BIOTERRORISM & INFECTIOUS DISEASE MANUAL FOR CLINICIANS

2006

Yolo County Health Department

WOODLAND, CALIFORNIA 95695
(530) 666-8645 (24/7)
(530) 669-1549 fax

Bette G. Hinton, MD, MPH, Health Officer

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County of Yolo

HEALTH DEPARTMENT

Bette G. Hinton, M.D.
Director – Health Officer

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March 2006

To: All Yolo County Health Care Providers

From: Bette G. Hinton, M.D., M.P.H.

The Yolo County Health Department has updated the *Bioterrorism & Infectious Disease Manual for Clinicians 2006*. This reference book is being distributed to hospitals, clinics and private physicians as a resource in the event of a biological terrorist attack or other public health emergency, such as pandemic influenza. Included in this updated version are sections on emergency preparedness, infection control, avian influenza, chemical agents and radiologic emergencies.

Primary health care providers may be the first to encounter victims of a public health emergency and are encouraged to remain on the alert for **unusual cases** or **unusual clusters** of illness. The occurrence of even a single unusual case of infection that is suspicious or not endemic to our region should be reported immediately 24/7 to:

Yolo County Health Department

(530) 666-8645

Additional information is available at the following web sites:

- Yolo County Health Department: ***www.yolohealth.org***
- California DHS, Emergency Preparedness Office: ***www.dhs.ca.gov/epo/***
- Centers for Disease Control and Prevention (CDC): ***www.bt.cdc.gov***
- Pandemic influenza information: ***www.PandemicFlu.gov***

This manual is available online at ***www.yolohealth.org***. Health information is also available to the public through the California Office of Emergency Services toll-free phone: 1-800-550-5234.

Please contact the Yolo County Health Department if you have further questions or concerns.

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INTRODUCTION

Health care providers will be the first to recognize and respond to an emerging infectious disease or bioterrorism 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.**

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 weapons into three categories. The focus of this manual is on "Category A" agents. Ricin is included due to reports of terrorist interest in this agent. Avian influenza is included due to the possibility of an avian influenza pandemic. Chemical and radiologic sections have also been added for reference.

This manual is intended to serve as a resource and guide for clinical personnel regarding various aspects of large-scale biological, chemical, and radiologic events. Use of this guide is expected to strengthen surveillance for and response to such public health emergencies.

An electronic copy of this guide and updates regarding public health emergency preparedness are available at:

www.yolohealth.org

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CONTACT INFORMATION & RESOURCES

YOLO COUNTY HEALTH DEPARTMENT

☎ (530) 666-8645 main number

🖷 (530) 669-1549 fax

Yolo County Health Department
10 Cottonwood St. (*after 1/1/07 address will change to* 137 N. Cottonwood St.)
Woodland, CA 95695

www.yolohealth.org

INTERNET RESOURCES:

PUBLIC HEALTH EMERGENCY PREPAREDNESS & RESPONSE

Yolo County
www.yolocounty.org

CDC Bioterrorism Site
www.bt.cdc.gov

California Hospital Bioterrorism Response Planning Guide
www.emsa.cahwnet.gov/dms2/ca_hosp_guide.pdf

APIC
www.apic.org

Red Cross
www.redcross.org

US HHS Pandemic Flu Site
www.PandemicFlu.gov

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ACKNOWLEDGEMENTS

The content and design of this manual owes much to manuals developed by the San Francisco Department of Public Health and the Los Angeles County Public Health Department. The Yolo County Health Department would like to acknowledge their outstanding work and thank these agencies for sharing materials and giving the Yolo County Health Department permission to reproduce their materials.

References:

San Francisco Department of Public Health, *Infectious Disease Emergencies: A Preparedness And Response Guide for San Francisco Clinicians*, 2005.

Los Angeles County Public Health Department, *Terrorism Agent Information and Treatment Guidelines for Hospitals and Clinicians,* 2003.

California Department of Health Services, *Surveillance and Epidemiologic Response Plan,* December 2001.

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 2001.

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.

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DISEASE REPORTING

There are over 80 legally reportable diseases and conditions in California that must be reported by health care providers to the local Health Department.

Physicians, veterinarians, podiatrists, nurses, nurse practitioners, nurse midwives, school nurses, infection control practitioners, physician assistants, dentists, coroners and medical examiners are all subject to disease reporting regulations. The requirement for laboratories to report is limited to relatively few diseases and does not replace a health care 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. (Title 17, California Code of Regulations, §2500). Refer to the following pages for a complete listing of reportable conditions and regulations.

COMMUNICABLE DISEASE REPORTING

Urgent Reports 24/7

☎ (530) 666-8645

After hours, you will be directed to County Communications.

Non-Urgent Reports

☎ (530) 666-8645
🖷 (530) 669-1549 fax
Woodland, CA 95695

Business hours: Mon - Fri 8 am - 5 pm

HOW THE HEALTH DEPARTMENT RESPONDS TO INFECTIOUS DISEASE REPORTS…

✓ INVESTIGATION

- **Case Investigation.** Interview cases and clinicians to identify risk factors and other potential contacts. Evaluate patients/contacts in sensitive occupations or settings that may pose a public health concern (e.g. food handlers, daycare attendees, health care workers).
- **Source Investigation.** Conduct an epidemiologic investigation to identify the source of infection and how it is being spread.
- **Lab Testing.** Provide guidance on obtaining lab tests to confirm diagnosis. Facilitate approval for specialized tests performed at city, state, or federal public health labs.

✓ INFECTION CONTROL

- **Recommendations.** Work with infection control practitioners to recommend measures to control and prevent the spread of disease in health care settings.
- **Information & Education.** Provide information to cases, contacts, and the general public to prevent and control the spread of disease in community settings. In the event of an infectious disease emergency, provide continued infection control guidance and recommendations.
- **State & National Notification.** Coordinate notification of state and national health officials and law enforcement, as necessary.

✓ TREATMENT RECOMMENDATIONS

Post-exposure & Preventive Treatment. Assess the need for and recommend preventive treatments such as antibiotics and vaccines. In case of mass exposure to a treatable infectious agent, activate the local system for providing mass treatment and/or prophylaxis.

✓ COMMUNICATION WITH CLINICIANS

- **Health Alerts.** Send Health Alerts, Advisories, and Updates to clinicians regarding situations of public health concern.
- **Analysis of Surveillance Data.** Analyze and disseminate public health surveillance data to clinicians and the general public.

UNUSUAL CONDITIONS TO REPORT

It is particularly important that suspected emerging infectious diseases and diseases that may result from bioterrorism are rapidly reported. Maintaining an index of suspicion for unusual case of illness and reporting them to the Health Department could save lives. Potentially unusual patterns of disease include:

1. **Multiple similarly presenting cases, especially if these are geographically associated or closely clustered in time**
   Example: persons who attended the same event or who work in the same building

2. **An increase in a common syndrome occurring out of season**
   Example: many cases of influenza-like illness in summer

3. **An unusual age distribution for common diseases**
   Example: many cases of chickenpox-like illness among adult patients who would be expected to be immune to varicella

4. **Serious, unexpected, unexplained acute illness with atypical host characteristics**
   Examples: severe illness in a young patient without immunologic defects, underlying illness, recent travel or other exposure to a potential source of infection

Important diseases and conditions with significant public health implications are shown in the table below. Due to their rarity, these diseases and conditions may not be immediately recognizable. However, maintaining a reasonable index of suspicion and reporting unusual conditions could assist in treating patients and safeguarding the public. Please refer to the following page for a complete list of all reportable diseases.

IMMEDIATE NOTIFICATION TO

YOLO COUNTY HEALTH DEPT REQUIRED (within ONE HOUR)…

- Anthrax*
- Botulism*
- Brucellosis*
- Cholera
- Dengue
- Diphtheria
- *E. coli* O157/H7 infection
- Hantavirus infection
- Hemolytic Uremic Syndrome
- Meningococcal infections
- Plague*
- Rabies
- Seafood poisoning *(i.e., Ciguatera fish poisoning, Domoic Acid poisoning, Scombroid fish poisoning)*
- Smallpox*
- Tularemia*
- Varicella (death or hospitalization only)
- Viral Hemorrhagic Fevers* *(e.g., Crimean-Congo, Ebola, Marburg, Yellow Fever)*

** Potential bioterror agents*

† *MMWR. 2001 Oct 19;50(41):893-7.*

FREQUENTLY ASKED QUESTIONS (FAQ)

Why report?
Early reporting of infectious disease may prevent further illness and death. The Health Department acts on reports to investigate outbreaks of infectious diseases and coordinate disease prevention measures.

Reporting also documents the burden of disease in the community and, for some diseases (*e.g.,* HIV, TB and STDs), directly determines the federal and state dollars communities receive for treatment and prevention.

Who is responsible for reporting?
According to Title 17, California Code of Regulations, **all health care providers** are required to notify their local Health Department about reportable communicable diseases. Failure to report a reportable disease may result in citation and fine. Labs are not required to report most reportable conditions, therefore do not rely on labs to report illness. See the following pages for more about specific regulations.

How do I report?
Most diseases can be reported by completing and submitting the top half of the Confidential Morbidity Report form (CMR) to the Health Department. Some diseases require immediate notification (refer to back of the CMR form). Secure web-based reporting will be an option in the future. The Health Department is your liaison to the State health department and CDC. In an emergency, reports may be received 24/7 by phone, by calling (530) 666-8645.

How does the Health Department protect patient confidentiality?
The Health Department has a long history of maintaining confidential vital records. Faxed disease reports are received on a dedicated fax in a secure area. HIPAA does not preclude reporting. The Health Department stores reports consistent with HIPAA until they may be destroyed.

How much time does it take to report a disease?
Reporting a disease should take no more than 2-3 minutes. The Health Department suggests that one person per facility be designated to make sure disease reporting occurs as mandated.

What if my patient doesn't live in Yolo County?
As with all other California counties, Yolo County asks that providers report to the local Health Department where their facility is located. Reports for non-county residents are immediately forwarded to the appropriate health authority.

Should I wait for lab confirmation before I report a suspected case of a highly infectious communicable disease (*e.g.,* measles, tuberculosis)?
No! The California Code of Regulations clearly states that health care providers should report all cases of serious illness as soon as that illness is suspected.

DISCLOSURES TO PUBLIC HEALTH AGENCIES UNDER THE HIPAA PRIVACY POLICY

Covered entities may disclose protected health information (PHI), without individual authorization, to a public health authority legally authorized to collect or receive the information for the purpose of preventing or controlling disease, injury or disability 45 CFR 164.512(b). Further, the Privacy Rule permits covered entities to make disclosures for public health purposes.

Without individual authorization, a covered entity may disclose PHI to a public health authority (or an entity working under a grant of authority) that is legally authorized to collect or receive the information for the purposes of preventing or controlling disease, injury, or disability including, but not limited to:

- Reporting of disease, injury, and vital events (e.g., birth or death)
- Conducting public health surveillance, investigations, and interventions

PHI may also be disclosed without individual authority to:

- Report child abuse or neglect to a public health or other government authority legally authorized to receive such reports
- A person subject to jurisdiction of the Food and Drug Administration (FDA) concerning the quality, safety, or effectiveness of an FDA-related product or activity for which that person has responsibility
- A person who may have been exposed to a communicable disease or may be at risk for contracting or spreading a disease or condition, when legally authorized to notify the person as necessary to conduct a public health intervention or investigation
- An individual's employer, under certain circumstances and conditions, as needed for the employer to meet the requirements of the Occupational Safety and Health Administration, Mine Safety, and Health Administration or similar state law.

REPORTING REGULATIONS

REPORTABLE DISEASES & CONDITIONS

Title 17. California Code of Regulations §2500

§2500 (b)

It shall be the duty of every health care provider, knowing of or in attendance on a case or suspected case of any of the diseases or conditions listed [see list and deadlines on following page], to report to the local health officer for the jurisdiction where the patient resides. Where no health care provider is in attendance, any individual having knowledge of a person who is suspected to be suffering from one of the diseases or conditions listed may make such a report to the local health officer for the jurisdiction where the patient resides.

§2500 (c)

The administrator of each health facility, clinic or other setting where more than one health care provider may know of a case, a suspected case or an outbreak of disease within the facility shall establish and be responsible for administrative procedures to assure that reports are made to the local health officer.

§2500 (a)(14)

'Health care provider' means a physician, surgeon, veterinarian, podiatrist, nurse practitioner, physician assistant, registered nurse, nurse midwife, school nurse, infection control practitioner, medical examiner, coroner, or dentist.

Health and Safety Code §105200

Failure to report is a misdemeanor and is citable offense under the Medical Board of California's Citation and Fine Program (Title 16, CCR, §1364).

PESTICIDE-RELATED ILLNESSES

Health and Safety Code §105200

Any physician who knows, or who has reason to believe, that a patient has a pesticide-related illness or condition must report the case to the local Health Department by telephone within 24 hours. This reporting requirement includes all types of pesticide-related illnesses: skin and eye injuries, systemic poisonings, suicides, homicides, home cases, and occupational cases. Failure to comply with the foregoing reporting requirement renders the physician liable for a civil penalty of $250.00. For occupational exposure there is an additional requirement to submit the "Doctor's First Report of Occupational Injury or Illness" to the Health Department within seven days.

CANCER

Under state law (Chapter 841. Statutes of 1985) invasive or *in situ* malignancies (including CIN III of the cervix), except basal and squamous cell carcinomas of the skin, diagnosed on or after June 1, 1988 which have not been admitted to a California hospital for diagnosis or treatment of cancer, and who will not be referred to a California hospital for diagnosis or treatment must be reported to the local Health Department on a Confidential Morbidity Report Form (CMR).

Summarized/excerpted from California Law (www.leginfo.ca.gov)

DISEASE REPORTING

YOLO COUNTY HEALTH DEPARTMENT

Last Updated March 2006

Physicians and health care providers must report the following conditions.
Suspected, lab-confirmed, and/or clinical diagnoses are reportable within specified time intervals.
Reporting enables appropriate public health interventions.

Report Diseases by Phone at (530) 666-8645

Report Diseases by Fax at (530) 669-1549

Report IMMEDIATELY by Phone:

Animal Bites
Anthrax
Avian Influenza (H5N1)
Botulism
Brucellosis
Cholera
Dengue
Diphtheria
E. coli O157:H7 Infection
Foodborne Illness
Hantavirus Infection
Hemolytic Uremic Syndrome
Meningococcal Infection
Plague
Rabies
SARS
Seafood poisoning
(Domoic Acid, Ciguatera, Paralytic Shellfish, Scombroid,)
Smallpox
Tularemia
Varicella (death/hosp only)
Viral Hemorrhagic Fevers
Yellow Fever
Outbreaks of any Disease
Any Unusual Disease

PHONE Or FAX Within ONE WORKING DAY:

Amebiasis
Anisakiasis
Babesiosis
Campylobacteriosis
Colorado Tick Fever
Conjunctivitis (newborn, acute infectious)
Cryptosporidiosis
Encephalitis (infectious)
Haemophilus influenzae (invasive)
Hepatitis A
Listeriosis
Lymphocytic Choriomeningitis
Malaria
Measles
Meningitis
Pertussis
Pesticide-related Illness
Poliomyelitis
Psittacosis
Q Fever
Relapsing Fever
Salmonellosis
Shigellosis
Streptococcal Infection (outbreaks, food handlers, dairy workers)
Swimmer's itch (Schistosomal dermatitis)
Syphilis
Trichinosis
Tuberculosis
Typhoid fever (cases & carrier)
Vibrio Infection
West Nile Virus Infection
Yersiniosis

ANY FOOD- OR WATER-BORNE ILLNESS

PHONE, FAX, OR MAIL WITHIN ONE WEEK:

AIDS/HIV
Alzheimer's Disease
Cancer (not basal/squamous cell)
Chancroid
Chlamydial Infection
Coccidioidomycosis
Cysticercosis
Echinococcosis
Ehrlichiosis
Giardiasis
Gonococcal Infection
Hepatitis B, C, D, other
Influenza (lab confirmed)
Kawasaki Syndrome
Lapse of Consciousness
Legionellosis
Leprosy
Leptospirosis
Lyme Disease
Mumps
NGU
PID
Reye Syndrome
Rheumatic Fever, acute
Rocky Mountain Spotted Fever
Rubella
Rubella Syndrome, Congenital
Tetanus
Toxic Shock Syndrome
Toxoplasmosis
Typhus Fever

Monday – Friday 8 AM to 5 PM, call:
Yolo County Health Department, Public Health Nursing
10 Cottonwood *(after1/1/07, 137 N. Cottonwood)*, Woodland, CA 95695 (530) 666-8645

CONFIDENTIAL MORBIDITY REPORT

NOTE: For STD, Hepatitis, or TB, complete appropriate section below. Special reporting requirements and reportable diseases on back.

DISEASE BEING REPORTED: _____

Patient's Last Name

Social Security Number ___ — ___ — ___

First Name/Middle Name (or initial)

Birth Date Month Day Year

Age

Address: Number, Street

Apt./Unit Number

City/Town

State

ZIP Code

Area Code **Home Telephone** ___ — ___ — ___

Gender M F

Pregnant? Y N Unk

Estimated Delivery Date Month Day Year

Area Code **Work Telephone** ___ — ___ — ___

Patient's Occupation/Setting

❒ Food service ❒ Day care ❒ Correctional facility

❒ Health care ❒ School ❒ Other _____

Ethnicity (check [✓] one)

❒ Hispanic/Latino

❒ Non-Hispanic/Non-Latino

Race (check [✓] all that apply)

❒ African-American/Black

❒ Asian:

- ❒ Asian-Indian
- ❒ Cambodian
- ❒ Chinese
- ❒ Hmong
- ❒ Japanese
- ❒ Korean
- ❒ Laotian
- ❒ Thai
- ❒ Vietnamese
- ❒ Other: _____

❒ Pacific Islander:

- ❒ Filipino
- ❒ Guamanian
- ❒ Hawaiian
- ❒ Samoan
- ❒ Other: _____

❒ Native American/Alaskan Native

❒ White: _____

❒ Other: _____

DATE OF ONSET Month Day Year

DATE DIAGNOSED Month Day Year

DATE OF DEATH Month Day Year

Reporting Health Care Provider

Reporting Health Care Facility

Address

City **State** **ZIP Code**

Telephone Number ( )

Fax ( )

Submitted by

Date Submitted (Month/Day/Year)

REPORT TO

YOLO COUNTY HEALTH DEPARTMENT

10 Cottonwood Street
Woodland, CA 95695

FAX: (530) 669 - 1549
PHONE: (530) 666 - 8645 or
(916) 375 - 6380

(Obtain additional forms from your local health department.)

