERGENCY DESK AT (213) 989-7140

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SECTION III

NUCLEAR / RADIOLOGICAL TERRORISM

INFORMATION and TREATMENT GUIDELINES for HOSPITALS and CLINICIANS

INTRODUCTION

There was a time when many people feared a possible nuclear attack by the former Soviet Union. In response to federal civil defense recommendations, families built bomb shelters in their basements, and stocked cellars with food and supplies in hope of surviving the nuclear fallout that was sure to follow. With the end of the Cold War, the threat of thermonuclear war has lessened considerably. Now, a new type of threat is confronting society in which nuclear/ radiological weapons may be directed against civilian targets by terrorists.

It is important that first responders [police, fire, EMS personnel] and first receivers [physicians, nurses, and other health care providers] understand radiation exposure and the consequences of conventional explosives to spread radioactive materials so that they may better respond to and treat victims of this type of incident. In responding to such an event, rescue should not be attempted until the incident scene is secured, routine monitoring is performed, and the responder is dressed in appropriate personal protective equipment (PPE).

TERRORIST USE OF NUCLEAR MATERIALS

Terrorist use of radioactive materials or a nuclear device constitutes a plausible threat. Such an incident could occur in one of five ways:

- Simple radiological device
- Radiological dispersal device
- Reactor sabotage
- Improvised nuclear device
- Nuclear weapon

The medical consequences will be dependent on the type of device used.

Simple Radiological Device (SRD)

This is the deliberate act of spreading radioactive material without the use of an explosive device. An example would be the placement of a high activity radioactive isotope in a public place exposing numerous individuals to various levels of radiation. Sealed sources could also be used to expose individuals near the source.

Radiological Dispersal Device (RDD)

A radiological dispersal device does not cause a nuclear reaction. Such a device is formed by combining an explosive agent with radioactive materials that may have been stolen, for example, from a hospital or local industry. The initial explosion kills or injures those closest to the bomb, while the radioactive substances remain to expose and contaminate survivors and emergency responders.

Nuclear Reactor Sabotage

Most people are aware of the reactor accidents of Three Mile Island and Chernobyl and most recently the Fukushima Daiichi power plant. The accident at Chernobyl was caused as the result of approximately eight safety systems being bypassed and Fukushima from several catastrophic events that included an earthquake, tsunami, loss of power lines and generator back up.

In the Western World, probability of terrorism involving a reactor is low. This is due to the high security surrounding a reactor together with the safety systems incorporated into the reactor. There is extensive shielding around a reactor; therefore, a significant amount of explosives would be required to breach this containment.

Improvised Nuclear Device (IND)

This is any device designed to cause a nuclear detonation. Construction of such a device would be difficult as it is not easy to get the weapon to detonate correctly. In some cases only the conventional high explosives in the IND will detonate. In this event, the IND is effectively a radiological dispersal device.

It is unlikely that terrorists will have the engineering sophistication and access to high-grade nuclear materials that are required to build an IND, but any detonation of an improvised or stolen device would generate high levels of radiation.

Nuclear Weapon

The probability of stealing a nuclear weapon in the Western World is very remote because of the high security surrounding these devices. However, a Russian general stated publicly that 50 to 100 one kiloton, suitcase nuclear weapons are unaccounted for in the former Soviet Union.

THE BASICS OF RADIATION

General Concepts

Examples of radiations include visible light, sound, radio waves, microwaves, heat, ionizing radiation, etc. Each example mentioned here has measurable physical properties and interacts with matter it comes in contact with. This module on the nuclear hazard will be concerned primarily with ionizing radiation.

Ionizing Radiation

As particles or energy emitted from a radioactive/radiation source pass through matter they can strip electrons from atoms/molecules causing them to become electrically charged or ionized, thus ionizing radiation. In living tissues/cells it is these ions produced by radiation that cause cellular damage and affect normal biological processes.

Ionizing radiation can be machine generated (i.e., X-rays), or it can come from radioactive atoms. Radioactive atoms are unstable atoms with too much energy or mass. The basic building block of all matter is the atom. The atom consists of a central nucleus with shells of electrons orbiting around this nucleus. The nucleus is made up of neutrons and protons. These protons, which are positively charge, have the tendency to repel each other. The protons are held together within the nucleus by a force (a super nuclear glue) that has three characteristics: it acts over a very short range, independent of charge, and is very strong. There is a ratio of protons to neutrons (1 to 1.2) for stability of an element. Each element has a defined number of protons. When an element is radioactive, usually there is an imbalance of this ratio of protons to neutrons; often the imbalance is due to an excess of neutrons.

With respect to a radioactive nuclide, for it to become stable, the nucleus has the ability to change a neutron into a proton with the ejection of a negative electron or, conversely, has the ability to change a proton into a neutron with the ejection of a positive electron known as a positron. The nucleus also has the capability of ejecting large particles, consisting of two protons and two neutrons, known as an alpha particle. Therefore, a radioactive nuclide achieves stability by ejecting particles until it has the correct ratio of protons to neutrons, remembering that the resultant element will be different than the original one. The reason for this is that within the nucleus there is an excess of energy. This excess energy is given off as electromagnetic energy of very short wave length. It is called gamma radiation. When all this excess energy is given off, the resultant element finally becomes stable.

The most common types of ionizing radiations are alpha particles, beta particles, gamma rays or X-rays, and neutrons. Gamma rays and X-rays may also be referred to as photons.

The basic building block of any tissue is the cell, and damage to the cell changes its chemistry or DNA. The chemical damage is instantaneous, but the clinical expression of this damage can take hours to years to express itself. At high doses, clinical expression can be within hours [e.g., the acute radiation syndrome (ARS)]. However, at lower doses or even after recovery from ARS, there is the probability, although low, of developing cancer 20-30 years later.

Alpha particles

Alpha particles are composed of two neutrons and two protons. Alpha radiation only travels a few centimeters in air. Alpha particles do not penetrate the skin and can be shielded by a thin layer of paper or clothing. Because the outer layer of skin is dead and several microns thick, the alpha particle is unable to penetrate through the dead layers of skin to reach the lower layers of living cells and generally will not cause any skin damage. If, however, an alpha emitter gets inside the body through inhalation, ingestion, or via a wound, the alpha emissions are near live tissue, and localized damage could occur.

Beta particles

Beta particles are high speed electrons formed by the splitting of a neutron into a proton and an electron. Beta radiation may travel meters in air and is moderately penetrating to human tissue. Beta radiation can penetrate human skin to the germinal layer, where new skin cells are produced. If beta emitting contaminants are allowed to remain on the skin for a prolonged period of time, they may cause skin injury. Beta emitting contaminants may be harmful if deposited internally. A sheet of aluminum foil a few millimeters thick will stop beta radiation, and PPE provides some protection against most beta radiation.

Gamma rays (photons)

Gamma radiation is able to travel many meters in air and many centimeters in human tissue. It readily penetrates most materials and is sometimes called penetrating radiation. X-rays are like gamma rays. They too, are penetrating radiation. Radioactive materials that emit gamma radiation constitute both an external and internal hazard to humans. Dense materials are needed to shield against gamma radiation. PPE provides little shielding from gamma radiation but will prevent contamination of the skin. Gamma radiation frequently accompanies the emission of alpha and beta radiation.

Neutrons

Neutrons are neutral particles emitted from the nucleus of an atom. Neutrons lose most of their energy through collisions with other atomic nuclei. An analogy that could be used is the billiard ball effect (i.e., when one billiard ball strikes another, energy is transferred from one ball to the other). Under certain circumstances, neutrons can be captured by a stable nucleus, making the nucleus radioactive. An example of this is Na-23 being changed (transmuted) into Na-24.

Radiation Detection

Unfortunately our body senses cannot detect radiation. We cannot see, smell, taste, feel, or hear radiation, but we have very good instrumentation to detect it. Radiation monitoring instruments detect the presence of radiation, usually by collecting charged particles (ions). The radiation measured is usually expressed as exposure per unit time, using various units of measure, including the curie (Ci), the becquerel (Bq), and counts per minute (CPM). The most commonly used instruments to detect the presence of radiation include:

Geiger Mueller Survey Meter or Geiger Counter

The Geiger-Mueller (GM) survey meter will detect low levels of gamma and most beta radiation. The instrument typically has the capability to distinguish between gamma and beta radiation. This instrument is used to measure background radiation levels and to quickly evaluate potentially contaminated victims. If a greater level of radiation emission is anticipated, a higher range instrument (such as an ionization chamber) should be used. At higher levels, the GM meter will often display incorrectly low or off-scale readings. All healthcare facilities must have staff that knows how to use a GM survey meter.