SEXUALLY TRANSMITTED DISEASES (STD)

Syphilis

- ❒ Primary (lesion present)
- ❒ Secondary
- ❒ Early latent < 1 year
- ❒ Latent (unknown duration)
- ❒ Late latent > 1 year
- ❒ Late (tertiary)
- ❒ Congenital
- ❒ **Neurosyphilis**

Syphilis Test Results

- ❒ RPR Titer: _____
- ❒ VDRL Titer: _____
- ❒ FTA/MHA: ❒ Pos ❒ Neg
- ❒ CSF-VDRL: ❒ Pos ❒ Neg
- ❒ Other: _____

Gonorrhea

- ❒ Urethral/Cervical
- ❒ PID
- ❒ Other: _____

Chlamydia

- ❒ Urethral/Cervical
- ❒ PID
- ❒ Other: _____

- ❒ **PID (Unknown Etiology)**
- ❒ **Chancroid**
- ❒ **Non-Gonococcal Urethritis**

STD TREATMENT INFORMATION

❒ **Treated (Drugs, Dosage, Route):**

_____

_____

Date Treatment Initiated Month Day Year

❒ **Untreated**

- ❒ Will treat
- ❒ Unable to contact patient
- ❒ Refused treatment
- ❒ Referred to: _____

VIRAL HEPATITIS

		Pos	Neg	Pend	Not Done
❒ **Hep A**	anti-HAV IgM	❒	❒	❒	❒
❒ **Hep B**	HBsAg	❒	❒	❒	❒
❒ **Acute**	anti-HBc	❒	❒	❒	❒
❒ **Chronic**	anti-HBc IgM	❒	❒	❒	❒
	anti-HBs	❒	❒	❒	❒
❒ **Hep C**	anti-HCV	❒	❒	❒	❒
❒ **Acute**	PCR-HCV	❒	❒	❒	❒
❒ **Chronic**					
❒ **Hep D (Delta)**	anti-Delta	❒	❒	❒	❒
❒ **Other:** _____		❒	❒	❒	❒

Suspected Exposure Type

❒ Blood transfusion ❒ Other needle exposure ❒ Sexual contact ❒ Household contact

❒ Child care ❒ Other: _____

TUBERCULOSIS (TB)

Status

- ❒ **Active Disease**
  - ❒ Confirmed
  - ❒ Suspected
- ❒ **Infected, No Disease**
  - ❒ Convertor
  - ❒ Reactor

Site(s)

- ❒ Pulmonary
- ❒ Extra-Pulmonary
- ❒ Both

Mantoux TB Skin Test

Date Performed Month Day Year

Results: _____ mm ❒ Pending ❒ Not Done

Chest X-Ray Month Day Year

Date Performed

❒ Normal ❒ Pending ❒ Not done

❒ Cavitary ❒ Abnormal/Noncavitary

Bacteriology

Date Specimen Collected Month Day Year

Source _____

Smear: ❒ Pos ❒ Neg ❒ Pending ❒ Not done

Culture: ❒ Pos ❒ Neg ❒ Pending ❒ Not done

Other test(s) _____

TB TREATMENT INFORMATION

❒ **Current Treatment**

❒ INH ❒ RIF ❒ PZA

❒ EMB ❒ Other: _____

Date Treatment Initiated Month Day Year

❒ **Untreated**

- ❒ Will treat
- ❒ Unable to contact patient
- ❒ Refused treatment
- ❒ Referred to: _____

REMARKS

Title 17, California Code of Regulations (CCR), §2500, §2593, §2641–2643, and §2800–2812
Reportable Diseases and Conditions*

§2500. REPORTING TO THE LOCAL HEALTH AUTHORITY.

- **§2500(b)** It shall be the duty of every health care provider, knowing of or in attendance on a case or suspected case of any of the diseases or conditions listed below, to report to the local health officer for the jurisdiction where the patient resides. Where no health care provider is in attendance, any individual having knowledge of a person who is suspected to be suffering from one of the diseases or conditions listed below may make such a report to the local health officer for the jurisdiction where the patient resides.
- **§2500(c)** The administrator of each health facility, clinic or other setting where more than one health care provider may know of a case, a suspected case or an outbreak of disease within the facility shall establish and be responsible for administrative procedures to assure that reports are made to the local health officer.
- **§2500(a)(14)** "Health care provider" means a physician and surgeon, a veterinarian, a podiatrist, a nurse practitioner, a physician assistant, a registered nurse, a nurse midwife, a school nurse, an infection control practitioner, a medical examiner, a coroner, or a dentist.

URGENCY REPORTING REQUIREMENTS [17 CCR §2500 (h) (i)]

☎ = Report **immediately** by **telephone** (designated by a ◆ in regulations).
† = Report **immediately** by **telephone** when **two or more cases** or suspected cases of foodborne disease from separate households are suspected to have the same source of illness (designated by a ● in regulations).
FAX ✆ ✉ = Report by **FAX, telephone, or mail within one working day of identification** (designated by a + in regulations).
= All other diseases/conditions should be reported by FAX, telephone, or mail within seven calendar days of identification.

REPORTABLE COMMUNICABLE DISEASES §2500(j)(1), §2641–2643

Acquired Immune Deficiency Syndrome (AIDS)
(HIV infection only: see "Human Immunodeficiency Virus")
FAX ✆ ✉ Amebiasis
FAX ✆ ✉ Anisakiasis
☎ Anthrax
FAX ✆ ✉ Babesiosis
☎ Botulism (Infant, Foodborne, Wound)
☎ Brucellosis
FAX ✆ ✉ Campylobacteriosis
Chancroid
Chlamydial Infections
☎ Cholera
☎ Ciguatera Fish Poisoning
Coccidioidomycosis
FAX ✆ ✉ Colorado Tick Fever
FAX ✆ ✉ Conjunctivitis, Acute Infectious of the Newborn, Specify Etiology
FAX ✆ ✉ Cryptosporidiosis
Cysticercosis
☎ Dengue
☎ Diarrhea of the Newborn, Outbreaks
☎ Diphtheria
☎ Domoic Acid Poisoning (Amnesic Shellfish Poisoning)
Echinococcosis (Hydatid Disease)
Ehrlichiosis
FAX ✆ ✉ Encephalitis, Specify Etiology: Viral, Bacterial, Fungal, Parasitic
☎ *Escherichia coli* O157:H7 Infection
† FAX ✆ ✉ Foodborne Disease
Giardiasis
Gonococcal Infections
FAX ✆ ✉ *Haemophilus influenzae* Invasive Disease
☎ Hantavirus Infections
☎ Hemolytic Uremic Syndrome
Hepatitis, Viral
FAX ✆ ✉ Hepatitis A
Hepatitis B (specify acute case or chronic)
Hepatitis C (specify acute case or chronic)
Hepatitis D (Delta)
Hepatitis, other, acute
Human Immunodeficiency Virus (HIV) (§2641–2643): reporting is NON-NAME (see www.dhs.ca.gov/aids)
Kawasaki Syndrome (Mucocutaneous Lymph Node Syndrome)
Legionellosis
Leprosy (Hansen Disease)
Leptospirosis
FAX ✆ ✉ Listeriosis
Lyme Disease
FAX ✆ ✉ Lymphocytic Choriomeningitis
FAX ✆ ✉ Malaria
FAX ✆ ✉ Measles (Rubeola)
FAX ✆ ✉ Meningitis, Specify Etiology: Viral, Bacterial, Fungal, Parasitic
☎ Meningococcal Infections
Mumps
Non-Gonococcal Urethritis (Excluding Laboratory Confirmed Chlamydial Infections)
☎ Paralytic Shellfish Poisoning
Pelvic Inflammatory Disease (PID)
FAX ✆ ✉ Pertussis (Whooping Cough)
☎ Plague, Human or Animal
FAX ✆ ✉ Poliomyelitis, Paralytic
FAX ✆ ✉ Psittacosis
FAX ✆ ✉ Q Fever
☎ Rabies, Human or Animal
FAX ✆ ✉ Relapsing Fever
Reye Syndrome
Rheumatic Fever, Acute
Rocky Mountain Spotted Fever
Rubella (German Measles)
Rubella Syndrome, Congenital
FAX ✆ ✉ Salmonellosis (Other than Typhoid Fever)
☎ Scombroid Fish Poisoning
☎ Severe Acute Respiratory Syndrome (SARS)
FAX ✆ ✉ Shigellosis
☎ Smallpox (Variola)
FAX ✆ ✉ Streptococcal Infections (Outbreaks of Any Type and Individual Cases in Food Handlers and Dairy Workers Only)
FAX ✆ ✉ Swimmer's Itch (Schistosomal Dermatitis)
FAX ✆ ✉ Syphilis
Tetanus
Toxic Shock Syndrome
Toxoplasmosis
FAX ✆ ✉ Trichinosis
FAX ✆ ✉ Tuberculosis
☎ Tularemia
FAX ✆ ✉ Typhoid Fever, Cases and Carriers
Typhus Fever
☎ Varicella (deaths only)
FAX ✆ ✉ *Vibrio* Infections
☎ Viral Hemorrhagic Fevers (e.g., Crimean-Congo, Ebola, Lassa and Marburg viruses)
FAX ✆ ✉ Water-associated Disease
FAX ✆ ✉ West Nile Virus (WNV) Infection
☎ Yellow Fever
FAX ✆ ✉ Yersiniosis
☎ **OCCURRENCE of ANY UNUSUAL DISEASE**
☎ **OUTBREAKS of ANY DISEASE** (Including diseases not listed in §2500). Specify if institutional and/or open community.

REPORTABLE NONCOMMUNICABLE DISEASES AND CONDITIONS §2800–2812 and §2593(b)

Disorders Characterized by Lapses of Consciousness
Cancer (except (1) basal and squamous skin cancer unless occurring on genitalia, and (2) carcinoma in-situ and CIN III of the cervix)
Pesticide-related illness or injury (known or suspected cases)**

LOCALLY REPORTABLE DISEASES (If Applicable):

Influenza (lab-confirmed only)

Varicella (hospitalized cases)

---

* This form is designed for health care providers to report those diseases mandated by Title 17, California Code of Regulations (CCR). Failure to report is a misdemeanor (Health and Safety Code §120295) and is a citable offense under the Medical Board of California's Citation and Fine Program (Title 16, CCR, §1364.10 and 1364.11).

** Failure to report is a citable offense and subject to civil penalty ($250) (Health and Safety Code §105200).

PM 110 (9/05) (Edited 10/05)

CLINICIAN ROLE IN AN EMERGENCY

Time and again, astute health care providers are among the first to recognize, respond to and report a public health emergency.

KEY CLINICIAN ROLES

Recognize an infectious disease emergency.

Action Items

- See "Unusual Conditions to Report" on p. 2 of the Reporting chapter of this manual.
- Review disease chapters and the "Bioterrorism Syndromes" poster to learn how to recognize critical diseases.

Respond appropriately including implementation of infection control measures, initiation of diagnostic testing, and therapy and prophylaxis (if needed).

Action Items

- Familiarize yourself with initial patient management protocols and infection control measures.
- Visit and bookmark the Yolo County website: www.yolohealth.org
- Register to receive Health Alerts from Yolo County Health Department. See instructions in the Appendix of this manual.

Report the incident to response partners.

Action Items

- Keep Health Department contact information and the names and contact information of hospital infection control staff readily available.

Yolo County Disease Reporting

☎ (530) 666-8645 *24/7*
🖷 (530) 669-1549 fax

EMERGENCY TO DO LIST

Initial Steps

- ❑ Implement infection control measures
  - o If patient is in the hospital, notify Infection Control.
- ❑ Notify Yolo County Health Department.
- ❑ Notify your clinical lab and ensure appropriate specimens are obtained for routine and referral testing. Referral testing may be coordinated through the Public Health Lab system.
- ❑ Initiate patient management.
- ❑ If present, request that family and other contacts remain for public health interviews and prophylaxis if needed.
- ❑ Ensure that family and contacts are educated about infection prevention.
- ❑ If family or other close contacts are not present, obtain their contact information to provide to Yolo County Health Department.

Subsequent Steps

- ❑ Follow incident progress and recommendations via Health Alerts and/or website: www.yolohealth.org.
- ❑ Make sure that your family, your staff, and the families of your staff are safe.
- ❑ Keep office open unless advised otherwise.
- ❑ Educate patients about measures to take to prevent exposure and disease.
- ❑ Assess and care for the worried well.

PREPARING FOR INFECTIOUS DISEASE EMERGENCIES

Health care providers are encouraged to be both personally and professionally prepared to respond to a variety of infectious disease emergencies. The following are suggested preparedness activities:

FAMILY PLAN

Ensure that your family is well prepared.

Action Items

- Create and practice a family disaster plan. For more information see the Family Plan guides put out by the Red Cross.
    - Red Cross, Your Family Disaster Plan: www.prepare.org/basic/DisasterPlan.pdf
- Place fully stocked disaster kits in your home and car with a three-day supply of food and water.
    - Red Cross, Emergency supply Kit Guide: www.prepare.org/basic/SuppliesKit.pdf
- Encourage staff to develop and practice family disaster plans.

CLINIC & OFFICE PLAN

Take steps to ensure the safety and well being of your staff. For suggestions and resources, see page 5 of this chapter "Clinic/Office Disaster & Emergency Planning."

Action Items

- Provide personal emergency kits and emergency contact numbers to staff.
- Make a telephone tree to notify staff in an emergency.
- Develop and practice your clinic or office disaster and evacuation plan.
- Know the expected clinic/office roles and responsibilities (including who assists patients and who will account for them when leaving the building).
- Review clinician roles and responsibilities in a community disaster.
- Identify items that should be taken in an evacuation (medicine, backup data, etc.)

EMERGENCY INFORMATION

Know where to obtain reliable Yolo County specific information.

Action Items

- Visit and bookmark the Yolo County Health Department website:

  www.yolohealth.org

- Register to receive our Health Alerts. See instructions in the appendix.
- Note the designated radio stations that will provide emergency information:

  KCTC 1320 AM

  KRAK 1470 AM

  KFBK 1530 AM

PREPARE FOR AN INFECTIOUS DISEASE EMERGENCY

Know the details of infectious disease emergencies.

Action Items

- Know what to report. See the "Reporting" chapter of this manual containing:
  - List of diseases clinicians are legally required to report.
  - List of unusual conditions for which we request reports.
- Review the potential bioterrorism-related syndromes and the biological threat diseases (e.g., anthrax, avian influenza, botulism, brucellosis, plague, smallpox, tularemia, viral hemorrhagic fevers):
  - See the Bioterrorism Syndromes poster.
- Maintain a reasonable index of suspicion.

LEARN HOW TO RESPOND

Know the details about appropriate response.

Action Items

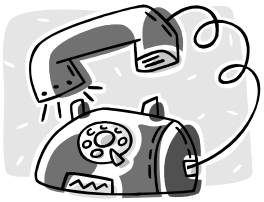
- Practice and refine emergency plans.
- Share this manual with staff and place it in a prominent and easily accessible location.
- Review the "Clinician Role in an Emergency" section of this chapter, which contains a To Do List.
- Review the "Reporting" chapter of this manual.
- Become knowledgeable and train staff on infection control measures. See the "Infection Control" chapter of this manual.

REPORT TO YOLO COUNTY HEALTH DEPARTMENT ON A ROUTINE BASIS

Routinely use components of your response plan. Informing Yolo County Health Department about diagnosed or suspected cases of reportable communicable diseases assists Health Department disease control interventions and improves the ability to communicate with Health Department in emergencies.

Action Items

- Review and post or have easily available:
  - List of diseases clinicians are legally required to report
  - List of unusual conditions for which we request reports.
- Place Yolo County Health Department contact information in Rolodex files and on or near primary phones.



EMERGENCY SERVICE CONTACTS

Yolo County Office of Emergency Services
☎ (530) 666-8930
🖱 www.yolo.com/oes

California Office of Emergency Services
☎ (800) 550-5234 (multiple languages)
(800) 550-5281 (hearing impaired)
🖱 www.oes.ca.gov

PERSONAL OFFICE DISASTER KIT

For the workplace, where you might be confined for several hours, or perhaps overnight, the following supplies are recommended. More information is at: www.redcross.org/services/disaster/beprepared

❑ Flashlight with extra batteries

Use the flashlight to find your way if the power is out. Do not use candles or any other open flame for emergency lighting.

❑ Battery-powered radio

News about the emergency may change rapidly as events unfold. You also will be concerned about family and friends in the area. Radio reports will give information about the areas most affected.

❑ Food

Enough non-perishable food to sustain you for at least one day (three meals) is suggested. Select foods that require no refrigeration, preparation or cooking, and little or no water. The following items are suggested:

- Ready-to-eat canned meals, meats, fruits, and vegetables.
- Canned juices.
- High-energy foods (granola/energy bars, etc.)

❑ Water

Keep at least one gallon of water available, or more if you are on medications that require water or that increase thirst. Store water in plastic containers such as soft drink bottles. Avoid using containers that will decompose or break, such as milk cartons or glass bottles.

❑ Medications

Include usual non-prescription medications that you take, including pain relievers, stomach remedies, etc.

If you use prescription medications, keep at least three-day's supply of these medications at your workplace. Consult with your physician or pharmacist how these medications should be stored, and your employer about storage concerns

❑ First Aid Supplies

If your employer does not provide first aid supplies, have the following essentials:

(20) Adhesive bandages, various sizes.
(1) 5" x 9" sterile dressing.
(1) Conforming roller gauze bandage.
(2) Triangular bandages.
(2) 3 x 3 Sterile gauze pads.
(2) 4 x 4 Sterile gauze pads.
(1) Roll 3" cohesive bandage.
(2) Germicidal hand wipes or waterless alcohol-based hand sanitizer.
(6) Antiseptic wipes.
(2) Pair large medical grade non-latex gloves
Adhesive tape, 2" width.
Anti-bacterial ointment.
Cold pack.
Scissors (small, personal).
Tweezers.
CPR breathing barrier, such as a face shield

❑ Tools and Supplies

- Emergency "space" blanket (Mylar).
- Paper plates and cups, plastic utensils
- Non-electric can opener.
- Personal hygiene items, including a toothbrush, toothpaste, comb, brush, soap, contact lens supplies, and feminine supplies.
- Plastic garbage bags, ties (for personal sanitation uses).
- Include at least one complete change of clothing and footwear, including a long sleeved shirt and long pants, as well as closed-toed shoes or boots.
- If you wear glasses, keep an extra pair with your workplace disaster supplies.

❑ General Information

- Your kit should be adjusted based on your own personal needs.
- Do not include candles, weapons, toxic chemicals, or controlled drugs unless prescribed by a physician.

Excerpted from the American Red Cross Personal Workplace Disaster Supplies Kit

CLINIC/OFFICE DISASTER & EMERGENCY PLANNING

Most health facilities in California (e.g., hospitals, long term care facilities, primary care clinics, adult day care centers) are required by State law to have a plan or program for addressing disasters. Medical offices are required to comply with local business ordinances including building and fire codes. It is also prudent for medical offices to develop disaster plans.

Several organizations have created documents to assist in the development of disaster plans. The California Office of Emergency Services (CA OES) and the California Primary Care Association have developed guidance and templates for clinic disaster plans.* The CDC and Red Cross provide guides for developing business disaster plans.*

Ideally plans should coordinate with neighborhood, local hospital, County and State partners. The Licensing and Certification Division of the California Department of Health Services (CDHS) is available to answer questions regarding disaster plans for CDHS-licensed health care facilities at (916) 552-9365.

SUGGESTED ITEMS TO INCLUDE IN A CLINIC OR OFFICE DISASTER PLAN

- ❑ Purpose of the disaster plan
- ❑ Scope of the disaster plan
- ❑ Plan activation
  - Who can activate the plan
  - Circumstances when the plan should be activated.
- ❑ Disaster plan mission statement
- ❑ Leadership/succession of leadership
- ❑ Delegation of authority
- ❑ Supporting plans and resources
- ❑ Legal authorities, codes and policies
- ❑ Plan administration (e.g., distribution, updates)
- ❑ Staff activation/call down procedures
- ❑ Mutual aid agreements
- ❑ Communication procedures
- ❑ Organization chart
- ❑ Job Action sheets

Specific plans

- ❑ Evacuation plan
- ❑ Transportation plan
- ❑ Medical Management .

* EMERGENCY PLAN RESOURCES

Yolo County Office of Emergency Services

- www.yolo.com/oes

Red Cross

- www.redcross.org, click on *Get Prepared*

California Primary Care Association

- Clinic Disaster Plan Template: www.cpca.org/resources/cepp
- Regulations addressing disaster planning for licensed health care facilities: www.cpca.org/resources/cepp, click on *Appendix U*

California Office of Emergency Services, Clinic Disaster Plan Guide & Templates:

- www.oes.ca.gov, click on *Plans and Publications*, then click *Clinic Disaster Plan Guidance*

CDC Emergency Preparedness For Business

- www.cdc.gov/niosh/topics/prepared

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Yolo County Health Department
Health Alert Network

The Yolo County Health Department (YCHD) periodically sends Health Alerts, Advisories, and Updates to Yolo County clinicians and other public health partners. Health Alerts provide important, timely information on the recognition, diagnosis, management, and reporting of communicable disease threats.

SIGN UP TO RECEIVE HEALTH ALERTS
KEEP YOUR CONTACT INFORMATION UP-TO-DATE

- Fax contact information to: (530) 666-8645
  OR
- Mail contact information to: California Health Alert Network (CAHAN) Coordinator
  Yolo County Health Department
  10 Cottonwood Street *(after 1/1/07 address = 137 N. Cottonwood)*
  Woodland, CA 95695

Name: _____ Degree: _____

Title: _____ Specialty: _____

Company/Organization: _____

Department: _____

Address: _____

City: _____ Zip: _____

Business Fax: _____ Business Phone: _____

Pager: _____ Mobile: _____

Email: _____

Note: All contact information provided to YCHD is kept confidential.

Yolo County Health Department
10 Cottonwood Street • Woodland, CA 95695
Phone: (530) 666-8645 • Fax: (530) 666-8674 • www.yolohealth.org

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INFECTION CONTROL PRECAUTIONS

Outline

STANDARD PRECAUTIONS

Use Standard Precautions, or the equivalent, for the care of all patients.

Standard Precautions apply to 1) blood; 2) all body fluids, secretions, and excretions except sweat, regardless of whether or not they contain visible blood; 3) non-intact skin; and 4) mucous membranes. Standard Precautions are designed to reduce the risk of transmission of microorganisms from both recognized and unrecognized sources of infection in hospitals.

Handwashing (Hand Decontamination)

When hands are visibly dirty or visibly soiled with blood or other body fluids:

- Wash with either antimicrobial or non-antimicrobial soap & water

If hands are not visibly soiled:

- Use an alcohol-based hand rub or wash with soap & water

Decontaminate hands before:

- Having direct contact with patients
- Donning sterile gloves before sterile procedures
- Moving from a contaminated-body site to a clean-body site during patient care

Decontaminate hands after:

- Contact with a patient's intact skin
- Contact with body fluids or excretions, mucous membranes, non-intact skin, and wound dressings, inanimate objects in the immediate vicinity of the patient
- Removing gloves

Before eating and after using a restroom:

- Wash with either antimicrobial or non-antimicrobial soap & water

If exposure to *Bacillus anthracis* (anthrax) is suspected or confirmed:

- Wash with either antimicrobial or non-antimicrobial soap & water. The physical action of washing and rinsing hands under such circumstances is recommended because alcohols, chlorhexidine, iodophors, and other antiseptic agents have poor activity against spores.

Gloves

Wear gloves (clean, nonsterile gloves are adequate) when touching blood, body fluids, secretions, excretions, and contaminated items. Put on clean gloves just before touching mucous membranes and non-intact skin.

Change gloves between tasks and procedures on the same patient after contact with material that may contain a high concentration of microorganisms. Remove gloves promptly after use, before touching non-contaminated items and surfaces, and before going to another patient, and wash hands immediately to avoid transfer of microorganisms to other patients or environments.

Mask, Eye Protection, Face Shield

Wear a mask and eye protection or a face shield to protect mucous membranes of the eyes, nose, and mouth during procedures and patient-care activities that are likely to generate splashes or sprays of blood, body fluids, secretions, and excretions.

Gown

Wear a gown (a clean, nonsterile gown is adequate) to protect skin and to prevent soiling of clothing during procedures and patient-care activities that are likely to generate splashes or sprays of blood, body fluids, secretions, or excretions. Select a gown that is appropriate for the activity and amount of fluid likely to be encountered. Remove a soiled gown as promptly as possible and wash hands to avoid transfer of microorganisms to other patients or environments.

Patient-Care Equipment

Handle used patient-care equipment soiled with blood, body fluids, secretions, and excretions in a manner that prevents skin and mucous membrane exposures, contamination of clothing, and transfer of microorganisms to other patients and environments. Ensure that reusable equipment is not used for the care of another patient until it has been cleaned and reprocessed appropriately. Ensure that single-use items are discarded properly.

Environmental Control

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, and ensure that these procedures are being followed.

Linen

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.

Occupational Health and Bloodborne Pathogens

Take care to prevent injuries when using, cleaning, and disposing of sharp instruments.

Never recap used needles, manipulate them using both hands, or use any other technique that involves directing the point of a needle toward any part of the body; rather, use either a one-handed "scoop" technique or a mechanical device designed for holding the needle sheath.

Do not remove used needles from disposable syringes by hand, and do not bend, break, or otherwise manipulate used needles by hand. Place used sharp items in appropriate puncture-resistant containers.

Use mouthpieces, resuscitation bags, or other ventilation devices as an alternative to mouth-to-mouth resuscitation methods in areas where the need for resuscitation is predictable.

Patient Placement

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.

DROPLET PRECAUTIONS

Droplet transmission involves contact of the conjunctivae or the mucous membranes of the nose or mouth of a susceptible person with large-particle droplets (larger than 5 µm in size) containing microorganisms generated from a person who has a clinical disease or who is a carrier of the microorganism. Droplets are generated from the source person primarily during coughing, sneezing, or talking and during the performance of certain procedures such as suctioning and bronchoscopy.

Transmission via large-particle droplets requires close contact between source and recipient persons, because droplets do not remain suspended in the air and generally travel only short distances, usually 3 ft or less, through the air. Because droplets do not remain suspended in the air, special air handling and ventilation are not required to prevent droplet transmission.

Mask

In addition to wearing a mask as outlined under Standard Precautions, wear a mask when working within 3 ft of the patient. (Logistically, some hospitals may want to implement the wearing of a mask to enter the room.)

Patient Placement

Place the patient in a private room. If a private room is not available, place the patient in a room with a patient(s) who has active infection with the same microorganism but with no other infection (cohorting). When a private room is not available and cohorting is not achievable, maintain spatial separation of at least 3 ft between the infected patient and other patients and visitors. Special air handling and ventilation are not necessary, and the door may remain open.

Patient Transport

Limit the movement and transport of the patient from the room to essential purposes only. If transport or movement is necessary, minimize patient dispersal of droplets by masking the patient.

CONTACT PRECAUTIONS

Direct-contact transmission involves skin-to-skin contact and physical transfer of microorganisms to a susceptible host from an infected or colonized person, such as occurs during patient-care activities that require physical contact. Direct-contact transmission also can occur between two patients (e.g., by hand contact), with one serving as the source of infectious microorganisms and the other as a susceptible host. Indirect-contact transmission involves contact of a susceptible host with a contaminated intermediate object, usually inanimate, in the patient's environment.

Patient Placement

Place the patient in a private room. If a private room is not available, place the patient in a room with a patient(s) who has active infection with the same microorganism but with no other infection (cohorting).

Gloves and Handwashing

In addition to wearing gloves as outlined under Standard Precautions, wear gloves (clean, nonsterile gloves are adequate) when entering the room.

Change gloves between tasks and procedures on the same patient after contact with material that may contain a high concentration of microorganisms. Remove gloves promptly after use, before touching non-contaminated items and surfaces, and before going to another patient or leaving the room, and wash hands immediately.

After glove removal and handwashing, ensure that hands do not touch potentially contaminated environmental surfaces or items in the patient’s room to avoid transfer of microorganisms to other patients or environments.

Gown

In addition to wearing a gown as outlined under Standard Precautions, wear a gown (a clean, nonsterile gown is adequate) when entering the room if you anticipate that your clothing will have substantial contact with the patient, environmental surfaces, or items in the patient's room. Remove the gown before leaving the patient's environment. After gown removal, ensure that clothing does not contact potentially contaminated environmental surfaces to avoid transfer of microorganisms to other patients or environments.

Patient Transport

Limit the movement and transport of the patient from the room to essential purposes only. If the patient is transported out of the room, ensure that precautions are maintained to minimize the risk of transmission of microorganisms to other patients and contamination of environmental surfaces or equipment.

Patient-Care Equipment

When possible, dedicate the use of non-critical patient-care equipment to a single patient (or cohort of patients infected or colonized with the pathogen requiring precautions) to avoid sharing between patients. If use of common equipment or items is unavoidable, then adequately clean and disinfect them before use for another patient.

AIRBORNE PRECAUTIONS

Airborne transmission occurs by dissemination of either airborne droplet nuclei (small-particle residue [5 µm or smaller in size] of evaporated droplets that may remain suspended in the air for long periods of time) or dust particles containing the infectious agent. Microorganisms carried in this manner can be dispersed widely by air currents and may become inhaled by or deposited on a susceptible host within the same room or over a longer distance from the source patient, depending on environmental factors; therefore, special air handling and ventilation are required to prevent airborne transmission.

Patient Placement

Place the patient in a private room that has: 1) monitored negative air pressure in relation to the surrounding areas; 2) 6 to 12 air changes per hour; and 3) appropriate discharge of air outdoors or monitored high-efficiency filtration of room air before the air is circulated to other areas in the hospital. Keep the room door closed and the patient in the room. If a private room is not available, place the patient in a room with a patient who has active infection with the same microorganism but with no other infection (unless otherwise recommended).

Respiratory Protection

Wear respiratory protection (e.g., N95 respirator) when entering the room of a patient with known or suspected infection.

Patient Transport

Limit the movement and transport of the patient from the room to essential purposes only. If transport or movement is necessary, minimize patient dispersal of droplet nuclei by placing a surgical mask on the patient, if possible.

REFERENCES

Garner JS, Hospital Infection Control Practices Advisory Committee. Guideline for isolation precautions in hospitals. Infect Control Hosp Epidemiol 1996;17:53-80, and Am J Infect Control 1996;24:24-52. Web Version, 11/2004, at: www.cdc.gov/ncidod/hip/ISOLAT/ISOLAT.HTM

CDC/HICPAC. Hand Hygiene in Health Care Settings. MMWR October 25, 2002 / 51(RR16);1-44

San Francisco Department of Public Health. Infectious Disease Emergencies: A Preparedness and Response Guide for San Francisco Clinicians. August 2005. (www.sfcdcp.org)

Isolation Guidelines

Patient Management **IMPORTANT PHONE NUMBERS** **Infectious Diseases_____-_____** **Infection Control _____-_____** **Yolo County Health Department** (530) 666-8645	BACTERIAL AGENTS	**Anthrax**	**Brucellosis**	**Cholera**	**Glanders**	**Bubonic Plague**	**Pneumonic Plague**	**Tularemia**	**Q Fever**	**VIRUSES**	**Smallpox**	**Viral Encephalitis**	**Viral Hemorr. Fevers**	**BIOLOGICAL TOXINS**	**Botulism**	**Ricin**	**T-2 Mycotoxins**	**Staph. Enterotoxin B**
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 each patient encounter)				X***	X*	X*					X		X				X*	
Airborne Precautions (negative pressure room and N95 mask for all individuals entering the room)											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 disinfectant		X	X	X	X	X	X	X	X		X	X			X	X	X	X
Disinfect surfaces with 10% bleach solution or phenolic disinfectant													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 added											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 filter							X				X		X**					
Routine terminal cleaning of room with hospital approved disinfectant		X	X	X	X	X	X	X	X		X	X	X		X	X	X	X
Disinfect surfaces with 10% bleach solution or phenolic disinfectant													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 improvement							X											
Until all scabs separate											X							
Until skin decontamination completed (1 hour contact time)																	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

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ANTHRAX 2006

Outline

By law, health care providers must report suspected or confirmed Anthrax to the local health department immediately (within 1 hr).

Even a single case of Anthrax is considered an outbreak and is a public health emergency.

To report: call YCHD (24/7 (530) 666-8645).

Upon receipt, YCHD will initiate the public health response and can facilitate lab testing.

AGENT

Bacillus anthracis is a large, gram-positive, spore-forming, aerobic, encapsulated, rod-shaped bacterium. In an environment rich in nutrients, the spores germinate and form bacteria. Conversely, when nutrients in the environment are exhausted, the bacteria form spores. Anthrax spores are resistant to drying, heat, ultraviolet light, gamma radiation, and some disinfectants. Spores can persist in soil for years, whereas anthrax bacteria survive poorly outside of mammalian hosts.

EPIDEMIOLOGY

Anthrax as a Biological Weapon

Several countries have had anthrax weaponization programs in the past, including the US. In 1979 an outbreak of anthrax in the Soviet Union resulted from accidental release of anthrax spores from a facility where weaponized anthrax was being produced. Of 77 reported human cases, all but 2 were inhalational, and there was an 86% fatality rate.

Anthrax was successfully used as a biological weapon in the US in October 2001. Cases resulted from direct or indirect exposure to mail that was deliberately contaminated with anthrax spores. In total, 22 cases were identified, 11 with inhalational (5 fatal) and 11 with cutaneous anthrax.

As a result of this outbreak, the US Postal Service has deployed autonomous detection systems for anthrax (the Biohazard Detection System [BDS]) in select mail processing and distribution centers across the United States, including the US Postal Service Mail Processing and Distribution Center in West Sacramento (see Environmental Testing, below).

Aerosol release of weaponized spores is the most likely mechanism for use of anthrax as a biological weapon. Weaponization for aerosol release generally involves use of highly

concentrated spores, treated to reduce clumping and reduce particle size, and potentially the use of antimicrobial-resistant or genetically modified strains to increase virulence or escape vaccine protection.

Deliberate contamination of food or water with anthrax spores also is a possibility. Spores remain stable in water for at least several days following inoculation. *B. anthracis* spores are not destroyed by pasteurization, making contamination of milk another theoretical possibility.

Naturally Occurring Anthrax

B. anthracis spores are found in soil in many areas of the world, including rural Northern California counties with cattle grazing.

Anthrax is predominantly a disease of animals. Livestock or other herbivores acquire infection from consuming contaminated soil or feed. Anthrax in animals is endemic in many areas of the world. In the USA, anthrax outbreaks in animals occur sporadically. In 2001, an outbreak of bovine anthrax caused the death of 21 beef cattle in a rural section of Santa Clara County.

Naturally occurring anthrax in humans occurs after exposure to infected animals or contaminated animal products.

- Cutaneous anthrax generally occurs via contact with infected tissues of dead animals. Occupational exposures include butchering and processing of animal hides. In the US, cutaneous anthrax represents 95% of naturally occurring cases. Since 1990, only two cases of naturally occurring anthrax have been reported in the US; both had cutaneous disease, and neither case was in California.
- Gastrointestinal (GI) anthrax is associated with consumption of contaminated, undercooked meat.
- Inhalational anthrax results from contact with contaminated hair, wool, or hides, particularly during processing. In 2006, a drum maker contracted inhalation anthrax in the US while working with hides from Africa.

Person-to-person transmission of *B anthracis* does not occur with GI or inhalational anthrax, but has been reported rarely with cutaneous anthrax.

CLINICAL FEATURES

Clinical manifestations of anthrax 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. High-dose powder dissemination, as with contaminated mail, resulted in cases of both inhalational and cutaneous anthrax in the 2001 outbreak. A terrorist may develop cutaneous or inhalational anthrax after working with the agent.

The bacillus produces high levels of 2 toxins: edema toxin causes massive edema at the site of germination, and lethal toxin initiates the cascade of inflammatory mediators that leads to sepsis. High levels of toxin in the blood lead to death even if the bacteria are killed with antibiotics.