Ionization Chamber Survey Meter

This device measures gamma ray dose/rate when high level radiation hazards are suspected. Low level gamma contamination is not detected.

Alpha Monitors

Alpha Monitors are designed to measure the presence of alpha particles. Since alpha particles travel short distances, they might not be detected in wounds because blood and tissue fluids may shield the particles from reaching the monitor's surface. Because of these factors experienced persons such as the Radiation Safety Officer (RSO) should do alpha surveys.

Dose Rate Meters

These measure mrad/hour or rad/hour units of personal radiation. To find the dose an individual received, multiply the dose rate by the time. Dose = Dose Rate X Time

Pocket or Personal Dosimeters
These simple devices measure accumulated radiation to gamma rays. Some devices basically contain a piece of film embedded in a badge of varying densities.

Other Devices Used
TLD (lithium fluoride) and QFD Quartz Fiber Dosimeters, and Electronic Readout Dosimeters.

Radiation Units

The basic unit for measuring radiation is the rad (radiation absorbed dose). The rad is defined as the deposition of 0.01 joule of energy per kilogram (kg) of tissue. To quantify the amount of damage that is suspected from a radiation exposure, rads are converted into rems (which at one time stood for Roentgen Equivalent Man). The rem is adjusted to reflect the type of radiation absorbed and the likelihood of damage to tissues/cells. For beta, gamma, and X-rays the rad will be equivalent to the rem (1 rem = 1,000 millirem).

The rem was introduced to take into account this variation in potential tissue damage. This is important because radiation may be of mixed type. For example, a standard X-ray machine was used to deliver 100 rads of radiation and to compare the biological endpoint with other types of radiation. It was found that 100 rads of gamma and beta radiation produced the same effect as 100 rads of X-ray. However, it was found that only 20 rads of neutrons and 5 rads of alpha were found to produce the same effect as 100 rads of X-ray. Therefore, neutron and alpha radiations were more potent and required fewer rads to produce the same effect. (This concept applies only to occupational exposure.) Now weighting factors are used for each organ/tissue.

Radioactive Materials

Radioactive materials, materials that emit ionizing radiation, are used in diagnosis (nuclear medicine), therapy (cancer treatment), industry (non-destructive testing), and for research purposes. A number of radioactive materials, including radioactive waste, are commercially shipped in specialized containers.

Radioactive materials are chemically and physically identical to their non-radioactive counterparts and behave in the body the same as their non-radioactive counterparts (for example, radioactive iodine behave the same as stable iodine). For practical purposes, after 10 half-lives, most of the radioactivity in a particular quantity of radioactive material is gone.

Radioactivity has existed for millions of years in the crust of the earth, in building materials, in the food we eat, the air we breathe, and in virtually everything that surrounds us. Radiation from these materials, as well as cosmic radiation from the sun and universe, makes up the background radiation to which we are constantly exposed.

Most individuals are exposed to about 620 millirems per year through natural causes and manmade sources. Smoking 1.5 packs of cigarettes a day for 1 year produces an accumulative radiation doses of 16 rem to the bifurcation of the bronchus. If an individual is exposed to more than 100 rads at one time, predictable signs and symptoms will develop within a few hours, days, or weeks depending on the dose. Fifty percent of individuals exposed to a single dose of 450 rems will die without medical intervention.

Radiation Protection Guidelines

Time

The shorter the time in a radiation field, the less the radiation exposure. Work quickly and efficiently. A rotating team approach can be used to keep individual radiation exposures to a minimum. (Dose = Dose Rate x Time, Ex: 25 mrem= 100 mrem/hr x 0.25 hr (15 min)

Distance

The farther a person is from a source of radiation, the lower the radiation dose. Do not touch radioactive materials. Use shovels, brooms, forceps, etc., to move materials to avoid physical contact.Radiation dose can be calculated using the inverse square law. (Dose $Rate_1$ X $Distance_1^2$ = Dose $Rate_2$ X $Distance_2^2$.) Basically, if you double your distance from the radiation source, then you decrease your dose by a fourth. However, if you decrease your distance by half then you increase your dose four times of what it was originally.

Shielding

Although not always practical in emergency situations, shielding offered by barriers can reduce radiation exposure.

Quantity

Limit the amount of radioactive material in the working area to decrease exposure.

RADIATION INJURY

Types of Radiation Injury

Regardless of where or how an accident involving radiation happens, *three types of radiation-induced injury can occur: external irradiation, contamination with radioactive materials, and incorporation of radioactive material into body cells, tissues, or organs.*

External Irradiation

External irradiation occurs when all or part of the body is exposed to penetrating radiation from an external source. During exposure this radiation can be absorbed by the body or it can pass completely through. A similar thing occurs during an ordinary chest x-ray. Following external exposure, an individual is not radioactive and can be treated like any other patient.

Contamination

The second type of radiation injury involves contamination with radioactive materials. Contamination means that radioactive materials in the form of gases, liquids, or solids are released into the environment and contaminate people externally, internally, or both. An external surface of the body, such as the skin, can become contaminated. These victims can pose a threat to health care providers and should be decontaminated based on injuries as described in the triage of radiation causality section. If radioactive materials get inside the body through the lungs, gut, or wounds, the contaminant can become deposited internally.

Incorporation

The third type of radiation injury that can occur is incorporation of radioactive material. Incorporation refers to the uptake of radioactive materials by body cells, tissues, and target organs such as bone, liver, thyroid, or kidney. In general, radioactive materials are distributed throughout the body based upon their chemical properties. Incorporation cannot occur unless contamination has occurred.

Severity of Injury

In general, the higher the dose, the more severe the early effects will be and the greater the possibility of delayed effects. Obviously, one can increase the dose until the cell is killed outright. However, it is found that a much lower dose can stop cell division.

For example, if we consider the hematopoietic system, an individual hematopoietic stem cell has the capability of producing millions of mature cells. Preventing stem cell division means the loss of these cells. The importance of this is that a sub-lethal dose produces these effects.
Two important organ systems that have rapidly dividing cell lines are the hematopoietic and gastrointestinal systems.

After the dropping of the atomic bombs in Japan, experiments were carried out on various animals to determine the dose that would kill 50 percent of the experimental animal population within a set time period. Accident data on humans that were not treated indicate the lethal dose (LD) 50 was in the region of 350 rads to 450 rads.

Acute Radiation Syndrome (ARS)

Definition

An acute illness, which follows a roughly predictable course over a period of time ranging from a few hours to several weeks after exposure to ionizing radiation. The acute radiation syndrome is produced if enough radiation reaches enough sensitive tissue. Important factors are:

- High dose
- High dose rate
- Whole body exposure
- Penetrating irradiation

Signs and Symptoms

The signs and symptoms that develop in ARS occur through four distinct phases:

Prodromal phase

Depending on the total amount of radiation absorbed, patients may experience a variety of symptoms including loss of appetite, nausea, vomiting, fatigue, and diarrhea. After high radiation doses, additional symptoms such as prostration, fever, respiratory difficulties, and increased excitability may develop. This is the stage at which most victims seek medical care.

Latent phase
This is the transitional period in which many of the initial symptoms resolve, and may last for up to 3 weeks depending on the original radiation dose. This time interval decreases as the initial dose increases.

Illness phase
The period of time when overt illness develops, often characterized by infection, bleeding, electrolyte imbalance, diarrhea, changes in mental status, and shock.

Recovery or death phase
This follows the period of overt illness, which may take weeks or months to resolve.

AFFECTED SYSTEMS

Hematopoietic or Blood Forming System
This system shows the earliest indication of the severity of the radiation exposure through the rapidity and degree of drop in the cell count (lymphocytes, granulocytes, thrombocytes, and reticulocytes). This reduction in the cell count is commonly associated with fever, sepsis, and hemorrhagic complications.