Inhalational Anthrax

Inhalational anthrax is caused by inhalation of spores that reach the alveoli, undergo phagocytosis and travel to regional lymph nodes. The spores then germinate to become bacterial cells, which multiply in the lymphatic system and cause lymphadenitis of the mediastinal and peribronchial lymph nodes. The bacteria cause focal, hemorrhagic necrosis in the lungs, accompanied by intra-alveolar edema and pleural effusion. Bacteria entering the bloodstream lead to septicemia, septic shock, and death.

INHALATIONAL ANTHRAX: CLINICAL FEATURES	
Incubation Period	2-7 days (up to 43 days or longer)
Signs & Symptoms	Illness often biphasic Initial Phase • Flu-like picture with mild, nonspecific respiratory illness, nonproductive cough, low-grade fever, malaise, myalgia • Occasionally abdominal pain, mild chest discomfort Acute Phase • Develops after 2-5 days of prodrome, occasionally preceded by 1-2 days of improvement • Severe respiratory distress, cyanosis • Profuse sweating • High fever • Progresses to shock, death in 24-36 hours if left untreated
Laboratory Findings	• Elevated WBC with left shift • Abnormal CXR: ~ Mediastinal widening ~ Infiltrates, consolidation ~ Pleural effusion • Abnormal CT scan: ~ Mediastinal adenopathy, widening ~ Pleural effusion ~ Infiltrates, consolidation

Cutaneous Anthrax

In cutaneous anthrax, spores or bacilli are introduced through preexisting skin breaks. Germination at the site of introduction leads to localized necrosis with eschar formation and soft-tissue or mucosal edema. Organisms are phagocytosed and carried to regional lymph nodes, often causing painful lymphadenopathy and lymphangitis. Septicemic complications of cutaneous anthrax occur in 10-20% of untreated cases.

CUTANEOUS ANTHRAX: CLINICAL FEATURES	
Incubation Period	1-7 days (up to 12 days)
Signs & Symptoms	Initial lesion • Begins as small, pruritic papule or vesicle • Lesions tend to occur on exposed areas of body (*e.g.*, face, hands, arms, neck) • By second day, papule ulcerates with central necrosis and drying • Painless • Localized, nonpitting edema develops, surrounding ulcerated area • Fine vesicles may encircle ulcer Lesion Progression • After 1 to 2 days, black eschar forms over ulcerated area • Lesion itself is painless (though regional adenopathy may be painful) • Eschar sloughs off after 12-14 days • Lesions resolve without complications or scarring in 80%-90% of patients • Nonpitting edema, lymphangitis, and painful lymphadenopathy may occur • Fever and malaise are common • Despite antibiotic treatment, the lesion will progress through all stages • Treatment is aimed at preventing systemic dissemination, as 10-20% of untreated cutaneous anthrax becomes systemic
Laboratory Findings	• WBC count often is normal or may be slightly elevated • Gram stain of lesion may reveal gram-positive rods; neutrophils are uncommon

Gastrointestinal Anthrax

GI anthrax results from ingestion of *B. anthracis* bacteria, such as may be found in poorly cooked meat from infected animals. The incubation period for GI anthrax is 1-7 days. Two clinical presentations have been described.

With intestinal anthrax, intestinal lesions occur and are followed by regional lymphadenopathy. Symptoms of intestinal anthrax are initially nonspecific and include nausea, vomiting, anorexia and fever. As disease progresses, abdominal pain, hematemesis and bloody diarrhea develop, occasionally accompanied by ascites. The patient may present with findings of an acute surgical abdomen. Hematogenous spread with resultant septicemia can occur.

In oropharyngeal anthrax, a mucosal ulcer occurs initially in the mouth or throat, associated with fever. This is followed by cervical edema and lymphadenopathy. Hematogenous spread with resultant septicemia can occur.

Gram stain of peritoneal fluid or oropharyngeal ulcers may show gram-positive rods. Elevated WBC with left shift may be present. *B anthracis* can be cultured from oropharyngeal swabs and stool specimens.

Anthrax Meningitis

Anthrax meningitis may occur as a complication of cutaneous, inhalational, or GI anthrax. Symptoms of the primary site of infection usually will be present; however meningitis may be the presenting illness. Characteristic features of bacterial meningitis are usually present. A hemorrhagic meningoencephalitis is not uncommon.

DIFFERENTIAL DIAGNOSIS

Because of its mild, nonspecific nature, a high index of suspicion is necessary to make the diagnosis of anthrax in the early stages. However, early diagnosis is desirable as prompt administration of antibiotics can be critical to patient survival.

Differential: Inhalational Anthrax

Early disease mimics influenza and other respiratory infections. However nasal symptoms are typically not present and rapid diagnostic tests, such as nasopharyngeal swabs for detection of respiratory virus antigens, would typically be negative.

Key features that distinguish inhalational anthrax from other conditions are:

- **CXR is abnormal even during early stages of flu-like illness**
- **CXR or Chest CT show widened mediastinum and pleural effusion but minimal or no pneumonitis**

Other conditions to consider:

- Community-acquired pneumonia (e.g. bacterial, Mycoplasma, Chlamydia)
- Influenza
- Other viral pneumonia (e.g. RSV, CMV, hantavirus)
- Q fever
- Pneumonic plague
- Tularemia
- Primary mediastinitis
- Dissecting aortic aneurysm

Differential: Gastrointestinal Anthrax

The differential diagnosis for the intestinal form of the disease includes:

- Any cause of acute abdomen
- Bacterial peritonitis
- Acute bacterial gastroenteritis (e.g. *Campylobacter, Shigella*, toxigenic *E. coli, Yersinia*)
- Typhoid fever
- Intestinal tularemia

The differential diagnosis for the oropharyngeal form of the disease includes:

- Streptococcal pharyngitis
- Infectious mononucleosis
- Enteroviral vesicular pharyngitis

- Herpetic pharyngitis
- Diptheria
- Anaerobic pharyngitis (Vincent's angina)
- *Yersinia enterocolitica* pharyngitis
- Pharyngeal tularemia

Differential: Cutaneous Anthrax

Key features that distinguish cutaneous anthrax are:

- **Painlessness of the lesion itself**
- **Large extent of local edema**

Other conditions to consider:

- Ecthyma gangrenosum
- Ulceroglandular tularemia
- Bubonic plague
- Staphylococcal or streptococcal cellulitis
- Brown recluse spider bite (rare in CA)
- Necrotizing soft tissue infections, (e.g. group A Strep and Clostridia)
- Rickettsial pox
- Scrub typhus
- Necrotic herpes simplex infection

Differential: Anthrax Meningitis

A key feature that distinguishes anthrax meningitis is bloody CSF containing gram-positive bacilli.

LABORATORY DIAGNOSIS

The gold standard for anthrax diagnosis is direct culture of clinical specimens onto blood agar with demonstration of typical gram stain, motility, and biochemical features.

- For suspected cutaneous anthrax, collect a sterile sample for gram stain and culture from the fluid of an unroofed vesicle, or from the exudate of an ulcer or eschar. If there is no visible exudate, the edge of the eschar can be lifted with forceps and the fluid near the edge collected. A negative culture does not exclude the diagnosis of cutaneous anthrax.

If you are testing or considering testing for Anthrax, you should:

- **IMMEDIATELY notify YCHD (24/7 (530) 666-8645). YCHD can authorize and facilitate testing, and will initiate the public health response as needed.**
- **Inform your lab that Anthrax is under suspicion. Labs may view gram-positive bacilli as contaminants and may not pursue further identification unless notified.**

- For suspected inhalational anthrax, collect sputum for gram stain and culture if sputum is being produced. Obtain blood for smear and culture. If pleural effusion is present, collect a specimen for gram stain and culture.

- For suspected GI anthrax, obtain a stool specimen for culture (or a rectal swab from patients unable to produce stool). Obtain blood for smear and culture. If ascites is present, obtain a specimen for gram stain and culture.

- For suspected anthrax meningitis, obtain a CSF specimen for gram stain and culture and obtain blood for smear and culture.

Blood cultures should be obtained prior to antibiotic administration if possible, as they are positive nearly 100% of the time in inhalational anthrax but there is rapid sterilization of blood after a single dose of antibiotics.

Other diagnostic tests are under investigation or are available only at designated reference laboratories. These include serologic tests (useful for retrospective diagnosis), direct fluorescent antibody (DFA) testing, PCR-based assays, and immunohistochemistry methods. Reference lab testing is accessed via YCHD. Specimens should be submitted to your clinical lab, which will coordinate with the YCHD Public Health Lab as needed.

Testing for Exposure to Aerosolized Anthrax

Nasal swab cultures have been used to study exposure to aerosolized anthrax in non-symptomatic patients. However, nasal swabs are not recommended for use in the clinical setting, as the sensitivity, specificity, and predictive value of nasal swab cultures is not known.

TREATMENT AND PROPHYLAXIS

These recommendations are current as of this document date. YCHD will provide periodic updates as needed and situational guidance in response to events (www.yolohealth.org).

Treatment of Confirmed or Suspected Anthrax

This section refers to individuals with confirmed anthrax or who are ill with suspected anthrax.

The basic components of treatment for anthrax consist of hospitalization with intensive supportive care and IV antibiotics. Antimicrobials should be started immediately upon suspicion and prior to confirmation of the diagnosis. As susceptibility data will be delayed, initial antibiotics must be chosen empirically.

Recommendations for initial empiric therapy of confirmed or suspected inhalational, GI, or CNS anthrax are shown in the table below. Empiric therapy with at least 2 agents is recommended due to the potential for infection with strains of *B. anthracis* engineered to be penicillin- and/or tetracycline-resistant. Once susceptibilities are determined, the regimen may be further tailored, in consultation with an infectious disease specialist or in accordance with YCHD recommendations.

INITIAL IV THERAPY FOR INHALATIONAL, GI, OR CNS ANTHRAX‡	
Patient Category	**Therapy Recommendation**
Adults	Ciprofloxacin, 400 mg IV q12 hr ‡‡ ***or*** Doxycycline, 100 mg IV q12 hr** ***and*** One or two additional antimicrobials (agents with *in vitro* activity include rifampin, vancomycin, penicillin, ampicillin, chloramphenicol, imipenem, clindamycin, and clarithromycin)††
Children *	Ciprofloxacin, 10-15 mg/kg IV q12 hr, not to exceed 1 g/day‡‡ ***or*** Doxycycline**: >8 yr and >45 kg: 100 mg IV q12 hr >8 yr and ≤45 kg: 2.2 mg/kg IV q12 hr ≤8 yr: 2.2 mg/kg every IV q12 hr ***and*** One or two additional antimicrobials (see agents listed above)††
Pregnant women *	Same as for non-pregnant adults
Immunocompromised	Same as for non-immunocompromised persons and children

‡ Steroids may be considered an adjunct therapy for patients with severe edema and for meningitis based on experience with bacterial meningitis of other etiologies.

* High death rates from infection outweigh the relative contraindications of doxycyline and fluoroquinolones in children and pregnant women.

** If meningitis is suspected, doxycycline may be less optimal because of poor CNS penetration.

†† Because of concerns of beta-lactamases in *B. anthracis* isolates, penicillin and ampicillin should not be used alone. Consultation with an I.D. specialist is advised. *B. anthracis* strains are naturally resistant to sulfamethoxazole, trimethoprim, cefuroxime, cefotaxime sodium, aztreonam, and ceftazidime.

‡‡ If IV ciprofloxacin is not available, oral ciprofloxacin may be acceptable as it is rapidly and well absorbed from the GI tract with no substantial loss by first-pass metabolism. Maximum serum concentrations are attained 1-2 hours after oral dosing but may not be achieved if vomiting or ileus is present.

Source: Working Group on Civilian Biodefense. Inglesby et al, JAMA 2002;287(17):2236-52

After clinical improvement is noted, treatment can be switched to oral therapy with ciprofloxacin or doxycycline, based on susceptibilities and clinical considerations, at doses identical to the IV doses. **Therapy should be continued for a total duration of 60 days** because of the potential persistence of spores after an aerosol exposure.

Localized cutaneous anthrax can usually be treated with a single oral antibiotic, either ciprofloxacin or doxycycline, at doses equivalent to the IV doses shown above. Therapy should be continued for 60 days duration. If in addition to cutaneous lesions there are signs of systemic disease or extensive edema, or if lesions are present on the head or the neck, then the multi-drug IV regimen in the table above should be followed.

Prophylaxis of Persons Exposed but Without Symptoms

Post-exposure prophylaxis is the administration of antibiotics, with or without vaccine, after suspected exposure to anthrax has occurred but before symptoms are present. (If symptoms are

present, see section on treatment, above). In general, post-exposure prophylaxis is recommended for those exposed to an air space where a suspicious material may have been aerosolized or which may be the source of an inhalational anthrax case. As there is no known person-to-person transmission of inhalational anthrax, prophylaxis should not be offered to contacts of cases, unless also exposed to the original source.

Post-exposure prophylaxis of potential inhalational anthrax consists of oral administration of either ciprofloxacin or doxycyline, at doses equivalent to the IV doses above. Therapy should be continued for 60 days duration. Patients treated for exposure should be informed of the importance of completing the full course of antibiotic prophylaxis regardless of the absence of symptoms.

Due to concerns about use of doxycycline or ciprofloxacin in children and about doxycycline use in pregnant women, the CDC has indicated that for prophylaxis, therapy can be switched to amoxicillin in these groups if the isolate is determined to be susceptible. Amoxicillin may also be considered for patients allergic to both ciprofloxacin and doxycycline.

Anthrax Vaccine

The anthrax vaccine adsorbed (AVA) is available but only in limited supply that is controlled by federal authorities. It is an inactivated cell-free filtrate of an avirulent strain of *B. anthracis.* Local reactions and mild systemic reactions are common. Severe allergic reactions are rare (<1 per 100,000).

AVA is licensed for pre-exposure use to prevent cutaneous anthrax in healthy, non-pregnant adults 18-65 years of age who have a high likelihood of coming into contact with anthrax, including certain laboratory workers and animal processing workers. AVA is not currently licensed for post-exposure use, and must be given in this context under an FDA investigational drug protocol. The CDC may recommend its use for post-exposure prophylaxis under some circumstances. Research is underway on a new anthrax vaccine.

INFECTION CONTROL*

These recommendations are current as of this document date. YCHD will provide periodic updates as needed and situational guidance in response to events (www.yolohealth.org).

There are no data to suggest that person-to-person transmission of inhalational or GI anthrax occurs. Therefore, **Standard Precautions** are considered adequate for patients with **inhalational** and/or **GI anthrax.** Patients do not require isolation rooms.

Person-to-person transmission has only rarely been reported for patients with cutaneous anthrax prior to the 2001 outbreak. Most authorities, including the Working Group on Civilian Biodefense, recommend **Standard Precautions** for patients with **cutaneous anthrax.**

* For description of Precautions, see chapter on Infection Control

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 or a 1:10 dilution of household bleach.

Decontamination of persons exposed to anthrax should involve:

- Removal of contaminated clothing. Clothing should be handled minimally to avoid aerosolization, stored in labeled plastic bags, and then laundered.
- Showering thoroughly with soap and water.

ENVIRONMENTAL TESTING

New environmental sampling systems are currently in use to detect possible release of anthrax.

One such system, the Biohazard Detection System (BDS), has been deployed by the US Postal Service to assist with early detection of *B. anthracis* at mail processing and distribution centers across the US. **A BDS system is now active at the main postal processing facility in West Sacramento.** The BDS is a fully automated air-sampling system consisting of an aerosol collector, PCR cartridge and controller computer. Positive BDS signals will be confirmed by a public health reference lab. In the event of a positive signal, an emergency response plan has been developed in coordination with YCHD, the Postal Service and other emergency partners.

BioWatch is a federal program that continuously collects outdoor air samples, screening the environment for harmful aerosolized biological agents. Specialized air sampling devices are mounted on existing outdoor air quality monitors. The air sampling filters are retrieved and transported regularly to a local CDC-coordinated laboratory for PCR analysis. If a biological pathogen is detected, the laboratory performs a second PCR test for confirmation. A culture may also be initiated to assess viability and antimicrobial sensitivities. A confirmed positive result would initiate a major response from local, state, and federal agencies. **BioWatch sensors are not currently deployed in the Sacramento Metropolitan Area, but have been deployed in the Bay area and in other large metropolitan areas in California.**

In the event of a positive signal from either the BDS or the BioWatch systems, updated information and instructions for Yolo County health care providers will be available at www.yolohealth.org.

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AVIAN INFLUENZA 2006

Outline

Influenza A is not a reportable condition under California law. However, health care providers are required to report any UNUSUAL disease to the local health department within one hour.

In the event of an Avian Influenza outbreak, guidelines for case identification, infection control, and disease reporting will be available at www.yolohealth.org or PandemicFlu.gov.

YCHD communicable disease control may be contacted by phone at (530) 666-8645.

The status of Avian Flu is changing rapidly. Information presented here is current as of March 2006. For new developments, check PandemicFlu.gov frequently.

AGENT

Influenza viruses belongs to the Orthomyxovirus family. There are 3 types: A, B, and C, distinguishable by internal virus proteins. Influenza A is responsible for most human influenza disease, causes avian influenza, and is the source of all past influenza pandemics in humans. Influenza B is a disease of humans only, while influenza C causes milder illness in both humans and swine and occurs uncommonly.

Influenza A is subtyped based on viral envelope glycoproteins hemagglutinin (HA) and neuraminidase (NA). There are 16 different HA antigens (H1 to H16) and 9 different NA antigens (N1 to N9) for influenza A. Human disease has historically been related to 3 subtypes of HA (H1, H2, and H3) and 2 subtypes of NA (N1 and N2).

Influenza A infects humans, birds, pigs, horses, whales, seals, and has recently been recognized in felines. Avian influenza A can infect a variety of domestic and wild bird species. Avian influenza in domestic chickens and turkeys is classified according to disease severity, with two recognized forms: highly pathogenic avian influenza (HPAI), and low-pathogenic avian influenza (LPAI). Avian influenza viruses that cause HPAI are highly virulent and mortality rates in infected flocks often approach 100%. All known subtypes of influenza A can be found in birds, but only subtypes H5 and H7 have caused HPAI outbreaks.

EPIDEMIOLOGY

Influenza Pandemics

Pandemics differ from seasonal outbreaks or "epidemics" of influenza, which are caused by subtypes of influenza viruses that already exist among people. A pandemic is a global outbreak that occurs when a new, highly pathogenic strain of influenza type A virus emerges in the human population and spreads easily from person-to-person worldwide, aided by the lack of human immunity to the novel strain.

Past influenza pandemics have led to high levels of illness, death, social disruption, and economic loss. There were 3 influenza A pandemics during the 20th century:

- 1918-19, "Spanish flu," (H1N1), caused >500,000 deaths in the US and >50,000,000 deaths worldwide. Nearly half of those who died were young, healthy adults.
- 1957-58, "Asian flu," (H2N2), first identified in China in early 1957, caused about 70,000 deaths in the US by June 1957.
- 1968-69, "Hong Kong flu," (H3N2), caused about 34,000 deaths in the US. Influenza A (H3N2) viruses still circulate today.

Influenza in Bird Populations

All birds are believed susceptible to infection with avian influenza. Migratory waterfowl – most notably wild ducks – are the natural reservoir of avian influenza viruses, however domestic poultry, including chickens and turkeys, are particularly susceptible to epidemics of rapidly fatal influenza. Recent research has shown that viruses of low pathogenicity can quickly mutate into highly pathogenic viruses. For example, during a 1999–2001 avian influenza epidemic in Italy, the H7N1 virus, initially of low pathogenicity, mutated within 9 months to a highly pathogenic form. More than 13 million birds died or were destroyed.

Standard control measures aimed at preventing spread of HPAI in a country's poultry population include quarantining of infected farms and destruction of infected or potentially exposed flocks. In the absence of prompt control measures backed by good surveillance, epidemics can last for years. For example, an epidemic of H5N2 avian influenza, which began in Mexico in 1992, started with low pathogenicity, evolved to the highly fatal form, and was not controlled until 1995.

Mechanism of Transmission to Humans

Influenza A viruses are genetically labile and well adapted to elude host defenses. Influenza viruses lack mechanisms for the "proofreading" and repair of errors that occur during replication. As a result of these uncorrected errors, the genetic composition of a virus changes during passage through humans and animals, and the existing strain is replaced with a new antigenic variant. These changes in the antigenic composition of influenza A viruses are known as antigenic drift.

Influenza A viruses, including subtypes from different species, can also swap or reassort genetic materials. This process -- known as antigenic shift – creates a novel virus subtype that differs

genetically from both parent viruses. As populations will have no immunity to the new subtype, and as no existing vaccines can confer protection, antigenic shift has historically resulted in highly lethal pandemics. For this to happen, a subtype of avian influenza needs to acquire genes from human influenza viruses that enable person-to-person transmission.

Conditions favorable for the emergence of antigenic shift are thought to involve humans living in close proximity to domestic poultry and pigs. Because pigs are susceptible to infection with both avian and mammalian viruses, including human strains, they can serve as a "mixing vessel" for the scrambling of genetic material from human and avian viruses, resulting in the emergence of a novel subtype. In addition, evidence is mounting that, for at least some avian influenza virus subtypes circulating in bird populations, humans themselves can serve as the "mixing vessel".

The Current H5N1 Threat

Of the avian influenza subtypes, currently the H5N1 subtype is of greatest pandemic concern for the following reasons:

- Rapid spread throughout poultry flocks in Asia; now appears to be endemic in eastern Asia
- Mutates rapidly
- Propensity to acquire genes from viruses infecting other animal species
- Causes severe disease in humans, with a high case-fatality rate
- There is ongoing exposure and infection of humans in rural Asia, where many households keep free-ranging poultry flocks for income and food

The first documented infection of humans with an avian influenza virus occurred in Hong Kong in 1997, when the H5N1 strain caused severe respiratory disease in 18 humans, of whom 6 died. The infection of humans coincided with an epidemic of HPAI, caused by the same strain, in Hong Kong's poultry population. Close contact with live infected poultry was the source of human infection, and the virus was shown to have jumped directly from birds to humans. Transmission to health care workers occurred, but did not cause severe disease. Rapid destruction of Hong Kong's entire poultry population, estimated at around 1.5 million birds, reduced opportunities for further direct transmission to humans, and may have averted a pandemic.

Alarm has continued to mount since 2003, when an outbreak of HPAI caused by the H5N1 strain spread rapidly through poultry farms in southeastern Asia. The strain circulating since 2003 appears highly pathogenic for humans, and immunity in the human population is generally lacking. If H5N1 continues to circulate widely among poultry and wild birds, the potential for emergence of a pandemic strain remains high. Probable person-to-person transmission was identified in Thailand involving transmission from an ill child to her caregivers. However, the strain has not yet been shown to be easily transmitted between humans, and sustained person-to-person transmission has not occurred as of March 2006.

For a list of countries currently reporting avian flu in birds or humans, go to:

www.oie.int/downld/AVIAN%20INFLUENZA/A_AI-Asia.htm

CLINICAL FEATURES

In many patients, the disease caused by avian influenza (H5N1) follows an unusually aggressive clinical course, with rapid deterioration and high fatality. Clinical data from cases in 1997 and the current outbreak are beginning to provide a picture of the clinical features of disease, but much remains to be learned. **Moreover, the current picture could change given the propensity of this virus to mutate rapidly and unpredictably – check PandemicFlu.gov often for updates.**

The incubation period for H5N1 avian influenza may be longer than that for normal seasonal influenza, which is around two to three days. Current data for H5N1 infection indicate an incubation period ranging from 2-8 days and possibly as long as 17 days.

Initial symptoms include a high fever (usually higher than 38°C) and influenza-like symptoms. Many patients have lower respiratory symptoms when they first seek treatment. Based on present evidence, difficulty breathing develops around five days following the first symptoms. Respiratory distress, a hoarse voice, and a crackling sound when inhaling are commonly seen. Sputum production is variable and sometimes bloody. Most recently, blood-tinted respiratory secretions have been observed in Turkey. Almost all patients develop pneumonia. During the Hong Kong outbreak, all severely ill patients had primary viral pneumonia, which did not respond to antibiotics. Limited data on patients in the current outbreak indicate the presence of a primary viral pneumonia in H5N1, usually without microbiological evidence of bacterial supra-infection at presentation. Turkish clinicians have also reported pneumonia as a consistent feature in severe cases; as elsewhere, these patients did not respond to treatment with antibiotics. Common laboratory abnormalities include leukopenia (mainly lymphopenia), mild-to-moderate thrombocytopenia, elevated aminotransferases, and with some instances of disseminated intravascular coagulation.

The spectrum of clinical symptoms for avian influenza may be broader, and not all confirmed patients have presented with respiratory symptoms. Watery diarrhea without blood appears to be more common in H5N1 patients than in normal seasonal influenza patients. In two patients from southern Viet Nam, the clinical diagnosis was acute encephalitis; neither patient had respiratory symptoms at presentation. In another case from Thailand, the patient presented with fever and diarrhea, but no respiratory symptoms. All three patients had a recent history of direct exposure to infected poultry.

In patients infected with avian influenza (H5N1), clinical deterioration is rapid. In Thailand, the time between onset of illness to the development of acute respiratory distress was around 6 days, with a range of 4-13 days. In severe cases in Turkey, clinicians have observed respiratory failure 3-5 days after symptom onset. Another common feature is multiorgan dysfunction.

In an outbreak of avian influenza among humans, the clinical picture of primary viral pneumonia is expected to predominate. However, given that the virus responsible for human-to-human transmission will be a novel strain, the specifics of its clinical presentation will not be known until the outbreak actually occurs.

The status of Avian Flu is changing rapidly. Information presented here is current as of March 2006. For new developments, check PandemicFlu.gov frequently.

LABORATORY DIAGNOSIS

As of March 2006, CDC recommendations for enhanced surveillance of patients at risk for avian influenza are still in effect. These are:

1) Testing for influenza A (H5N1) in the US is indicated for hospitalized patients with:

- Radiographically confirmed pneumonia, acute respiratory distress syndrome (ARDS), or other severe respiratory illness for which an alternate diagnosis has not been established, AND
- History of travel within 10 days of symptom onset to a country with documented H5N1 avian influenza in poultry and/or humans. H5N1-affected countries at **www.oie.int/downld/AVIAN%20INFLUENZA/A_AI-Asia.htm**.

If you consider testing for Avian Influenza, you should:

- **IMMEDIATELY notify YCHD (24/7 (530) 666-8645) to facilitate testing and initiate the public health response. Testing for H5N1 subtype of influenza A occurs at specialized labs and requires YCHD authorization.**
- **Inform your lab that Avian Influenza is under suspicion, so that appropriate biosafety procedures will be followed.**

2) Testing for influenza A (H5N1) should be considered on a case-by-case basis in consultation with the local health department for hospitalized or ambulatory patients with:

- Documented temperature of >38°C (>100.4°F), AND
- At least one: cough, sore throat, shortness of breath, AND
- History of contact with domestic poultry (e.g., visited a poultry farm, household raising poultry, or bird market) or a known or suspected human case of influenza A (H5N1) in an H5N1-affected country within 10 days of symptom onset.

Clinical specimens from suspect influenza A (H5N1) cases may be tested by PCR assays under strict biosafety precautions at public health reference laboratories. Virus isolation studies carry higher risks of inadvertent transmission and require even more stringent precautions.

The Yolo County Health Department is prepared to transport specimens to the State Viral and Rickettsial Disease Lab (VRDL) in Richmond for cases that meet the surveillance definition for influenza A (H5N1) shown above. Contact the Health Department 24/7 immediately regarding probable cases to arrange testing at (530) 666-8645.

TREATMENT AND PROPHYLAXIS

Detailed guidelines for Avian Influenza treatment/prophylaxis have not yet been issued. For updates and situational guidance in response to events, check www.yolohealth.org.

Antiviral Agents

Limited evidence suggests that oseltamivir (commercially known as Tamiflu), can reduce the duration of viral replication and improve prospects of survival, provided it is administered within 48 hours following symptom onset. There is no direct clinical trial evidence showing oseltamivir is effective in human H5N1 disease. Without such trials, the optimal dose and duration of oseltamivir treatment is uncertain and therefore doses used for seasonal human influenza continue to be recommended. The clinical course of human H5N1 disease may be different from normal seasonal influenza requiring a different dosing approach. Oseltamivir is not indicated for the treatment of children younger than one year of age.

Recommended doses of oseltamivir for the treatment of influenza are available at the manufacturer's web site (www.rocheusa.com/products/tamiflu/pi.pdf). The currently recommended doses are:

For treatment of influenza:

- Adults: 75 mg two times a day for five days.
- Children 1 year of age or older: weight adjusted doses
  - 30mg twice daily for =15 kg
  - 45mg twice daily for >15 to 23 kg
  - 60mg twice daily for >23 to 40kg
  - 75mg twice daily for >40kg
- Children up to 1 year of age: not recommended

According to WHO, clinicians should consider increasing the duration of treatment to seven to ten days in patients who are not showing a clinical response. In cases of severe infection with the H5N1 virus, clinicians may need to consider increasing the recommended daily dose or the duration of treatment, keeping in mind that doses above 300 mg/day are associated with increased side effects (mostly gastrointestinal). In severely ill H5N1 patients or in H5N1 patients with severe gastrointestinal symptoms, drug absorption may be impaired. This possibility should be considered when managing these patients.

For prevention of influenza:

- Adults and teenagers 13 years of age or older: 75 mg once a day for at least seven days.
- Children from 1 year to 13 years of age:
  - 30mg daily for =15 kg
  - 45mg daily for >15 to 23 kg
  - 60mg daily for >23 to 40kg
  - 75mg daily for >40kg
- Children up to 1 year of age: not recommended

For people with repeated or prolonged exposure, including health care workers and people involved in culling birds, continuous treatment for up to 6 weeks at 75 mg/day is generally well tolerated.

The status of Avian Flu is changing rapidly. Information presented here is current as of March 2006. For new developments, check PandemicFlu.gov frequently.

The H5N1 strain currently circulating appears to be resistant to adamantanes, therefore adamantanes are not recommended. Antiviral resistance of H5N1 may develop to other medications over time. Check PandemicFlu.gov regularly for updates.

Vaccine Development

Influenza vaccine must be both subtype- and strain-specific. Candidate vaccines against H5N1 subtype were developed during 2003 for protection against the strain that was isolated from humans in Hong Kong in February of that year. However, the current strain has since mutated and continues to change. Clinical trials of H5N1 vaccines are currently underway. However, it is not clear if prototype H5 vaccines will offer protection against an emergent pandemic strain. Typically, 4-6 months (minimum) is needed to develop a vaccine against a novel influenza virus strain.

INFECTION CONTROL*

Poultry Workers

Birds that are infected with avian influenza viruses can shed virus in saliva, nasal secretions, and feces. Activities that could result in exposure to avian influenza-infected poultry include euthanasia, carcass disposal, and cleaning and disinfection of premises affected by avian influenza. However, the CDC has written interim guidance for protection of persons involved in control of avian influenza outbreaks among poultry in the US available at www.cdc.gov/flu/avian/professional/protect-guid.htm.

Health Care Setting (as of 3/17/2006, CDHS)

General Precautions

Because (a) the clinical course of H5N1 infection may be unpredictable, (b) airborne precautions may be difficult to maintain in a setting other than a hospital, and (c) laboratory results for H5N1 testing should be available within 24-48 hours, physicians should strongly consider transferring or directing (with appropriate referrals) suspect patients to the nearest emergency department. The patient should, if possible, don a surgical or procedural mask during transport. Personnel involved in transporting suspect patients to the emergency department (ambulance staff) should wear the same personal protective equipment described below for health care workers when in contact with the suspect patient.

All patients who present to a health care setting with fever and respiratory symptoms at any time of the year should be managed with Respiratory Hygiene and Cough Etiquette Precautions**.** Visual alerts (in languages appropriate to community populations served) should be posted at all public entrances to healthcare facilities (e.g., emergency departments, physician offices, outpatient clinics, etc.) “Cover Your Cough” posters in various languages are available at www.yolohealth.org.

* For description of Precautions, see chapter on Infection Control

Visual Alerts/Signage for Patients

Visual alerts should instruct patients with fever and respiratory symptoms to:

- Wear a mask over their nose and mouth at all times after entering the healthcare facility. Only procedure or surgical masks (*i.e.*, masks with ear loops, cone shape mask with elastic head band or masks with ties) should be used. N95 or higher level of respiratory protection should not be used for patients. Patients should never wear any kind of respiratory protection that has an exhalation valve; this type of respirator does not prevent droplet nuclei from being expelled into the air;
- Inform the first point of contact healthcare worker (triage nurse or patient registration personnel) of symptoms of a respiratory infection;
- Cover the nose and mouth with a disposable tissue when coughing or sneezing;
- Dispose of soiled tissues immediately after use in the nearest waste receptacle; and
- Perform hand hygiene (*e.g.*, hand washing with soap and water, alcohol-based hand rub, or antiseptic hand wash) after contact with respiratory secretions (*e.g.*, sneezing, coughing or blowing the nose) and after hand contact with disposable tissues contaminated with respiratory secretions.

Reception Area Triage and Supplies

Health care workers in emergency, clinic and outpatient departments should:

- Provide procedure or surgical masks at the point of entry into waiting rooms;
- Provide disposable tissues, no-touch, plastic lined waste receptacles for tissue disposal and conveniently located dispensers of alcohol-based hand rub;
- Provide supplies near sinks for hand washing (*i.e.*, soap, disposable towels) that are consistently available;
- Practice Standard Precautions at all times;
- Triage patients with respiratory symptoms immediately; and
- Obtain a travel history to rule out recent visits to an H5N1-affected country (**www.oie.int/downld/AVIAN%20INFLUENZA/A_AI-Asia.htm**).

Place patients with symptoms of fever and respiratory infection but who do not meet the case definition of H5N1 avian influenza in a designated area of the waiting room. The designated area should be located at least three feet away from other asymptomatic patients, when possible. As an alternative, place patients in a treatment room until examined by a physician. Droplet Precautions (*e.g.*, wearing a surgical or procedure mask), in addition to Standard Precautions, should be practiced by health care providers at all times when within 3 feet of patients with fever and symptoms of any respiratory infection.

Isolation Precautions for Patients with Suspected H5N1

Patients who, at the time of triage, meet the case definition of suspected H5N1 avian influenza should be placed on isolation precautions as follows. **These include Airborne Infection Isolation, Contact and Standard Precautions**. In addition, **Eye Protection** should be utilized when within 3 feet of the patient. For complete information on these precautions see **www.cdc.gov/ncidod/dhqp/gl_isolation.html**. These precautions should be continued for 14 days after onset of symptoms or until either an alternative diagnosis is established or diagnostic tests performed by the State lab indicate that the patient is not infected with influenza A virus.

Suspect Cases – Infection Control

- Instruct the patient to wear a surgical mask over their nose and mouth at all times until placed in a designated airborne infection isolation room (AIR);
- Place hospitalized patients in a designated AIR, when available. AIRs should have monitored negative air pressure in relation to the corridor and 6 to 12 air changes per hour (ACH) exhausted directly to the outside or recirculated through a high efficiency particulate air (HEPA) filter. If an AIR is not available, place a portable HEPA filter in the room. The door should remain closed and a sign placed on the door informing visitors and staff of the appropriate precautions to take prior to entering the room;
- Place emergency department and outpatient clinic patients in an AIR, when available. If an AIR is not available, place the patient in an examination room with a portable HEPA filter and close the door;
- Allow the AIR to remain vacant with the door closed until the contaminated air has been be completely recirculated (the amount of time will depend on the number of air changes per hour, but minimally 1 hour);

Personal Protective Equipment & Hygiene (Health Care Workers)

- Wear fit-tested NIOSH-approved respiratory protection (N95 filtering face piece respirator or higher level of protection) when entering the room. Respirators should be used in the context of a complete respiratory protection program as required by the California Occupational Safety and Health Administration (Cal/OSHA). This includes training, fit-testing, and fit-checking to ensure appropriate respirator selection and use. To be effective, respirators must provide a proper sealing surface on the wearer's face;
- During procedures that may generate increased aerosols (*e.g.*, endotracheal intubations, nebulizer treatment, bronchoscopy), use of a powered air-purifying respirator (PAPR) is strongly recommended.
- Suspect patients should not be transported to other areas of the hospital unless absolutely necessary. The patient should wear a surgical mask during any transport, if tolerated. If an elevator is used, only the patient and transport team should be in the elevator. Notify the receiving area prior to transport.
- Wear eye or full facial protection (face shield or goggles) when within 3 feet of a patient;
- Wear a disposable long sleeve gown when direct contact with a patient or the patient's immediate environment is anticipated;
- Wear disposable, non-sterile gloves when direct contact with the patient or the patient's immediate environment is anticipated;
- Perform hand hygiene after gloved and ungloved contact with the patient's blood, body fluids and respiratory secretions, after contact with contaminated environmental surfaces and after removal of gloves. If hands are not visibly soiled, a waterless hand hygiene product can be used;

Other Instructions for Staff & Visitors

- Instruct health care workers and visitors not to touch the mucous membranes of their nose, eye or mouth with unwashed hands or contaminated gloves;

- Use dedicated or disposable equipment such as stethoscopes, blood pressure cuffs, thermometers;
- Restrict visitors to a minimum; visitors may be offered respiratory protection (i.e., N95) and should be instructed on the use of the respirator before entering the room (as per CDC recommendations for tuberculosis, December 30, 2005);
- Decontaminate environmental surfaces and equipment with a hospital-approved disinfectant after the patient has been discharged from the room.
- All staff including environmental services entering the room should wear an N95 respirator when entering the room until room cleaning has been completed or 1 hour, whichever comes later.