The absolute lymphocyte count at 48 hours after exposure is a good predictor for prognosis. For example, if the total lymphocyte count is greater than 1,200 it is unlikely that the patient has received a lethal dose. If at 48 hours the lymphocyte cell count is between 300 and 1,200, a significant exposure has occurred and the patient should be hospitalized with barrier protection isolation. Lymphocyte levels of less than 300 cells per/ml are usually critical and warrant the consideration of the use of colony-stimulating factors on an individual basis.

Gastrointestinal System
Symptoms in this system are regularly seen at acute doses greater than 600 rads and result from damage to the epithelial cells lining the intestinal tract. The higher the exposure, the sooner the symptoms of nausea and vomiting develop. The presence of these symptoms typically overlap with the drop in the cell count described previously. As a result, sepsis, loss of fluids, electrolytes and opportunistic infections complicate the picture. Persistent high fevers and bloody diarrhea is an ominous sign despite fluid and electrolyte replacement.

Central Nervous System (CNS)
Central nervous system symptoms are seen with acute radiation doses in excess of 1000 radsand are probably due to diffuse microvascular leaks within the brain. Damage to these blood vessels result in the loss of fluids and electrolytes, edema, increased intracranial pressure, and death. This injury is irreversible and the victim rarely lives long enough to suffer any hematological or gastrointestinal symptoms. Symptoms of shock may develop quickly in these patients. There is also associated cardiovascular collapse in this kind of patient.

Integumentary
Various skin changes occur depending on the radiation dose. The injuries tend to progress with dose level and there appears to be a threshold effect for these clinical signs. Early erythema is an important sign to look for. At doses around 300 rads, erythema will develop within a few hours, but

more importantly, it can disappear within a few hours only to reappear at a later time. Therefore, the patient should be examined on an hourly basis for this sign and ideally photographs should be taken to document this sign. If local radiation dermatitis develops with this sign, the dose is in the region of 1,000 rads. If blistering occurs then the dose is in the range of 1,500 rads. Also if necrosis develops, the dose is in the region of greater than 5,000 rads. Therefore, by noting these clinical signs, one is able to establish the approximate dose range the patient was subjected to and these doses would be confirmed by dosimetry at a later stage.

>300 rads: Epilation 17-21 days
>600 rads: Erythema that may disappear within a few hours
>1000 rads: Dry desquamation 2 - 4 weeks
>1500 rads: Moist desquamation 2 - 8 weeks
>5000 rads: Necrosis few days to months

Trauma and Radiation

Patients who have suffered trauma (from an explosion or burn) combined with an acute high exposure to penetrating radiation will have an increased chance of dying as compared to patients who have suffered from the same dose of radiation without trauma. All combined injuries are worse than radiation alone. If a patient has received an acute dose greater than 200 rads, effort must be made to close wounds, cover burns, reduce fractures, and perform surgical stabilizing and definitive treatments within the first 48 hours after injury. After 48 hours, surgical interventions should be delayed for 2 to 3 months.

Triage of Radiation Casualties

Triage of victims from a radiological event should follow the same principles used in sorting victims of a hazardous material incident. Victims are classified with regard to their need for treatment and will be classified as requiring minimal treatment, immediate care, delayed care, or as expectant. Since the degree of radiation injury will not be initially apparent, triage criteria will need to be based on associated injuries and complaints. The triage method used will vary according to local practices.

Those victims determined to have life threatening injuries should have their clothing quickly removed, and have treatment begun to stabilize their injuries without concern for removal of radiological contaminates. However, if a victim has received lethal doses of total body radiation, as indicated by a combination of clinical signs, including high fever, disorientation, bloody diarrhea, or vomiting they should be considered expectant and decontaminated and treated according to hospital protocol.

Those patients deemed to have non-life threatening injuries should be decontaminated before entering a hospital and receiving treatments.

Classification, Treatment, and Disposition

Once the radiological survey and decontamination procedure is complete, patients may be classified into one of 3 categories, based on their presenting signs and symptoms.

Survival Probable Group

This group of patients who present without any initial symptoms, or whose symptoms are so minimal (i.e., nausea and vomiting), that they resolve in a few hours. These individuals have most probably not received a lethal radiation dose, and most likely are exposed to < 100 rads. The initial CBC and sequential studies will not show a significant decrease in the lymphocyte or granulocyte counts. These patients can be safely sent home and instructed to return if symptoms redevelop.

Survival Possible Group

These victims present with nausea and vomiting, which typically last 24 to 48 hours followed by an asymptomatic period. During this latent phase, laboratory evaluations will show a drop in various cell counts (lymphocytopenia, leukocytopenia, and thrombocytopenia). If vomiting is severe, these patients should be admitted for fluid and electrolyte therapy and treated with antiemetics.

If the absolute lymphocyte count is less that 1,200 (or 50 percent of the baseline), protective isolation precautions should be implemented. These patients will have typically received a radiation dose in the range of 200 to 800 rads. The LD50 in mass casualty situations is in the range of 350 to 450 rads. Treatment is primarily supportive.

Blood replacement products, hyperalimentation, antibiotics, antivirals, and antifungal medications should only be administered after consultation with a hematologist, oncologist, or infectious disease specialist. Colony-stimulating factors will probably be indicated for pancytopenia.

Survival Improbable Group

Patients in this group have been exposed to whole-body irradiation in doses exceeding 800 rads. These victims present an acute onset of fulminating vomiting, diarrhea, and shock, requiring aggressive fluid and electrolyte therapy. The presence of any CNS symptoms (confusion, a change in mental status, etc.) signals that the patient has received a lethal dose of radiation.These victims will develop bone marrow suppression, leading to aplasia and pancytopenia that is uniformly fatal unless a successful hematopoietic stem cell transplant and/or colony stimulating factors are used. Treatment outcomes in some recent accidents suggest that exposure in the 800 to 1,200 rad range can be successfully managed through the hematopoietic crisis, although the individuals treated often succumbed to residual lung damage 6 to 12 months following exposure. In mass casualty situations, these victims are provided with comfort measures only (i.e., pain management).

CASUALTY MANAGEMENT IN A DISASTER

Activate the Hospital Plan

- Establish triage area outside the hospital
- Set up decontamination corridor, preferable outside the Emergency Department
- Plan to control contamination
- Set up a controlled area large enough to hold the anticipated number of victims. Demarcate controlled area with tape or floor markings.
- Prevent tracking of contaminants by covering floor areas
- Restrict access to the controlled area
- Monitor anyone or anything leaving the controlled area
- Use strict isolation precautions, including protective clothing and double bagging
- Use a buffer zone or secondary control line for added security
- Control waste by using plastic-lined container for clothing, linens, dressings, etc.
- Control ventilation
- Change instruments, outer gloves, drapes, etc. when they become contaminated
- Use waterproof materials to limit the spread of contaminated liquids; for example, waterproof aperture drapes
- Protective clothing for staff: gowns (preferably water-resistant), caps, masks, boots, and two pairs of gloves. Staff should wear dosimetry (if it is available) and eye protection.
- Notify Radiation Safety Officer (RSO) to issue dosimeters, prepare instruments and mobilize nuclear medicine staff to assist with surveys
- Designate storage area for waste (outside hospital)

Patient Arrival

- Determine if incident involves contamination. If contaminated, the patient should be directed to the decontamination area, if no life threatening injury exists.
- Upon arrival, all patient clothing should be removed under the guidance/direction of staff, so that further contamination of the patient is limited. Clothing and personal belongings are placed in a labeled bag.
- Patients suspected of being contaminated should be decontaminated, appropriately. If open wounds arepresent, they should be irrigated first. Then covered with a sterile, waterproof dressing priorto the total body washing. After decontamination, each patient should be surveyed or re-surveyed, if done previously.
- After decontamination, biological samples should be taken: nasal swabs, throat swabs, etc.
- Collect blood for CBC and differential.
- Note past medical history of patient. Important questions are history of renal disease, allergies, or nuclear medicine procedures.

Internal Contamination

Once radioactive materials cross cell membranes, they are said to be incorporated. Incorporation is a time-dependent, physiological phenomenon related to both the physical and chemical natures of the contaminant. The rate of incorporation can be quite rapid, occurring in minutes, or it can take days to months. Thus, time can be critical and treatment (decorporation) urgent. Several methods of preventing incorporation (e.g., catharsis, gastric lavage) might be applicable and can be prescribed by a physician. Some of the medications or preparations used in decorporation might not be available at the facility but should be stocked locally.