Monitoring Exposed Health Care Workers

Health care workers who have worked with suspect or confirmed H5N1 patients should:

- Be vigilant for the development of fever (*i.e.*, measure temperature twice daily), and respiratory symptoms for 10 days after the last day of work with those patients.
- If symptomatic, notify their primary care physician of the exposure when making an appointment. In addition, health care workers should notify the hospital's occupational health and infection prevention professionals.
- With the exception of visiting a primary care physician, be advised to stay home and restrict activity and contact with others until an alternative diagnosis is established or diagnostic tests performed by the State lab indicate that the patient is not infected with influenza A virus.
- Practice Respiratory Hygiene and Cough Etiquette Precautions when ill at home (see Home Care Settings) to lower the risk of transmission of virus to others.
- For health care workers with fever and symptoms strongly suggestive of influenza, after nasopharyngeal and throat specimens have been obtained, consider empiric antiviral treatment with input from CDHS and CDC and complete testing for alternative diagnoses.

Home Care Settings for Patients with Suspected H5N1 Influenza

It is not feasible to use Airborne Infection Isolation Precautions in the home setting. Therefore, the use of Respiratory Hygiene and Cough Etiquette, Droplet, and Contact Precautions are recommended. Prior to patient placement in a home setting, the local health department will interview the patient or patient's caregiver to determine if that setting meets minimum requirements, including the availability of a caregiver. Symptomatic patients who do not require hospitalization should not go to work, school, childcare centers or other public areas until fourteen days after the onset of symptoms. During this time, infection prevention recommendations, as described below, should be used to minimize the potential for transmission.

- Patient and household members should have separate sleeping arrangements, if possible;
- The patient should cover mouth and nose with a facial tissue when coughing or sneezing; wear a surgical mask when uninfected persons enter the room or, if unable, uninfected persons should wear a surgical mask when entering the room;

Caregivers should:

- Wear disposable gloves when in contact with the ill person's blood and body fluids (including respiratory secretions or items such as disposable tissues contaminated with respiratory secretions) and the immediate environment. Immediately after activities involving contact with blood and body fluids including respiratory secretions, gloves should be removed and discarded and hands should be washed. *Gloves are not intended to replace proper hand hygiene;*
- Wash hands with soap and water after gloved and ungloved contact with the ill person's blood and body fluids (including respiratory secretions or items such as disposable tissues contaminated with respiratory secretions) and the ill person's immediate environment. Alcohol-based hand hygiene products can be used after removing gloves when hands are not visibly soiled with respiratory secretions, blood and other body fluids. Gloves should never be washed or reused;
- Unwashed dishes and utensils should not be shared. Wash dishes and utensils with warm to hot water and any commercial detergent after each use. Disposable plates or eating utensils are not necessary;
- Clean and disinfect environmental surfaces in the kitchen, bathroom and bedroom at least daily with a household cleaner diluted and used according to manufacturer's instructions. Bleach, if used, should be diluted 1 part bleach to 10 parts water. A fresh solution should be mixed daily;
- Linens should not be shared between household members until they have been washed. Wash clothes, bed linens and towels in water at any temperature using any commercial laundry product and dry at an appropriate fabric temperature. Gloves should be worn when handling soiled linens;
- Dispose of waste soiled with respiratory secretions, blood or other body fluids, and surgical masks as normal household waste;
- Any rented, non-disposable medical or respiratory equipment should be placed in a plastic bag and labeled contaminated prior to their return.

Monitoring and Management of Household Members, Care Providers or Other Close Contacts of Patients with Suspected H5N1 Influenza

- Contacts should take their temperature twice daily for 10 days after the last day of exposure and contact their primary care provider if they develop a fever (temperature greater than 100.4°F [>38.0°C]), and/or respiratory symptoms.
- The primary care physician must notify the local health department immediately of symptomatic contacts.
- Symptomatic contacts should stay home and restrict activity and contact with others until an alternative diagnosis is established or diagnostic tests performed by the State lab indicate that the patient is not infected with influenza A virus.
- Symptomatic contacts should practice Respiratory Hygiene and Cough Etiquette Precautions when ill at home to lower the risk of transmission of virus to others.

The status of Avian Flu is changing rapidly. Information presented here is current as of March 2006. For new developments, check PandemicFlu.gov frequently.

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BOTULISM 2006

Outline

By law, health care providers must report suspected or confirmed Botulism to the local health department immediately (within 1 hr).

Even a single case of Botulism is considered an outbreak and is a public health emergency.

To report: call YCHD (24/7 (530) 666-8645).

Upon receipt, YCHD will initiate the public health response and can facilitate lab testing.

AGENT

Botulism is an intoxication caused by botulinum toxin, which is produced by *Clostridium botulinum* and, rarely, by other *Clostridium* species.

Organism. *Clostridium botulinum* is a gram-positive, strictly anaerobic, spore-forming bacillus commonly isolated from soil and from marine and lake sediments. There are several strains, all of which elaborate toxin. *C. botulinum* bacteria are not, in and of themselves, toxic to humans; disease is caused by exposure to the bacterial toxin.

Toxin. There are seven serotypes of the toxin, labeled A through G. Types A, B, and E (and rarely, F) cause natural disease in humans. Botulinum toxins are colorless, odorless and tasteless, and are the most lethal toxins known, causing death at doses of <1 mcg. The toxin is inactivated by heating to 100°C for 1 minute, 85°C for 5 minutes, or 80°C for 20 minutes. Antibiotics have no activity against the toxin itself.

Spores. In response to unfavorable environmental conditions (changes in pH, temperature, and water or nutrient availability), *C. botulinum* bacteria "sporulate" – i.e. they become dormant, do not reproduce, and alter their cellular processes to increase resistance to chemicals, heat, air, and drying. Thus, *C. botulinum* spores are hardy, resistant to desiccation, heat, UV light, and alcohols, and can survive boiling for up to 4 hours. (They are, however, readily killed by chlorine solutions.) Once the spores encounter more favorable conditions, such as are found in contact with human tissues, they will "germinate," thereby producing growing cells that are capable of reproducing and elaborating toxin.

EPIDEMIOLOGY

Botulinum Toxin as a Biological Weapon

Several countries, including the US, the Soviet Union, Japan, and Iraq have conducted research on use of botulinum toxin as a biological weapon and may have stockpiled weapons containing it. Likely modes of dissemination for toxin used as a weapon include:

- **Deliberate contamination of food or beverages**. Food or beverage items that are possible vehicles for botulinum toxin are those which are not heat-processed at 85°C (185°F) for 5 minutes before consumption, and those which are appropriately heat-processed but then become contaminated sometime after processing has occurred. Thus, even at typical pasteurization temperatures (74°C/165°F for 30 seconds), some of the toxin would remain intact.

- **Dispersion of aerosolized toxin.** Animal studies and rare cases of laboratory accidents have confirmed the pathogenicity of aerosolized toxin. Experts have estimated that 1 gm of aerosolized botulinum toxin could kill up to 1.5 million people; though technical factors would make such dissemination difficult.

- **Contamination of a water supply.** This is possible but felt to be unlikely due to the large amount of toxin needed to contaminate a water supply. Also, toxin is rapidly inactivated by standard drinking water treatment, and is naturally inactivated in fresh water within 3 to 6 days.

The following features of a botulism outbreak would suggest deliberate toxin release:

- **An outbreak involving a large number of cases**
- **An outbreak caused by an unusual toxin type (C, D, F, or G) or involving type E toxin without an apparent aquatic source**
- **Multiple simultaneous outbreaks with or without an apparent source**
- **Cases lack a common food exposure, but were in geographic proximity during the week before symptom onset (suggests aerosol release)**

Naturally Occurring Botulism

Naturally occurring botulism is a rare disease with an annual incidence of approximately 100 cases in the US.

Food-borne botulism is caused by ingestion of food contaminated with preformed botulinum toxin. In order for food-borne botulism to occur, the food item must be contaminated with *C. botulinum* spores, the spores must survive food preservation methods and then germinate and produce toxin under anaerobic, low-acid, warm conditions. Finally the food must not be reheated sufficiently to inactivate the heat-labile toxin before the food is consumed ($\geq$85°C for 5 minutes). Toxin types A, B, and E account for most cases of foodborne botulism.

Between 1990 and 2000, there was a median of 14 food-borne botulism events annually in the US, with a median of 1 case per event. From 1994-2003 there were 30 cumulative cases of food-borne botulism reported in California. Food-borne botulism (especially type E) is a significant public health problem among Alaskan natives due to consumption of fermented meat from aquatic mammals and fish.

Wound botulism is caused by infection of a contaminated wound with *C botulinum* organisms, and subsequent absorption into the circulation of locally produced toxin. Most cases are related to injection drug use. Recently, several cases of wound botulism have been reported among **injection** drug users in California, in association with use of black tar heroin.

Infant botulism is caused by ingestion of C botulinum spores. The spores colonize the GI tract, germinate, and produce toxin, which is absorbed into the circulation. The source of spores typically is unknown, although ingestion of corn syrup or raw honey accounts for some cases. From 1994-2003 there were 283 cumulative cases of infant botulism reported in California. Intestinal botulism similar to that in infants has been reported very rarely in adults.

Inhalational botulism does not occur in nature, but has been produced experimentally in laboratory animals. Three human cases occurred in 1962 in lab technicians working with aerosolized botulinum toxin.

Botulinum toxin is also used therapeutically. Purified, highly diluted, injectable botulinum toxin is used to treat a range of spastic or autonomic muscular disorders such as cervical dystonia and strabismus (toxin type B). Toxin type A is used in extremely minute doses for the treatment of facial wrinkles (Botox®). Systemic effects of the toxin have been noted very rarely after medical use or misuse of the product.

CLINICAL FEATURES

Botulism is caused by exposure to botulinum toxin. Exposure to toxin may occur through several mechanisms:

- Ingestion of preformed toxin (food-borne)
- Inhalation of preformed toxin
- Local production of toxin by *C. botulinum* organisms in the GI tract (infant; intestinal)
- Local production of toxin by *C. botulinum* organisms in devitalized tissue (wound)

Regardless of the route of intoxication the same neurologic syndrome develops. Botulinum toxin acts at the neuromuscular junction of skeletal muscle neurons and cholinergic autonomic synapses. It binds irreversibly to presynaptic receptors to inhibit the release of acetylcholine. The effect lasts weeks to months, until the synapses and axonal branches regenerate. Death from botulism results acutely from airway obstruction or paralysis of respiratory muscles.

Botulism is characterized by acute afebrile descending symmetric paralysis. Disease generally begins with cranial nerve dysfunction and then progresses to muscle weakness, with the proximal muscle groups involved first.

Severity of disease is variable, ranging from mild cranial nerve dysfunction to complete flaccid paralysis. Both the severity of disease and the rapidity of onset correlate with the amount of toxin absorbed into the circulation.

BOTULISM: CLINICAL FEATURES	
Incubation Period	• 12-72 hours (range 2 hrs - 8 days) • Dependent on dose of toxin
Signs & Symptoms	Early Presentation – cranial nerve abnormalities • Dysarthria • Blurred and/or double vision • Dry mouth • Ptosis • Symptoms may be slow in onset or rapidly progressive (dose-dependent) Later Presentation – descending paralysis • Dysphonia, dysphagia • Symmetrical, descending progressive muscular weakness • Dilated or fixed pupils • Decreased gag reflex • Respiratory failure • Autonomic nerve dysfunction; may include urinary retention, orthostasis • Normal mental status, though may appear lethargic and have difficulty with communication • Normal sensory nerve function • Afebrile unless there is complicating infection
Laboratory Findings	• Normal CSF glucose, protein, cell count • Normal CBC • Normal imaging of brain and spine (CT scan or MRI) Characteristic EMG findings include: • Incremental response (facilitation) to repetitive stimulation at 50 Hz • Short duration of motor unit potentials • Normal sensory nerve function • Normal nerve conduction velocity

DIFFERENTIAL DIAGNOSIS

Botulism is frequently misdiagnosed. A high index of suspicion is necessary for early presumptive diagnosis as there are no readily available rapid confirmatory tests. Diagnosis is primarily made on the basis of clinical presentation and epidemiologic evidence of potential exposure. However it must be recognized that in the event of bioterrorist attack, the source of exposure may be unclear.

Important questions to ask:

- Recent history of eating home-canned vegetable, fruit, and fish products
- Other known individuals with similar symptoms
- Recent travel to Alaska or consumption of Alaskan seafood products
- Recent history of IVDU, particularly with black tar heroin or cocaine

Key features that distinguish botulism are the constellation of:

- **Descending paralysis**
- **Cranial nerves prominently involved**
- **Symmetric bilateral impairment**
- **Normal CSF studies**
- **Characteristic EMG findings**
- **Absence of paresthesias**
- **Afebrile illness**
- **Normal mental status**

Other conditions to consider:

- Guillain-Barre syndrome (particularly Miller-Fisher variant)
- Myasthenia gravis
- Stroke
- Intoxication with CNS depressants
- Lambert-Eaton syndrome
- Diabetic neuropathy
- Sudden infant death syndrome
- Magnesium intoxication
- Tick paralysis
- Poliomyelitis
- CNS infections, particularly of brainstem
- CNS tumor
- Psychiatric illness (i.e. conversion paralysis)
- Inflammatory myopathy
- Paralytic shellfish poisoning

LABORATORY DIAGNOSIS

Diagnosis is primarily made on the basis of clinical presentation. Laboratory confirmation can be achieved in most cases by detection of botulinum toxin in serum via mouse bioassay, in which mice are injected with the patient sample and observed for the development of characteristic symptoms. Detection of toxin is dependent on the total dose of toxin absorbed and the time from symptom onset to testing. The mouse test is able to detect fractional nanogram amounts of toxin. The test requires 1-4 days to complete and is performed only at reference laboratories. Test results may be negative if the samples were collected late or the quantity of toxin is small; thus lack of detection of botulinum toxin does not necessarily rule out the diagnosis of botulism. Tests other than the mouse bioassay are currently investigational.

If you are testing or considering testing for Botulism, you should:

- **IMMEDIATELY notify YCHD (24/7 (530) 666-8645. YCHD can authorize and facilitate testing, and will initiate the public health response as needed.**

For mouse bioassay, obtain at least 30 cc of serum. (If directed by public health personnel, obtain 20-50 cc of stool, enema fluid and/or gastric aspirate.) Serum specimens must be taken before

antitoxin treatment in order to demonstrate the presence of botulinum toxin. The lab should be notified if the patient has received Tensilon or "stigmine" drugs prior to testing. Serum, stool, and gastric specimens should be kept refrigerated, not frozen.

Potentially contaminated food samples may be collected (10-50 gm), sealed, and transported under refrigeration. Environmental specimens with potential contamination may be collected (soil, 50-100 gm; water >100 cc) and transported at room temperature.

In case of suspected inhalational exposure, toxin may be present in nasal mucosa for up to 24 hours. However the utility of nasal sampling is unknown.

Routine laboratory tests on serum and CSF are generally within normal limits unless a secondary process has occurred. Cultures of blood, stool, sputum, and urine are not helpful in confirming a diagnosis of botulism. Viable organisms are generally present only in wound or infant botulism. Patients do not generally develop an antibody response due to the sub-immunogenic amount of toxin necessary to produce disease.

TREATMENT AND PROPHYLAXIS

These recommendations are current as of this document date. YCHD will provide periodic updates as needed and situational guidance in response to events (www.yolohealth.org).

Supportive care, including mechanical ventilation and parenteral nutrition, and timely administration of botulinum antitoxin are the mainstays of care for botulism. Ventilatory support may be required for several weeks or more. With modern intensive care methods, case-fatality rates for botulism in the USA have dropped to <10%.

Note: aminoglycosides and clindamycin are contraindicated for treatment of secondary infections since they may exacerbate the neuromuscular blockade.

Antitoxin Treatment

To obtain antitoxin, phone YCHD (24/7 (530) 666-8645). If the clinical picture is compatible with botulism, antitoxin may be released emergently.

Antitoxin is provided by the CDC but is available for release only via state and local health departments. Once antitoxin is requested, it generally can be delivered within 12 hours. The currently available formulation is botulinum antitoxin bivalent for types A and B (licensed by FDA). Botulinum antitoxin type E is investigational. A trivalent preparation (types A, B, E) has been discontinued. The military is testing a heptavalent antitoxin (type A through G).

One 10-ml vial of each preparation of antitoxin is sufficient to neutralize circulating toxin from most naturally occurring intoxications. A repeat dose is not usually necessary.

Antitoxin is most effective when given within 24 hours after symptom onset. It cannot reverse any existing paralysis. However it binds to any toxin remaining in the circulation and can slow progression of further disease and potentially decrease the duration of ventilatory support and increase the likelihood of survival.

Since antitoxin is of equine origin, hypersensitivity reactions, including anaphylaxis, serum sickness, and febrile reactions have occurred in up to 9% of patients receiving antitoxin. Skin testing for hypersensitivity should be performed in all patients before administering antitoxin. If skin testing is positive, the patient can be desensitized over several hours before the full dose of antitoxin is administered. Diphenhydramine and epinephrine should be available during administration.