If internal contamination is suspected or has occurred, the physician, or RSO should request samples of urine, feces, vomitus, wound secretions, etc. Whole-body counting and radioassayalso can help evaluate the magnitude of the problem and the effect of any treatment. The contaminated patient admitted with an airway device or endotracheal tube must be considered to be internally contaminated.

KEY POINTS

Hospital personnel should be prepared for a nuclear reactor accident, industrial incident, or terrorist event. It will present many unique challenges to hospital personnel.

Hospital emergency department personnel should always use proper priorities in caring for accident victims where potential radiation hazards exist: treat life-threatening problems first, limit the radiation dose to both victim and personnel, and control the spread of radioactive contaminants. *Serious medical problems have priority over the concerns about radiation, such as radiation monitoring, contamination control, and decontamination.*

Irradiation of the whole body or some specific body part does not constitute a medical emergency even if the amount of radiation received is high. The effects of irradiation usually are not evident for days to weeks and while medical treatment is needed, it is not needed on an emergency basis. On the other hand, contamination accidents must be considered medical emergencies since they *might* lead to internal contamination and subsequent incorporation. Incorporation can result in adverse health effects several years later if the amount of incorporated radioactive material is high.

Carefully evaluating the initial presenting signs and symptoms (such as nausea, vomiting, diarrhea, changes in mental status, shock, and lymphocyte count over the first 48 hours) becomes the most reliable indicator of the radiation dose and patient's ultimate prognosis.

Since no antidote exists for radiation exposure, treatment is primarily supportive with more specialized care directed towards patients with high dose irradiation and those with internal contamination. Consultation with specialists in hematology, oncology, radiation, and infectious disease should be obtained.

The need for initial treatment for internally contaminated patients is determined based on the patient's medical condition, history, biological samples (nasal swabs), and definitive evaluation of internal contamination. Whole body counting may be needed if internal contamination is suspected.

MEDICATIONS AND MECHANISMS OF DECORPORATION

(Modified Form Safety Series 47, IAEA)

Radionuclide	Medication	Ingestion/Inhalation	Wound	Principle of Action
Iodine	KI	130 mg (tab.) stat, followed by 130 mg q.d. x 7 if indicated	Same	Blocking
Rare earths Plutonium TransplutonicsY ttrium	DTPA	1 gmCa-DTPA in 500 ml 5 percent D/W IV over 60 min; or 1 gm (4ml) in 6 ml 5 percent D/W by slow IV injection (1 min)		Chelation
Polonium Mercury Arsenic Bismuth Gold	BAL	One ampule (=300 mg) IM q 4 hrs for 3 days - (first test for sensitivity with 3 amp.)	Same	Promotes excretion
Uranium	Bicarbonate	Slow IV infusion of bicarbonatedphysiologi cal solution (250 ml at 14 percent)	Slow IV infusion of bicarbonated physiological solution (250 ml at 14 percent) and wash with bicarbonate	Alkalinization of urine; reduces chance of ATN
Cesium Rubidium Thallium	Prussian Blue [Ferrihexacyano-F errate(II)]	1 gm in 100-200 ml water p.o.t.i.d. for several days	Same	Mobilization from organs and tissues - reduction and absorption
Radium	Ca-gluconate	May be tried; 20 percent Ca-gluconate10 ml IV once or twice daily	Same	Displacement
Strontium	Ammonium chloride	3 gmt.i.d. p.o.	Same	Demineralizing agent
Tritium	Water	Force liquid	Same	Isotopic dilution
Strontium Radium	$BaSO_4$	100 gm $BaSO_4$ in 250 ml of water	Same	Reduces absorption
Calcium Barium	Sodium Alginate	10 gm in a large glass of water	Same	Inhibits absorption
Copper Polonium Lead Mercury Gold	D-penicillamine	1 gm IV q.d. or 0.9 gmp.o. 14 - 6 hours	Same	Chelation

FACT SHEET

Acute Radiation Syndrome: A Fact Sheet for Physicians

Acute Radiation Syndrome (ARS) (sometimes known as radiation toxicity or radiation sickness) is an acute illness caused by irradiation of the entire body (or most of the body) by a high dose of penetrating radiation in a very short period of time (usually a matter of minutes). The major cause of this syndrome is depletion of immature parenchymal stem cells in specific tissues. Examples of people who suffered from ARS are the survivors of the Hiroshima and Nagasaki atomic bombs, the firefighters that first responded after the Chernobyl Nuclear Power Plant event in 1986, and some unintentional exposures to sterilization irradiators.

The required conditions for Acute Radiation Syndrome (ARS) are:

- **The radiation dose must be large** (i.e., greater than 0.7 Gray (Gy)1,2 or 70 rads).
  - o Mild symptoms may be observed with doses as low as 0.3 Gy or 30 rads.
- **The dose usually must be external** (i.e., the source of radiation is outside of the patient's body).
  - o Radioactive materials deposited inside the body have produced some ARS effects only in extremely rare cases.
- **The radiation must be penetrating** (i.e., able to reach the internal organs).
  - o High energy X-rays, gamma rays, and neutrons are penetrating radiations.
- **The entire body** (or a significant portion of it) must have received the dose.3
  - o Most radiation injuries are local, frequently involving the hands, and these local injuries seldom cause classical signs of ARS.
- **The dose must have been delivered in a short time** (usually a matter of minutes).
  - o Fractionated doses are often used in radiation therapy. These large total doses are delivered in small daily amounts over a period of time. Fractionated doses are less effective at inducing ARS than a single dose of the same magnitude.

The three classic ARS Syndromes are:

- Bone marrow syndrome (sometimes referred to as hematopoietic syndrome): the full syndrome will usually occur with a dose greater than approximately 0.7 Gy (70 rads) although mild symptoms may occur as low as 0.3 Gy or 30 rads.4
  - o The survival rate of patients with this syndrome decreases with increasing dose. The primary cause of death is the destruction of the bone marrow, resulting in infection and hemorrhage.
- Gastrointestinal (GI) syndrome: the full syndrome will usually occur with a dose greater than approximately 10 Gy (1000 rads) although some symptoms may occur as low as 6 Gy or 600 rads.

1 The Gray (Gy) is a unit of absorbed dose and reflects an amount of energy deposited into a mass of tissue (1 Gy = 100 rads). In this document, the referenced absorbed dose is that dose inside the patient's body (i.e., the dose that is normally measured with personal dosimeters).

2 The referenced absorbed dose levels in this document are assumed to be from beta, gamma, or x radiation. Neutron or proton radiation produces many of the health effects described herein at lower absorbed dose levels.

3 The dose may not be uniform, but a large portion of the body must have received more than 0.7 Gy (70 rads).

4 Note: although the dose ranges provided in this document apply to most healthy adult members of the public, a great deal of variability of radiosensitivity among individuals exists, depending upon the age and condition of health of the individual at the time of exposure. Children and infants are especially sensitive.

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- o Survival is extremely unlikely with this syndrome. Destructive and irreparable changes in the GI tract and bone marrow usually cause infection, dehydration, and electrolyte imbalance. Death usually occurs within 2 weeks.

•**Cardiovascular (CV)/ Central Nervous System (CNS) syndrome:** the full syndrome will usually occur with a dose greater than approximately 50 Gy (5000 rads) although some symptoms may occur as low as 20 Gy or 2000 rads.

- o Death occurs within 3 days. Death likely is due to collapse of the circulatory system as well as increased pressure in the confining cranial vault as the result of increased fluid content caused by edema, vasculitis, and meningitis.

The four stages of ARS are:

- **Prodromal stage** (N-V-D **stage):** The classic symptoms for this stage are nausea, vomiting, as well as anorexia and possibly diarrhea (depending on dose), which occur from minutes to days following exposure. The symptoms may last (episodically) for minutes up to several days.
- **Latent stage:** In this stage, the patient looks and feels generally healthy for a few hours or even up to a few weeks.
- **Manifest illness stage:** In this stage, the symptoms depend on the specific syndrome (see Table 1) and last from hours up to several months.
- **Recovery or death:** Most patients who do not recover will die within several months of exposure. The recovery process lasts from several weeks up to two years.

These stages are described in more detail in Table 1.

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Table 1. Acute Radiation Syndromes

Syndrome	Dose*	Prodromal Stage	Latent Stage	Manifest Illness Stage	Recovery
Hematopoietic (Bone marrow)	> 0.7 Gy (> 70 rads) (mild symptoms may occur as low as 0.3 Gy or 30 rads)	• Symptoms are anorexia, nausea and vomiting. • Onset occurs 1 hour to 2 days after exposure. • Stage lasts for minutes to days.	• Stem cells in bone marrow are dying, although patient may appear and feel well. • Stage lasts 1 to 6 weeks.	• Symptoms are anorexia, fever, and malaise. • Drop in all blood cell counts occurs for several weeks. • Primary cause of death is infection and hemorrhage. • Survival decreases with increasing dose. • Most deaths occur within a few months after exposure.	• In most cases, bone marrow cells will begin to repopulate the marrow. • There should be full recovery for a large percentage of individuals from a few weeks up to two years after exposure • Death may occur in some individuals at 1.2 Gy (120 rads). • The $LD_{50/60}$† is about 2.5 to 5 Gy (250 to 500 rads).
Gastrointestinal (GI)	> 10 Gy (> 1000 rads) (some symptoms may occur as low as 6 Gy or 600 rads)	• Symptoms are anorexia, severe nausea, vomiting, cramps, and diarrhea. • Onset occurs within a few hours after exposure. • Stage lasts about 2 days.	• Stem cells in bone marrow and cells lining GI tract are dying, although patient may appear and feel well. • Stage lasts less than 1 week.	• Symptoms are malaise, anorexia, severe diarrhea, fever, dehydration, and electrolyte imbalance. • Death is due to infection, dehydration, and electrolyte imbalance. • Death occurs within 2 weeks of exposure.	• The LD_{100}‡ about 10 Gy (1000 rads).
Cardiovascular (CV)/ Central Nervous System (CNS)	> 50 Gy (5000 rads) (some symptoms may occur as low as 20 Gy or 2000 rads)	• Symptoms are extreme nervousness and confusion; severe nausea, vomiting, and watery diarrhea; loss of consciousness; and burning sensations of the skin. • Onset occurs within minutes of exposure. • Stage lasts for minutes to hours.	• Patient may return to partial functionality. • Stage may last for hours but often is less.	• Symptoms are return of watery diarrhea, convulsions, and coma. • Onset occurs 5 to 6 hours after exposure. • Death occurs within 3 days of exposure.	• No recovery is expected.

* The absorbed doses quoted here are "gamma equivalent" values. Neutrons or protons generally produce the same effects as gamma, beta, or X-rays but at lower doses. If the patient has been exposed to neutrons or protons, consult radiation experts on how to interpret the dose.
†The LD50/60 is the dose necessary to kill 50% of the exposed population in 60 days.
‡ The LD100 is the dose necessary to kill 100% of the exposed population.

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Cutaneous Radiation Syndrome (CRS)

The concept of cutaneous radiation syndrome (CRS) was introduced in recent years to describe the complex pathological syndrome that results from acute radiation exposure to the skin.

ARS usually will be accompanied by some skin damage. It is also possible to receive a damaging dose to the skin without symptoms of ARS, especially with acute exposures to beta radiation or X-rays. Sometimes this occurs when radioactive materials contaminate a patient's skin or clothes.

When the basal cell layer of the skin is damaged by radiation, inflammation, erythema, and dry or moist desquamation can occur. Also, hair follicles may be damaged, causing epilation. Within a few hours after irradiation, a transient and inconsistent erythema (associated with itching) can occur. Then, a latent phase may occur and last from a few days up to several weeks, when intense reddening, blistering, and ulceration of the irradiated site are visible.

In most cases, healing occurs by regenerative means; however, very large skin doses can cause permanent hair loss, damaged sebaceous and sweat glands, atrophy, fibrosis, decreased or increased skin pigmentation, and ulceration or necrosis of the exposed tissue.

Patient Management

Triage: If radiation exposure is suspected:

- Secure ABCs (airway, breathing, circulation) and physiologic monitoring (blood pressure, blood gases, electrolyte and urine output) as appropriate.
- Treat major trauma, burns, and respiratory injury if evident.
- In addition to the blood samples required to address the trauma, obtain blood samples for CBC (complete blood count), with attention to lymphocyte count, and HLA (human leukocyte antigen) typing prior to any initial transfusion and at periodic intervals following transfusion.
- Treat contamination as needed.
- If exposure occurred within 8 to 12 hours, repeat CBC, with attention to lymphocyte count, 2 or 3 more times (approximately every 2 to 3 hours) to assess lymphocyte depletion.

Diagnosis

The diagnosis of ARS can be difficult to make because ARS causes no unique disease. Also, depending on the dose, the prodromal stage may not occur for hours or days after exposure, or the patient may already be in the latent stage by the time they receive treatment, in which case the patient may appear and feel well when first assessed.

If a patient received more than 0.05 Gy (5 rads) and three or four CBCs are taken within 8 to 12 hours of the exposure, a quick estimate of the dose can be made (see Ricks, et. al. for details). If these initial blood counts are not taken, the dose can still be estimated by using CBC results over the first few days. It would be best to have radiation dosimetrists conduct the dose assessment, if possible.

If a patient is known to have been or suspected of having been exposed to a large radiation dose, draw blood for CBC analysis with special attention to the lymphocyte count, every 2 to 3 hours during the first 8 hours after exposure (and every 4 to 6 hours for the next 2 days). Observe the patient during this time for symptoms and consult with radiation experts before ruling out ARS.

If no radiation exposure is initially suspected, you may consider ARS in the differential diagnosis if a history exists of nausea and vomiting that is unexplained by other causes. Other indications are bleeding, epilation, or white blood count (WBC) and platelet counts abnormally low a few days or weeks after unexplained nausea and vomiting. Again, consider CBC and chromosome analysis and consultation with radiation experts to confirm diagnosis.

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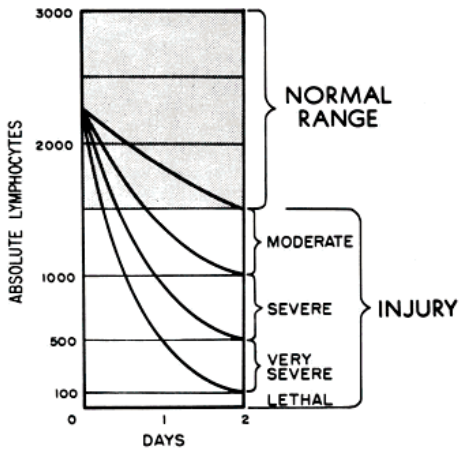
Initial Treatment and Diagnostic Evaluation

Treat vomiting[5] and repeat CBC analysis with special attention to the lymphocyte count every 2 to 3 hours for the first 8 to 12 hours after exposure (and every 4 to 6 hours for the following 2 or 3 days). Sequential changes in absolute lymphocyte counts over time are demonstrated below in the Andrews Lymphocyte Nomogram (see Figure 1). Precisely record all clinical symptoms, particularly nausea, vomiting, diarrhea, and itching, reddening or blistering of the skin. Be sure to include time of onset.

Figure 1: Andrews Lymphocyte Nomogram



From Andrews GA, Auxier JA, Lushbaugh CC. *The Importance of Dosimetry to the Medical Management of Persons Exposed to High Levels of Radiation.* In *Personal Dosimetry for Radiation Accidents.*Vienna: International Atomic Energy Agency; 1965.

Note and record areas of erythema. If possible, take color photographs of suspected radiation skin damage. Consider tissue, blood typing, and initiating viral prophylaxis. Promptly consult with radiation, hematology, and radiotherapy experts about dosimetry, prognosis, and treatment options. Call the Radiation Emergency Assistance Center/Training Site (REAC/TS) at (865) 576-3131 (M-F, 8 am to 4:30 am EST) or (865) 576-1005 (after hours) to record the incident in the Radiation Accident Registry System.

After consultation, begin the following treatment (as indicated):

- supportive care in a clean environment (if available, the use of a burn unit may be quite effective)
- prevention and treatment of infections
- stimulation of hematopoiesis by use of growth factors
- stem cell transfusions or platelet transfusions (if platelet count is too low)
- psychological support
- careful observation for erythema (document locations), hair loss, skin injury, mucositis, parotitis, weight loss, or fever
- confirmation of initial dose estimate using chromosome aberration cytogenetic bioassay when possible. Although resource intensive, this is the best method of dose assessment following acute exposures.
- consultation with experts in radiation accident management

[5] Collect vomitus in the first few days for later analysis.