No Prophylaxis of Exposed Asymptomatic 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 post exposure 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 may experience anxiety and/or somatic symptoms that may include neurologic symptoms. These patients should be carefully assessed. Antitoxin supplies are limited, and therapy will be reserved for patients with compatible neurological findings.

Pre-exposure immunization with botulinum toxoid is restricted to certain laboratory and military personnel. Supplies are extremely limited and would not be available for the public.

INFECTION CONTROL*

These recommendations are current as of this document date. YCHD will provide periodic updates as needed and situational guidance in response to events (www.yolohealth.org).

Person-to-person transmission does not occur. **Standard Precautions** are adequate for the care of patients with botulism. Patients do not require isolation.

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* For description of Precautions, see chapter on Infection Control

BRUCELLOSIS 2006

Outline

By law, health care providers must report suspected or confirmed Brucellosis to the local health department immediately (within 1 hr).

Even a single case of Brucellosis is considered an outbreak and is a public health emergency.

To report: call YCHD (24/7 (530) 666-8645).

Upon receipt, YCHD will initiate the public health response and can facilitate lab testing.

AGENT

Brucellosis is a zoonotic disease of domestic and wild animals, caused by the non-motile, non-sporulating, small, gram-negative coccobacilli bacteria of the genus *Brucella.* Four species can be pathogenic in humans: *B. melitensis, B. abortus, B. canis* and *B. suis*. They are highly infectious, especially *B. melitensis* and *B. suis*.

Brucellae contain lipopolysaccharide (LPS) in the outer cell membrane, however this LPS is structurally different from that of the Enterobacteriaceae, and this feature may underlie the reduced pyrogenicity (less than 1/100th) of *Brucella* LPS compared with *E. coli* LPS.

EPIDEMIOLOGY

Brucellosis as a Biological Weapon

The US military developed *B. suis* as a biological weapon in the 1950's, but terminated this program in 1967. Their transmissibility by aerosol suggests that *Brucella* organisms might be a candidate for use as a bioweapon. Fewer than 100 organisms could constitute an infectious aerosol. 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. However, it might be used as an incapacitating agent as it often causes a protracted illness.

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. Bioterrorism might also be suggested by clusters of brucellosis cases without a travel history to endemic areas, without relevant foodborne or occupational exposures, or where the cases are linked in time and place (e.g. geographically related cases following a wind direction pattern).

Naturally Occurring Brucellosis

Brucella species infect mainly ruminant mammals, including cattle, sheep, goats, pigs, and camels, in which they cause genital infection, abortion, and fetal death. Additional animal reservoirs include elk, caribou, bison, deer, and wild and domestic canines. Animals may transmit *Brucella* organisms during septic abortion, at the time of slaughter, and in their milk. Humans are usually infected incidentally in one of three ways:

- Direct contact with the tissues of infected animals. Occupational exposures include those of veterinarians, shepherds, ranchers, and slaughterhouse workers, who are believed to become infected through skin abrasions, cuts, or conjunctival exposure.

- Ingestion of contaminated food or water. Consumption of contaminated milk products is the most common mode of acquisition worldwide. Pasteurization of dairy products prevents transmission and has drastically reduced the incidence of brucellosis in the developed world. Meat products are rarely the source of infection because they are not usually eaten raw and the number of organisms in muscle tissue is low.

- Inhalation of infectious aerosols. The inhalational route is of consequence for occupational exposures listed above, particularly slaughterhouse workers, and may also constitute a risk factor for laboratory workers who culture *Brucella* bacteria.

Naturally occurring exposures to brucellosis are unusual in the US and tend to be isolated. Fewer than 200 total cases per year are reported in the US, most of these in Texas and California. During the period 1994-2003 there were 275 total cases reported in California. The epidemiology of brucellosis in Texas and California has changed from a disease associated with exposure to cattle to one linked to the ingestion of unpasteurized goat milk products ("queso fresco") imported from Mexico.

Disease incidence is much higher in the Middle East and Mediterranean regions, and in China, India, and Latin America.

CLINICAL FEATURES

Brucellae are facultative intracellular pathogens that can 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.

Clinical manifestations of brucellosis are diverse and often non-specific, and the course of the disease is variable. For most exposures, the clinical syndrome does not clearly relate to the portal of entry of the organism; however those exposed via the aerosol route may have increased frequency of respiratory symptoms. *B. melitensis* tends to cause more severe, systemic illness than the other brucellae; *B. suis* is more likely to cause localized, suppurative disease.

BRUCELLOSIS: CLINICAL FEATURES	
Incubation Period	2-4 weeks (range 5 days to several months)
Signs & Symptoms	• Fever always occurs; spiking or "undulant" pattern may be apparent • May have acute, subacute, or chronic presentation • Other constitutional symptoms: malaise, anorexia, back pain, myalgias, arthralgias, headache • "Malodorous perspiration" • Mild lymphadenopathy (10-20%) • Hepatomegaly or splenomegaly (20-30%) • Nonspecific skin lesions (papules, ulcers, e. nodosum, petechiae) in 5% • Weight loss among chronically infected • Almost any organ system can be involved • Most affected persons recover in 3-12 months, however a minority may develop one or more of the complications below
Complications	• Skeletal: osteomyelitis (most common); also sacroiliitis, spondylitis, peripheral arthritis • Reproductive: spontaneous abortion; epididymo-orchitis • GI: acute ileitis, hepatitis, liver abscess, liver granuloma • CNS: meningitis, encephalitis, brain abscess, myelitis • CV: endocarditis, pericarditis • Pulmonary: bronchitis, pneumonia, lung nodules, abscess, hilar adenopathy, pleural effusion/empyema, lung abscess • Uveitis
Laboratory Findings	• Mild leukopenia with relative lymphocytosis • Mild anemia and thrombocytopenia may be present; DIC is rare • Other abnormalities are related to the organ system involved

DIFFERENTIAL DIAGNOSIS

Due to the non-specific presentation and numerous, varied complications of brucellosis in humans, the differential diagnosis is vast and will not be addressed in detail here. A high index of suspicion is necessary to diagnose brucellosis, due both to the non-specific presentation and to the relatively long latency period between inoculation and the development of symptoms.

Key clinical questions that help to suggest naturally-acquired brucella infection include:

- History of contact with ruminant mammals, via occupational or recreational exposures (veterinarians, slaughterhouse workers, ranchers, shepherds, laboratory workers, visitors to dairy farms or petting zoos)
- Consumption of unpasteurized milk products (e.g. "queso fresco")
- Travel to areas where brucellae are established in the animal population

In the setting of intentional attack using brucella, these exposures may be notably absent.

LABORATORY DIAGNOSIS

Definitive diagnosis of brucellosis is made when brucellae are recovered from infected tissues, typically blood or bone marrow. The rate of isolation ranges from 15-70%. The organism has also been recovered from urine, CSF, synovial fluid, and biopsies of liver and lymph nodes. *Brucella* species often require several weeks to grow in culture, so this method is not useful for rapid identification.

If you are testing or considering testing for Brucellosis, you should:

- **IMMEDIATELY notify YCHD (24/7 (530) 666-8645)**
- **Notify the lab that Brucellosis is suspected, as the organism may pose a risk to personnel.**

Neither CDC nor the Working Group on Civilian Biodefense has issued bioterrorism-specific treatment/prophylaxis recommendations for Brucellosis. YCHD will provide situational guidance in response to events (www.yolohealth.org).

A presumptive diagnosis can be made using specific antibody titers. The serum agglutination test (SAT) is based on antibody against lipopolysaccharide. Most cases of active infection have a single titer of 1:160 or higher. Drawbacks of the SAT include the inability to diagnose *B. canis* infection, cross-reaction with other gram-negative organisms, and the lack of seroconversion in some cases. Also, SAT are not suitable for patient follow-up since titers can remain elevated for a prolonged period. The ELISA test for brucellosis relies on cytoplasmic antigens and is both more sensitive and more specific than SAT. However, like SAT, titers can remain elevated for prolonged periods. A number of variations of PCR tests are becoming available, but standardization is still lacking.

TREATMENT AND PROPHYLAXIS

These recommendations are current as of this document date. YCHD will provide periodic updates as needed and situational guidance in response to events (www.yolohealth.org).

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 regimens.

BICHAT, the European Commission's Task Force on Biological and Chemical Agent Threats, has recommended as first-line therapy: Doxycline 100 mg IV/PO twice daily, combined with **either** streptomycin 1 gm IM once or twice daily for up to 2 weeks; **OR** rifampin 600-900 mg PO daily for 6 weeks; **OR** gentamicin 5 mg/kg/day IV in 2 divided doses for up to 2 weeks. This regimen, dosage-adjusted to body weight, is also first-line treatment for children >8 years old. Treatment with trimethoprim-sulfamethoxazole (TMP-SMX) plus rifampin is recommended for pregnant women and for children <8 years of age. Quinolones have been used with success against

Brucellae, while macrolide antibiotics are not effective. Complications of brucellosis are also treated with 2-drug regimens, while neurobrucellosis has generally been treated with 3 agents.

Relapses occur in about 10% of cases, usually during the first year after infection, and are often milder in severity than the initial disease. Relapse has been managed with a repeated course of the usual antibiotic regimens. Most cases of relapse are felt to be caused by inadequate treatment.

Post-Exposure Prophylaxis

There is little evidence to support the utility of post-exposure prophylaxis against brucellosis in humans. BICHAT has recommended a 3-6 week course of doxycycline **OR** TMP-SMX, with the addition of rifampin to either drug. **In the event of outbreak, YCHD will provide updated, situational guidelines for prophylaxis (www.yolohealth.org).**

Vaccination

There is currently no licensed human vaccine available for brucellosis. Some limited clinical data exist on a live, attenuated vaccine candidate, but licensing and production of this vaccine are not anticipated.

INFECTION CONTROL*

These recommendations are current as of this document date. YCHD will provide periodic updates as needed and situational guidance in response to events (www.yolohealth.org).

Person-to-person transmission of brucellosis is extremely rare. **Standard Precautions** are considered adequate for patients with brucellosis.

Brucella is sensitive to exposure to heat and most disinfectants but can survive in the environment for up to two years under specific conditions, becoming a continuing threat to both humans and animals.

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PLAGUE 2006

Outline

By law, health care providers must report suspected or confirmed Plague to the local health department immediately (within 1 hr).

Even a single case of Plague is considered an outbreak and is a public health emergency.

To report: call YCHD (24/7 (530) 666-8645).

Upon receipt, YCHD will initiate the public health response and can facilitate lab testing.

AGENT

Yersinia pestis is one of the three pathogenic *Yersinia* species within the family *Enterobacteriaceae*. *Y. pestis* is a pleomorphic, nonmotile, nonsporulating, intracellular, gram-negative bacillus that has a characteristic bipolar appearance on Wright, Giemsa, and Wayson's stains. There are three virulent strains: *antiqua, medievalis,* and *orientalis*. A fourth strain, *microtus*, is nonvirulent.

The *Y. pestis* genome encodes for several virulence factors that enable the pathogen to survive and multiply within its hosts. Several proteins (F1, V, W, and Yops) inhibit phagocytosis, while the V antigen also facilitates survival within macrophages. Lipopolysaccharide endotoxin causes the classic features of endotoxic shock.

EPIDEMIOLOGY

Plague as a Biological Weapon

In the late 20th century, biological weapons programs in the US and the Soviet Union developed techniques for aerosolizing *Y. pestis* in order to enhance its dissemination.

Pneumonic plague is thought to be the most likely clinical presentation in the event of a bioterrorist attack. Intentional release of aerosolized plague could result in an outbreak of pneumonic plague with a high case-fatality rate and the potential for widespread person-to-person transmission.

Aerosolized plague used as a bioweapon would be expected to have the following features:

- Previously healthy patients with severe, rapidly progressive pneumonia
- Many similar cases would occur, generally 2-4 days after release

- Acute multilobar pneumonia accompanied by hemoptysis, associated GI symptoms, and a fulminant clinical course would be very suspicious for pneumonic plague
- Buboes characteristic of bubonic plague would not be present
- No risk factors for plague exposure or recent travel to a plague-endemic region
- Lack of a recent, prior, local plague epizootic with rodent deaths

Naturally Occurring Plague

Reservoirs. A number of animal species are the natural reservoirs for *Y. pestis.* Most are wild rodents, including rats, squirrels, mice, gerbils, guinea pigs, prairie dogs, and marmots. Humans are not part of the natural life cycle of *Y. pestis.* Disease occurrence in humans is dependent on the frequency of infection in local rodent populations and the degree of contact between rodents and humans. Naturally occurring outbreaks in humans usually are preceded by epizootics – *i.e.*, large-scale deaths in susceptible animal hosts. Mammalian species other than rodents (*e.g.*, cats, dogs, rabbits, deer) are also incidental hosts for *Y. pestis,* and can occasionally serve as sources of human exposure, either through direct contact or via flea vectors.

Vectors. The organisms most commonly are transmitted between animal reservoirs and to humans via bites of infected fleas, but may also occur via direct contact with infected animal carcasses. Pneumonic plague may be transmitted via inhalation of respiratory droplets from infected animals or persons.

Three bubonic plague pandemics have been recorded throughout history. The most recent began in 1894 in China and caused an estimated 12 million deaths. In California, small outbreaks of pneumonic plague with person-to-person spread occurred twice in the 20th century due to infected urban rat populations: 1919, Oakland (13 cases) and 1924, Los Angeles (39 cases).

Plague exists in wild rodent populations all over the Western US and human cases continue to occur in persons exposed to them. Naturally occurring plague generally occurs during the summer months. From 1994 to 2003, 8 cases of plague were reported in California. Approximately 1,800 worldwide cases of plague are reported to the WHO annually, from all continents except Europe and Australia.

CLINICAL FEATURES

The classic forms of plague are bubonic plague, septicemic plague, and pneumonic plague; these are presented in detail below. Other syndromes caused by *Y. pestis* infection include:

- **Plague meningitis.** Meningitis may occur as a complication of bacteremia and may be the presenting clinical syndrome for some cases.
- **Plague pharyngitis.** Plague pharyngitis is similar to severe pharyngitis or acute tonsillitis of other causes, with inflamed cervical nodes or a cervical bubo usually present.
- **Pestis minor.** Pestis minor is a milder form of bubonic plague in which the nodes drain and patients recover without therapy. Subclinical infections can occur, as well.

Pneumonic Plague

Y. pestis can enter the lungs either through direct inhalation of respiratory droplets from infected humans or animals (primary pneumonic plague) or through hematogenous spread as a complication of bubonic or septicemic plague (secondary pneumonic plague).

PRIMARY PNEUMONIC PLAGUE: CLINICAL FEATURES	
Incubation Period	1-4 days (up to 6 days)
Signs & Symptoms	Acute, often fulminant onset of: • Fever, malaise, headache, myalgias • Associated GI symptoms including nausea, vomiting, diarrhea, and abdominal pain • Dyspnea, cyanosis, chest pain, and (in children) tachypnea • Productive cough, commonly with hemoptysis
Laboratory Findings	• CXR findings include alveolar infiltrates progressing to lobar consolidation, pleural effusion • Rarely, mediastinal widening on CXR due to adenopathy • Gram-negative bipolar bacilli usually visible on sputum gram stain

Bubonic Plague

Y. pestis survives in the flea midgut after a blood meal from an infected host. The organism is transmitted to a new host when the flea regurgitates into the bloodstream during its next feeding. *Y. pestis* migrates to regional lymph nodes where it causes hemorrhagic lymphadenitis, creating the swollen, painful buboes that are characteristic of bubonic plague. The organisms often enter the bloodstream, causing hemorrhagic lesions in other lymph nodes and organs.

BUBONIC PLAGUE: CLINICAL FEATURES	
Incubation Period	1-8 days
Signs & Symptoms	• Sudden onset of fever, chills, headache, lethargy • Painful swollen lymph node – a "bubo" - occurs in groin, axilla, and/or cervical region, proximal to the inoculation site • Buboes may suppurate and rupture • Skin lesions may occur at site of flea bite (i.e., papules, vesicles, pustules) but are present in <10% of cases • Nausea, vomiting, and/or diarrhea are common May progress to secondary pneumonic plague or secondary septicemic plague
Laboratory Findings	• Elevated WBC with left shift • Gram-positive bipolar bacilli usually visible on smear of bubo aspirate • Additional findings correlate with progression to sepsis, pneumonia, and/or meningitis

Septicemic Plague

In primary septicemic plague there is systemic sepsis caused by *Y. pestis,* but without noticeable, preceding lymph node or pulmonary involvement. Up to 25% of naturally-occurring plague cases may present with primary septicemic plague. Secondary septicemic plague occurs commonly with either bubonic or pneumonic plague.

Septicemic plague causes a gram-negative sepsis syndrome with multiorgan involvement, DIC, and shock. In the late stages of infection, high-density bacteremia often occurs, with identifiable organisms on peripheral blood smear. Meningitis can occur and is characterized by a thick, purulent exudate in CSF.

PRIMARY SEPTICEMIC PLAGUE: CLINICAL FEATURES	
Incubation Period	1-4 days
Signs & Symptoms	• Fever, chills, headache, malaise, and GI disturbances • Purpuric skin lesions and gangrene of the distal digits (acral necrosis) are common • May progress to meningitis and/or pneumonia • Often progresses rapidly to septic shock, DIC, multi-organ failure, and death
Laboratory Findings	• Consistent with severe bacterial infection and sepsis • Organisms may be identifiable on peripheral blood smear

DIFFERENTIAL DIAGNOSIS

Diagnosis of plague during the initial stages requires a high index of suspicion because of the nonspecific, flu-like picture early in the disease. Early diagnosis is desirable as prompt administration of antibiotics can be critical to survival.

Differential: Pneumonic Plague

The differential diagnosis of pneumonic plague includes any severe pneumonia, and should be considered in any case of severe gram-negative pneumonia.