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For More Help

Technical assistance can be obtained from the Radiation Emergency Assistance Center/Training Site (REAC/TS) at (865) 576-3131 (M-F, 8 am to 4:30 pm EST) or (865) 576-1005 (after hours), or on their web site at www.orau.gov/reacts, and the Medical Radiobiology Advisory Team (MRAT) at (301) 295-0316.

Also, more information can be obtained from the CDC Health Alert Network at www.bt.cdc.gov or by calling (800) 311-3435.

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For more information, visit www.bt.cdc.gov/radiation, or call CDC at
800-CDC-INFO (English and Spanish) or 888-232-6348 (TTY).

FACT SHEET

Cutaneous Radiation Injury: Fact Sheet for Physicians

Injury to the skin and underlying tissues from acute exposure to a large external dose of radiation is referred to as cutaneous radiation injury (CRI). Acute radiation syndrome (ARS)[1] will usually be accompanied by some skin damage; however, CRI can occur without symptoms of ARS. This is especially true with acute exposures to beta radiation or low-energy x-rays, because beta radiation and low-energy x-rays are less penetrating and less likely to damage internal organs than gamma radiation is. CRI can occur with radiation doses as low as 2 Gray (Gy) or 200 rads2 and the severity of CRI symptoms will increase with increasing doses. Most cases of CRI have occurred when people inadvertently came in contact with unsecured radiation sources from food irradiators, radiotherapy equipment, or well depth gauges. In addition, cases of CRI have occurred in people who were overexposed to x-radiation from fluoroscopy units.

Early signs and symptoms of CRI are itching, tingling, or a transient erythema or edema without a history of exposure to heat or caustic chemicals. Exposure to radiation can damage the basal cell layer of the skin and result in inflammation, erythema, and dry or moist desquamation. In addition, radiation damage to hair follicles can cause epilation. Transient and inconsistent erythema (associated with itching) can occur within a few hours of exposure and be followed by a latent, symptom-free phase lasting from a few days to several weeks. After the latent phase, intense reddening, blistering, and ulceration of the irradiated site are visible. Depending on the radiation dose, a third and even fourth wave of erythema are possible over the ensuing months or possibly years.

In most cases, healing occurs by regenerative means; however, large radiation doses to the skin can cause permanent hair loss, damaged sebaceous and sweat glands, atrophy, fibrosis, decreased or increased skin pigmentation, and ulceration or necrosis of the exposed tissue.

With CRI, it is important to keep the following things in mind:

- The visible skin effects depend on the magnitude of the dose as well as the depth of penetration of the radiation.
- Unlike the skin lesions caused by chemical or thermal damage, the lesions caused by radiation exposures do not appear for hours to days following exposure, and burns and other skin effects tend to appear in cycles.
- The key treatment issues with CRI are infection and pain management.[3]

See "Acute Radiation Syndrome: A Fact Sheet for Physicians" at http://www.bt.cdc.gov/radiation/arsphysicianfactsheet.asp.

Both the Gray (Gy) and the rad are units of absorbed dose and reflect the amount of energy deposited in a mass of tissue (1 Gy = 100 rads). In this document, the absorbed dose refers to that dose received by at least 10 cm2 of the basal cell layer of the skin. The referenced absorbed dose levels in this document are assumed to be from beta, gamma, or x-radiation. Neutron or proton radiation produces many of the health effects described herein at lower absorbed dose levels.

On occasion a patient might also be contaminated with radioactive material. To address patient decontamination, please go to the following Web site: http://www.orau.gov/reacts/emergency.htm.

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Stages and Grades of CRI

CRI will progress over time in stages and can be categorized by grade, with characteristics of the stages varying by grade of injury, as shown in Table 1. **Appendix A** gives a detailed description of the various skin responses to radiation, and **Appendix B** provides color photographs of examples of some of these responses.

Prodromal stage (within hours of exposure)—This stage is characterized by early erythema (first wave of erythema), heat sensations, and itching that define the exposure area. The duration of this stage is from 1 to 2 days.

Latent stage (1-2 days postexposure)—No injury is evident. Depending on the body part, the larger the dose, the shorter this period will last. The skin of the face, chest, and neck will have a shorter latent stage than will the skin of the palms of the hands or the soles of the feet.

Manifest illness stage (days to weeks postexposure)—The basal layer is repopulated through proliferation of surviving clonogenic cells. This stage begins with main erythema (second wave), a sense of heat, and slight edema, which are often accompanied by increased pigmentation. The symptoms that follow vary from dry desquamation or ulceration to necrosis, depending on the severity of the CRI (see Table 1).

Third wave of erythema (10-16 weeks postexposure, especially after beta exposure)—The exposed person experiences late erythema, injury to blood vessels, edema, and increasing pain. A distinct bluish color of the skin can be observed. Epilation may subside, but new ulcers, dermal necrosis, and dermal atrophy (and thinning of the derm is layer) are possible.

Late effects (months to years postexposure; threshold dose ~10 Gy or 1000 rads)—Symptoms can vary from slight dermal atrophy (or thinning of dermis layer) to constant ulcer recurrence, dermal necrosis, and deformity. Possible effects include occlusion of small blood vessels with subsequent disturbances in the blood supply (telangiectasia); destruction of the lymphatic network; regional lymphostasis; and increasing invasive fibrosis, keratosis, vasculitis, and subcutaneous sclerosis of the connective tissue. Pigmentary changes and pain are often present. Skin cancer is possible in subsequent years.

Recovery (months to years)

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Table 1. Grades of cutaneous radiation injury

	Skin dose*	Prodromal stage	Latent stage	Manifest illness stage	Third wave of erythemaf	Recovery	Late effects
I	> 2 Gy (200 rads)‡	1-2 days postexposure or not seen	no injury evident for 2-5 weeks postexposure§	• 2 – 5 weeks postexposure, lasting 20-30 days: redness of skin, slight edema, possible increased pigmentation • 6-7 weeks postexposure, dry desquamation	not seen	complete healing expected 28-40 days after dry desquamation (3-6 months postexposure)	• possible slight skin atrophy • possible skin cancer decades after exposure
II	>15Gy (1500 rads)	6-24 hours postexposure with immediate sensation of heat lasting 1-2 days	no injury evident for 1-3 weeks postexposure	• 1-3 weeks postexposure; redness of skin, sense of heat, edema, skin may turn brown • 5-6 weeks postexposure, edema of subcutaneous tissues and blisters with moist desquamation • possible epithelialization later	• 10-16 weeks postexposure, injury of blood vessels, edema, and increasing pain • epilation may subside, but new ulcers and necrotic changes are possible	healing depends on size of injury and the possibility of more cycles of erythema	• possible skin atrophy or ulcer recurrence • possible telangiectasia (up to 10 years postexposure) • possible skin cancer decades after exposure

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Cutaneous Radiation Injury: Fact Sheet for Physicians
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Grade	Skin dose*	Prodromal stage	Latent stage	Manifest illness stage	Third wave of erythema†	Recovery	Late effects
III	> 40 Gy (4000 rads)	4-24 hours	none or less than 2 weeks	• 1-2 weeks postexposure: redness of skin, blisters, sense of heat, slight edema, possible increased pigmentation • followed by erosions and ulcerations as well as severe pain	• 10-16 weeks	can involve ulcers that are extremely difficult to treat and that can require months to years to heal fully	• possible skin atrophy, depigmentation, constant ulcer recurrence, or deformity • possible occlusion of small vessels with subsequent disturbances in the blood supply, destruction of the lymphatic network, regional lymphostasis, and increasing fibrosis and sclerosis of the connective tissue • possible telangiectasia • possible skin cancer decades after exposure

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Grade	Skin dose*	Prodromal stage	Latent stage	Manifest illness stage	Third wave of erythema†	Recovery	Late effects
IV	> 550 Gy (55,000 rads)	Occurs minutes to hours	none	• 1-4 days postexposure accompanied by blisters • early ischemia (tissue turns white, then dark blue or black with substantial pain) in most severe cases • tissue becomes necrotic within 2 weeks following exposure, accompanied by substantial pain	does not occur due to necrosis of skin in the affected area	recovery possible following amputation of severely affected areas and possible skin grafts	• continued plastic surgery may be required over several years • possible skin cancer decades after exposure

*Absorbed dose to at least 10 cm2 of the basal cell layer of the skin
†Especially with beta exposure
‡The Gray (Gy) is a unit of absorbed dose and reflects an amount of energy deposited in a mass of tissue (1 Gy = 100 rads). §Skin of the face, chest, and neck will have a shorter latent phase than the skin of the palms of the hands and the skin of the feet.

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Patient Management

Diagnosis

The signs and symptoms of CRI are as follows:

- Intensely painful burn-like skin injuries (including itching, tingling, erythema, or edema) without a history of exposure to heat or caustic chemicals
  Note: Erythema will not be seen for hours to days following exposure, and its appearance is cyclic.
- Epilation
- A tendency to bleed
- Possible signs and symptoms of ARS

As mentioned previously, local injuries to the skin from acute radiation exposure evolve slowly over time, and symptoms may not manifest for days to weeks after exposure. Consider CRI in the differential diagnosis if the patient presents with a skin lesion without a history of chemical or thermal burn, insect bite, or skin disease or allergy. If the patient gives a history of possible radiation exposure (such as from a radiography source, x-ray device, or accelerator) or a history of finding and handling an unknown metallic object, note the presence of any of the following: erythema, blistering, dry or wet desquamation, epilation, ulceration.

Regarding lesions associated with CRI be aware that,

- days to weeks may pass before lesions appear;
- unless patients are symptomatic, they will not require emergency care; and
- lesions can be debilitating and life threatening after several weeks.

Medical follow-up is essential, and victims should be cautioned to avoid trauma to the involved areas.

Initial Treatment

Localized injuries should be treated symptomatically as they occur, and radiation injury experts should be consulted for detailed information. Such information can be obtained from the Radiation Emergency Assistance Center/Training Site (REAC/TS) at www.orau.gov/reacts/ or (865) 576-1005.

As with ARS, if the patient also has other trauma, wounds should be closed, burns covered, fractures reduced, surgical stabilization performed, and definitive treatment given within the first 48 hours after injury. After 48 hours, surgical interventions should be delayed until hematopoietic recovery has occurred.

A baseline CBC and differential should be taken and repeated in 24 hours. Because cutaneous radiation injury is cyclic, areas of early erythema should be noted and recorded. These areas should also be sketched and photographed, if possible, ensuring that the date and time are recorded. The following should be initiated as indicated:

- Supportive care in a clean environment (a burn unit if one is available)
- Prevention and treatment of infections
- Use of the following:
  - o Medications to reduce inflammation, inhibit protealysis, relieve pain, stimulate regeneration, and improve circulation o Anticoagulant agents for widespread and deep injury
- Pain management
- Psychological support

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Recommendations for Treatment by Stage

The following recommendations for treatment by stage of the illness were obtained by summarizing recommendations from Ricks et al. (226) and Gusev et al. (231), but they do not represent official recommendations of CDC.

Prodromal Stage—Use antihistamines and topical antipruriginous preparations, which act against itch and also might prevent or attenuate initiation of the cycle that leads to the manifestation stage. Anti-inflammatory medications such as corticosteroids and topical creams, as well as slight sedatives, may prove useful.
Latent Stage—Continue anti-inflammatory medications and sedatives. At midstage, use proteolysis inhibitors, such as Gordox®.
Manifestation Stage—Use repeated swabs, antibiotic prophylaxis, and anti-inflammatory medications, such asLioxasol®, to reduce bacterial, fungal, and viral infections
o Apply topical ointments containing corticosteroids along with locally acting antibiotics and vitamins.
o Stimulate regeneration of DNA by using Lioxasol® and later, when regeneration has started, biogenic drugs, such as Actovegin® and Solcoseril®. o Stimulate blood supply in third or fourth week using Pentoxifylline® (contraindicated for patients with atherosclerotic heart disease).
o Puncture blisters if they are sterile, but do not remove them as long as they are intact, o Stay alert for wound infection. Antibiotic therapy should be considered according to the individual patient's condition, o Treat pain according to the individual patient's condition. Pain relief is very difficult and is the most demanding part of the therapeutic process, o Debride areas of necrosis thoroughly but cautiously.

Treatment of Late Effects

After immediate treatment of radiation injury, an often long and painful process of healing will ensue. The most important concerns are the following:

- Pain management
- Fibrosis or late ulcers
  Note: Use of medication to stimulate vascularization, inhibit infection, and reduce fibrosis may be effective Examples include Pentoxifylline®, vitamin E, and interferon gamma. Otherwise, surgery may be required.
- Necrosis
- Plastic/reconstructive surgery
  Note: Surgical treatment is common. It is most effective if performed early in the treatment process. Full-thickness graft and microsurgery techniques usually provide the best results.
- Psychological effects, such as posttraumatic stress disorder
- Possibility of increased risk of skin cancer later in life

For More Assistance

Technical assistance can be obtained from the Radiation Emergency Assistance Center/Training Site (REAC/TS) at (865) 576-3131 (M-F, 8 AM to 4:30 PM EST) or (865) 576-1005 (after hours), or at http://www.orau.gov/reacts/, and from the Medical Radiobiology Advisory Team (MRAT) at (301) 295-0316.

Also, more information can be obtained from the CDC Health Alert Network at http://www.bt.cdc.gov/HAN/ or 1-800-311-3435.

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Appendix A: Responses of the Skin to Radiation

Acute epidermal necrosis (time of onset: < 10 days postexposure; threshold dose: ~550 Gy or 55,000 rads)—Interphase death of postmitotic keratinocytes in the upper visible layers of the epidermis (may occur with high-dose, low-energy beta irradiation)

Acute ulceration (time of onset: < 14 days postexposure; threshold dose: ~20 Gy or 2000 rads)—Early loss of the epidermis—and to a varying degree, deeper dermal tissue—that results from the death of fibroblasts and endothelial cells in interphase

Dermal atrophy (time of onset: > 26 weeks postexposure; threshold dose: ~10 Gy or 1000 rads)—Thinning of the dermal tissues associated with the contraction of the previously irradiated area

Dermal necrosis (time of onset > 10 weeks postexposure; threshold dose: ~20 Gy or 2000 rads)—Necrosis of the dermal tissues as a consequence of vascular insufficiency

Dry desquamation (time of onset: 3-6 weeks postexposure; threshold dose: ~8 Gy or 800 rads)—Atypical keratinization of the skin caused by the reduction in the number of clonogenic cells within the basal layer of the epidermis

Early transient erythema (time of onset: within hours of exposure; threshold dose: ~2 Gray [Gy] or 200 rads)—Inflammation of the skin caused by activation of a proteolytic enzyme that increases the permeability of the capillaries

Epilation (time of onset: 14-21 days; threshold dose: ~3 Gy or 300 rads)—Hair loss caused by the depletion of matrix cells in the hair follicles

Late erythema (time of onset: 8-20 weeks postexposure; threshold dose: ~20 Gy or 2000 rads)—Inflammation of the skin caused by injury of blood vessels. Edema and impaired lymphatic clearance precede a measured reduction in blood flow.

Invasive fibrosis (time of onset: months to years postexposure; threshold dose: ~20 Gy or 2000 rads)—Method of healing associated with acute ulceration, secondary ulceration, and dermal necrosis that leadsto scar tissue formation

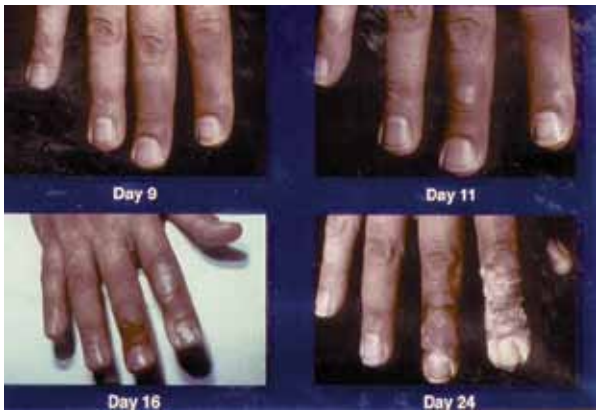
Main erythema (time of onset: days to weeks postexposure; threshold dose: ~3 Gy or 300 rads)—Inflammation of the skin caused by hyperaemia of the basal cells and subsequent epidermal hypoplasia (see photos 1 and 2)

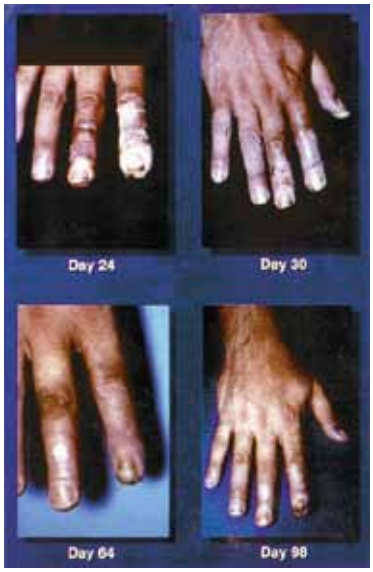
Moist desquamation (time of onset: 4-6 weeks postexposure; threshold dose: ~15 Gy or 1500 rads)—Loss of the epidermis caused by sterilization of a high proportion of clonogenic cells within the basal layer of the epidermis

Secondary ulceration (time of onset: > 6 weeks postexposure; threshold dose: ~15 Gy or 1500 rads)—
Secondary damage to the dermis as a consequence of dehydration and infection when moist desquamation is severe and protracted because of reproductive sterilization of the vast majority of the clonogenic cells in the irradiated area

Telangiectasia (time of onset: > 52 weeks postexposure; threshold dose for moderate severity at 5 years: ~40 Gy or 4000 rads)—
Atypical dilation of the superficial dermal capillaries

Appendix B: Images





Figures 1 & 2. Erythema. These photos display the progression of erythema in a patient involved in an x-ray diffraction accident, 9 days to 96 days postexposure. The day following the exposure (not shown), the patient displayed only mild diffuse swelling and erythema of the fingertips. On day 9, punctuate lesions resembling telangiectasias were noted in the subungal region of the right index finger, and on day 11, blisters began to appear. Desquamation continued for several weeks. The patient developed cellulitis in the right thumb approximately 2 years following exposure. The area of the right fingertip and nail continued to cause the patient great pain when even minor trauma occurred to the fingertip, and he required occasional oral narcotic analgesics to manage this pain. He continued to experience intense pain resulting from minor trauma to the affected areas for as long as 4 years postexposure.

(photos courtesy of Gusev IA and reprinted with permission)

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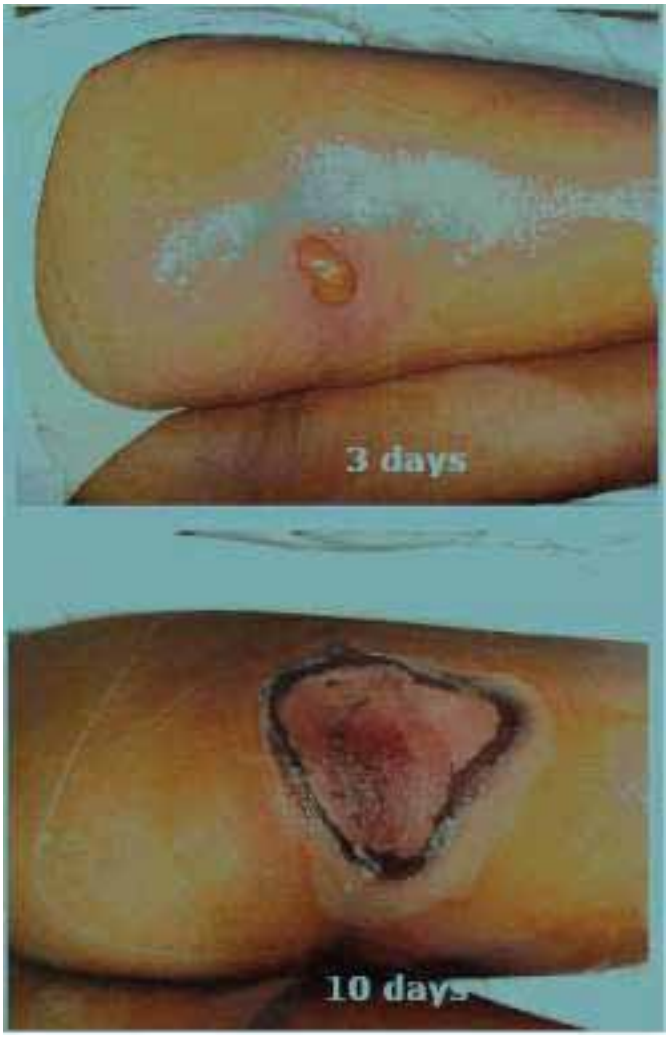

(photos courtesy of Ricks RC and reprinted with permission)

Figures 3 & 4.Acute ulceration. These photos show acute ulceration in a Peruvian patient who inadvertently placed a 26-Ci (0.962-TBq) irridiun-192 (^{1} 9^{2}Ir) source in his back pocket, 3 days and 10 days postexposure. The source remained in the patient's pocket for approximately 6.5 hours, at which time he complained to his wife about pain in his posterior right thigh. He sought medical advice and was told he probably had been bitten by an insect. In the meantime, his wife sat on the patient's pants (her case appears on the next page) while breastfeeding the couple's 1^{1}/2-year-old child. The source was recovered several hours later by nuclear regulatory authorities, and the patient was transported to Lima for treatment. This patient exhibited a drastic reduction in lymphocyte count by day 3 postexposure, and a 4-by-4-cm lesion appeared on day 4. Eventually he suffered with a massive ulceration and necrosis of the site with infection, and his right leg was amputated. Grade II and III CRI was also evident on his hands, left leg, and perineum, but he survived and returned to his family.

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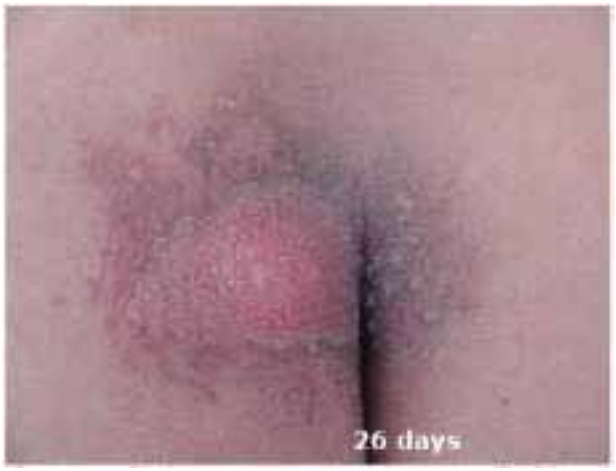

Figure 5.Moist desquamation. This patient is the wife of the previous case study, 26 days postexposure. She was exposed to the ^{192}Ir source when she sat on her husband's pants (still containing the source) for approximately 20 minutes after he had changed clothes that evening.

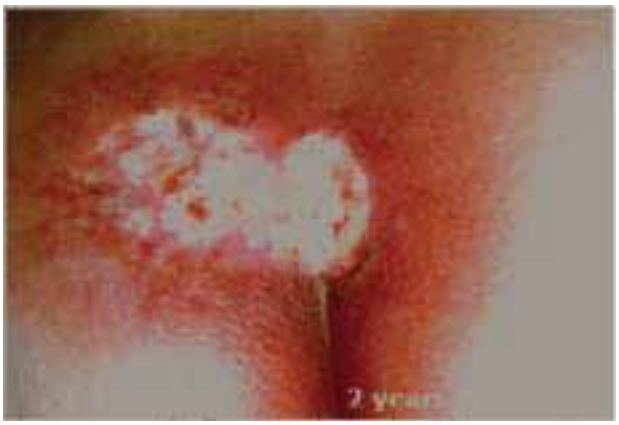

Figure 6.Necrosis, fibrosis, and telangiectasia. Same patient, 2 years following exposure, (photos courtesy of Ricks RC and reprinted with permission)

For more information, visit www.bt.cdc.gov/radiation, or call CDC at 800-CDC-INFO (English and Spanish) or 888-232-6348 (TTY).

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