Key features that may help to distinguish plague pneumonia are:

- **Bubo(es), if present (secondary pneumonic plague)**
- **No response to typical antibiotic therapy for community-acquired pneumonia**

Other conditions to consider:

- Community-acquired pneumonia (*e.g.*, bacterial, Mycoplasma, Legionella, Chlamydia)
- Viral pneumonia (e.g. influenza, RSV, CMV, hantavirus)
- Q fever
- Inhalational anthrax

- Tularemia
- Ricin

Differential: Bubonic Plague

Key features that may help to distinguish bubonic plague:

- **Presence of painful adenitis (buboes) progressing to systemic disease.**

Other conditions to consider:

- Cat scratch disease
- Ulceroglandular tularemia
- Staphylococcal or streptococcal adenitis
- Mycobacterial infection, including scrofula
- Lymphogranuloma venereum
- Chancroid
- Primary genital herpes
- Strangulated inguinal hernia

Differential: Septicemic Plague

A key feature that may help to distinguish septicemic plague from other sepsis syndromes is the presence of painful adenitis (buboes). However, primary septicemic plagues may occur in the absence of buboes.

Key feature that may help to distinguish septicemic plague:

- **Presence of painful adenitis (buboes) progressing to systemic disease.** (However, primary septicemic plague may occur in the absence of buboes.)

Other conditions to consider:

- Gram-negative sepsis
- Meningococcemia
- Rickettsiosis
- Malaria
- Appendicitis

LABORATORY DIAGNOSIS

There are no widely available, rapid diagnostic tests for plague. Initial identification of the organism relies on microscopic evaluation of blood, sputum, CSF, fluid aspirated from a bubo, or skin lesion scrapings (if a skin lesion is present).

If you are testing or considering testing for Plague, you should:

- **IMMEDIATELY notify YCHD (24/7 (530) 666-8645). YCHD can authorize and facilitate testing, and will initiate the public health response as needed.**
- **Inform your lab that Plague is under suspicion. Some commercial bacterial test systems cannot reliably identify *Y. pestis.***

Order a gram stain, culture, and Giemsa, Wright's, or Wayson's stain of the material. Store and transport blood at room temperature. Transport other samples at room temperature, but store under refrigeration if transport time will be > 2 hours. If plague is highly suspected, order an additional blood culture for incubation at

room temperature, which is optimal for *Y. pestis* growth. If a bubo is present, an aspirate may be obtained by inserting a 20-gauge needle on a 10-mL syringe, injecting 1-2 ml of sterile saline into the bubo, and withdrawing the fluid.

On gram stain, *Y. pestis* organisms appear as single cells or short chains of plump, gram-negative rods. With Giemsa, Wright's or Wayson's stains, *Y. pestis* appears as a bipolar "closed safety pin" whereas this bipolar morphology may or may not be evident on Gram stain. Bipolar staining is not exclusive to *Y. pestis* however it is still considered to be suggestive of the diagnosis.

Y. pestis is slow-growing in culture. Cultures of blood, bubo aspirate, sputum, CSF, or skin lesion scrapings may not demonstrate growth until 48 hours after inoculation. Also, many commercial bacterial identification systems do not include *Y. pestis* in the identification databank or may misidentify *Y. pestis* as another enteric pathogen (*Y. pseudotuberculosis, Shigella, H_2S-ngative Salmonella, or Acinetobacter)*. Consultation with YCHD is advised if plague is suspected, in order to obtain bacteriological confirmation at an approved public health laboratory.

Direct fluorescent antibody (DFA) testing for *Y. pestis* capsular (F1) antigen may be helpful for presumptive plague identification in patient samples. Several serologic tests are available at CDC reference labs, including passive hemagglutination and ELISA tests. A single titer of more than 1:10 is presumptively positive for plague if the patient has not been vaccinated previously. With paired sera 4-6 weeks apart, a fourfold increase in titer is considered confirmatory.

TREATMENT AND PROPHYLAXIS

These recommendations are current as of this document date. YCHD will provide periodic updates as needed and situational guidance in response to events (www.yolohealth.org).

Treatment of Plague

Supportive care and timely administration of 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 symptoms. Many patients would be expected to require intensive care with respiratory support owing to complications of gram-negative sepsis. In a contained casualty setting where the medical care delivery system can effectively manage the number of patients, IV antibiotics should be administered to all patients for 10 days **(Table 1)**. Oral antibiotics can be substituted once the patient's condition improves. In a mass casualty setting where the medical care delivery system is not able to meet the demands for patient care, use of oral antibiotics may be necessary (**Table 2)**.

Aminoglycosides are the drug of choice. Streptomycin is FDA-approved for plague. Gentamicin is not FDA-approved for plague, but has been used effectively and is recommended as an alternative to streptomycin. Tetracyclines, fluoroquinolones, and chloramphenicol are additional alternatives, albeit with potential for adverse events in children and pregnant women. Penicillins, cephalosporins, macrolides, rifampin, and aztreonam are ineffective. Natural antibiotic resistance

to the drugs of choice is rare, but genetically-engineered resistant strains could be encountered in a bioterrorism scenario.

TABLE 1. TREATMENT OF PLAGUE IN THE CONTAINED CASUALTY SETTING

Patient Category	Therapy Recommendation*
Adults: Preferred Choices	Streptomycin, 1 gm IM q12 hrs† ***or*** Gentamicin, 5 mg/kg IM or IV once daily, or 2 mg/kg loading dose followed by 1.7 mg/kg IM or IV q8 hrs‡§
Adults: Alternative Choices	Doxycycline, 100 mg IV q12 hrs or 200 mg IV once daily§ ***or*** Ciprofloxacin, 400 mg IV q12 hrs §†† ***or*** Chloramphenicol, 25 mg/kg IV q6 hrs (max 4 g/day)‡‡
Children: Preferred Choices	Streptomycin, 15 mg/kg IM q12 hrs (max 2 g/day) ***or*** Gentamicin 2.5 mg/kg IM or IV q8 hrs ‡
Children: Alternative Choices	Doxycycline: ≥45 kg, give adult dosage <45 kg, give 2.2 mg/kg IV q12 hrs (max 200 mg/day) ***or*** Ciprofloxacin, 15 mg/kg IV q12 hrs (max 1 g/day) †† ***or*** Chloramphenicol, 25 mg/kg IV q6 hrs (max 4 g/day)‡‡ §§

* Treatment duration is 10 days.

† In pregnant women, gentamicin is the only preferred choice; streptomycin can cause irreversible deafness in children exposed in utero.

‡ Aminoglycoside doses must be further adjusted for newborns, and according to renal function.

§ Acceptable for pregnant women. Although fetal toxicity may occur with doxycycline use, the recommendation is for doxycycline or ciprofloxacin if gentamicin is not available or if oral antibiotics must be used.

†† Other fluoroquinolones may be substituted at dosages appropriate for age.

‡‡ Therapeutic concentration 5 - 20 mcg/ml; concentrations >25 mcg/ml can cause reversible bone marrow suppression.

§§ According to the Working Group on Civilian Biodefense, children younger than 2 years of age should not receive chloramphenicol due to risk of 'gray baby syndrome'. However, the American Academy of Pediatrics (AAP) has recommended chloramphenicol as the drug of choice for plague meningitis in children.

Source: Working Group on Civilian Biodefense. Inglesby TV, JAMA 2000; 283(17):2281-2290.

Prophylaxis of Persons Exposed to Plague

Exposure is defined as proximity to aerosolized *Y. pestis* or close physical contact with a confirmed case. Close physical contact is defined as proximity less than 6.5 feet (2m) to a person who is symptomatic with plague and who has received <48 hours of appropriate antimicrobial therapy.

Household and health worker contacts should be considered exposed and receive prophylaxis. In the setting of an outbreak, certain persons with early, nonspecific symptoms such as fever >38.5ºC or a new cough may be recommended to begin antimicrobial therapy, and those who

develop fever or cough while receiving antibiotic prophylaxis may be recommended for immediate evaluation and treatment of plague. **In the event of an outbreak, YCHD will provide situational guidance on prophylaxis (www.yolohealth.org).**

TABLE 2. TREATMENT OF PLAGUE IN THE MASS CASUALTY SETTING OR POST-EXPOSURE PROPHYLAXIS

Patient Category	Therapy Recommendation*
Adults: Preferred Choices	Doxycycline, 100 mg PO BID§ ***or*** Ciprofloxacin, 500 mg PO BID§††
Adults: Alternative Choice	Chloramphenicol, 25 mg/kg PO QID (max 4 g/day)‡‡
Children: Preferred Choices	Doxycycline: ≥45 kg, give adult dosage <45 kg, give 2.2 mg/kg PO BID (max 200 mg/day) ***or*** Ciprofloxacin, 20 mg/kg PO BID (max 1 g/day) ††
Children: Alternative Choice	Chloramphenicol, 25 mg/kg PO QID (max 4 g/day)‡‡ §§

* Treatment duration in mass casualty setting is 10 days. Duration of post-exposure prophylaxis is 7 days.
§ Acceptable for pregnant women.
†† Other fluoroquinolones may be substituted at dosages appropriate for age.
‡‡ Therapeutic concentration 5 - 20 mcg/ml; concentrations >25 mcg/ml can cause reversible bone marrow suppression.
§§ According to the Working Group on Civilian Biodefense, children younger than 2 years of age should not receive chloramphenicol due to risk of 'gray baby syndrome'.

Source: Working Group on Civilian Biodefense. Inglesby TV, JAMA 2000; 283(17):2281-2290.

Vaccine

A formaldehyde-killed whole bacilli vaccine was discontinued by its manufacturers in 1999 and is no longer available. Plans for future production are unclear. Research is ongoing in the pursuit of a vaccine that protects against primary pneumonic plague.

INFECTION CONTROL*

These recommendations are current as of this document date. YCHD will provide periodic updates as needed and situational guidance in response to events (www.yolohealth.org).

* For description of Precautions, see chapter on Infection Control

Pneumonic plague is spread from person-to-person by respiratory droplet transmission (coughing, sneezing). For suspected or confirmed bubonic plague, **Droplet, Contact** and **Standard Precautions** should initially be observed. Contact Precautions should be maintained until 48-72 hours of appropriate antibiotics have been administered AND the patient is showing clinical improvement.

Aerosol-generating procedures should be avoided if possible. Since plague is not transmitted by airborne particles, negative air pressure isolation rooms are not indicated except for aerosol-generating procedures. Multiple patients with pneumonic plague may be cohorted as long as all patients are receiving appropriate antimicrobial therapy.

In general, environmental decontamination following an aerosol event has not been recommended, since experts have estimated that an aerosol of *Y. pestis* organisms would be infectious for only about 1 hour. A recent study demonstrated that *Y. pestis* can survive on selected environmental surfaces for at least several days; however the potential for re-aerosolization of these organisms was not addressed. Commercially available bleach or 0.5% hypochlorite solution (1:10 dilution of household bleach) is considered adequate for cleaning.

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RICIN 2006

Outline

By law, health care providers must report suspected or confirmed Ricin poisoning to the local health department immediately (within 1 hr).

Even a single case of Ricin poisoning is considered an outbreak and is a public health emergency.

To report: call YCHD (24/7 (530) 666-8645).

Upon receipt, YCHD will initiate the public health response and can facilitate lab testing.

AGENT

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. 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.

EPIDEMIOLOGY

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 US. 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.

Ricin as a Biological Weapon

Ricin is easily produced, inexpensive, highly toxic and stable. There are currently no specific treatments or vaccines for ricin. It has been weaponized by the former Soviet Union and used by the Soviet KGB as a method of assassination. As a weapon, ricin could be disseminated by aerosol, injection, 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

CLINICAL FEATURES

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 36 to 72 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 know 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. The death rate after ingestion even for symptomatic patients is generally low.

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

The diagnosis of ricin is primarily clinical or epidemiological and requires a high index of suspicion. Confirmatory tests include nasal or throat swabs for toxin within 24 hours post-exposure, serum for toxin assay and antibody response within 36-48 hours post-exposure, and serum IgM and IgG greater than 6 days post-exposure.

If you are testing or considering testing for Ricin intoxication, you should:

IMMEDIATELY notify YCHD (24/7 (530) 666-8645). YCHD can authorize and facilitate testing, and will initiate the public health response as needed.

These tests are available, or can be arranged at the CDC through the Yolo County Public Health Laboratory.

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 ricin poisoning must wear surgical gloves, protective gowns and shoe covers if performing procedures with high splash potential or risk of aerosolization. The dust of the castor bean plant and crushed castor beans

contain glucoproteins that are particularly allergenic. 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 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

These recommendations are current as of this document date. YCHD will provide periodic updates as needed and situational guidance in response to events (www.yolohealth.org).

Treatment is symptomatic and supportive. There is no specific antidote, vaccine or treatment available.

For aerosol (inhalational) 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, if patient has not vomited and if patient presents less than one hour after exposure, rinse mouth and consider gastric lavage. H2-blockers and decontamination with superactivated charcoal are also indicated. Early and aggressive intravenous fluid and electrolyte replacement is critical. Provide blood pressure support with intravenous vasopressors. Consider alternative diagnoses and treat appropriately. 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. Remove contaminated clothing and rinse skin with soap and water or shower. Following ocular exposure, immediately flush eyes with large amounts of tepid water for at least 15 minutes.

Consultation with public health and the National Poison Control Center Hotline 1-800-222-1222 is recommended.

Management of Exposed Persons

There is currently no available postexposure prophylaxis. Persons thought exposed to ricin should be referred to a hospital for evaluation. 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*

These recommendations are current as of this document date. YCHD will provide periodic updates as needed and situational guidance in response to events (www.yolohealth.org).

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).

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* For description of Precautions, see chapter on Infection Control

SMALLPOX 2006

Outline

By law, health care providers must report suspected or confirmed Smallpox to the local health department immediately (within 1 hr).

Even a single case of Smallpox is considered an outbreak and is a public health emergency.

To report: call YCHD (24/7 (530) 666-8645).

Upon receipt, YCHD will initiate the public health response and can facilitate lab testing.

AGENT

Smallpox is caused by variola virus, a large, enveloped, single-stranded DNA virus of the Poxvirus family and the *Orthopoxvirus* genus. One strain of virus is responsible for variola major, the more lethal form of the disease, while several additional strains comprise variola minor.

Variola replicates in the host cell cytoplasm, forming inclusion bodies, unlike varicella, which replicates in the cell nucleus. There is extensive cross-neutralization between orthopoxviruses, and this accounts for the protection against smallpox after vaccination by vaccinia virus.

EPIDEMIOLOGY

Smallpox as a Biological Weapon

Variola virus is believed to have been weaponized by the former Soviet Union to be mounted in missiles and bombs. Currently, variola virus is stored in two known facilities, one at the CDC, and the other in a Russian research laboratory, but may exist in other covert locations as well. Even if all stocks of naturally occurring smallpox virus are destroyed, it is now possible to genetically engineer a similar viral agent in the laboratory setting. This capability requires that the medical and public health communities maintain smallpox preparedness into the foreseeable future.

Smallpox is of concern as a biological weapon because:

- Much of the population (80%) is susceptible to infection
- The virus has a low infectious dose and carries a high rate of morbidity and mortality
- Vaccine is not yet available for general use
- Experience has shown that introduction of the virus creates havoc and panic.

Aerosol release of virus (such as into a transportation hub) would likely result in a high number of cases. Other possibilities include use of "human vectors" (i.e. persons who have been deliberately infected with smallpox) and use of fomites (e.g. contamination of letters sent through the mail).

Naturally Occurring Smallpox

Smallpox was eradicated globally by means of a 12-year, international campaign involving mass vaccination programs combined with surveillance and containment of outbreaks. The last reported case of endemic smallpox occurred in Somalia in 1977, and there have been no additional cases since a laboratory accident in 1978.

Infectivity

Before global eradication, the only reservoir for variola virus was humans. Vectorborne transmission does not occur. Smallpox is transmitted person-to-person mainly via inhalation of droplet nuclei, though inhalation of airborne particles and direct contact with skin lesions or infected body fluids have also been shown to transmit disease. Typically, smallpox transmission requires close face-to-face contact with an infected patient.

Historically, infectiousness in smallpox was correlated with rash onset, and patients in the prodromal phase were generally not considered infectious. However, variola virus is now known to be shed from oral lesions during the 1-2 days of fever preceding rash onset. Infectiousness is highest during the first week after rash onset when lesions in the mouth ulcerate and release large amounts of virus into the saliva.

Secondary attack rates among unvaccinated close contacts range from 30-80% and the average number of cases infected by a primary case is estimated at 3.5-6. In populations with little herd immunity, the transmission potential of smallpox has the capability to create a rapid rise in outbreak cases before control measures can be applied.

Communicability lasts until all the lesions have scabbed over and the scabs have fallen off. Viable viral particles can be detected in scabs, however scabs are considered relatively noninfectious since the viral particles are bound in the fibrin matrix of the scab. No chronic viral carrier state occurs.

CLINICAL FEATURES

The variola virus typically enters the body via respiratory or oral mucosa. The virus is carried by macrophages to regional lymph nodes where a primary viremia develops on the 3rd-4th day after infection. The reticuloendothelial organs are invaded and overwhelmed leading to a secondary viremia around the 8th-12th day after infection; this is followed by onset of fever and toxemia. Death most commonly results from overwhelming toxemia, probably associated with circulating immune complexes.

Variola Major

Historically there were 3 serious and 2 less-serious forms of variola major. The most common form, **ordinary smallpox**, occurred in 90% of cases and had case-fatality rates of 15-45%.

VARIOLA MAJOR: CLINICAL FEATURES OF 'ORDINARY SMALLPOX'	
Incubation Period	• 10-13 days (range 7-19 days)
Signs & Symptoms	Prodromal Phase • 2-4 days of fever, chills, headache, backache, and often GI symptoms Rash Phase • Enanthem (papules, vesicles, then ulcers) of oropharyngeal mucosa beginning 1 day before skin lesions appear • First few skin lesions often appear on face ("herald spots") • Lesions spread centrifugally from trunk to proximal then distal extremities • Palms and soles are usually involved, while truncal rash is usually sparse • Lesions initially maculopapular (days 1-2), then vesicular (days 3-5), then pustular (days 7-14) • Vesicles and pustules often have central umbilication • Pustules often called "shotty" (i.e. like small, embedded hard balls) • Lesions tend to progress at same rate • Are typically painful, cause pitted scars as they heal • May be discrete, semiconfluent, or confluent • Gradually scab over during days 13-18
Complications	• Viral bronchitis/pneumonitis • Third spacing with resulting electrolyte and renal abnormalities • Massive skin desquamation • Secondary bacterial infection, particularly skin and pulmonary • Spontaneous abortion, stillbirth • Rarely: corneal ulceration, encephalitis, osteomyelitis or arthritis, orchitis • Death may occur during 2nd week of illness, from high-level viremia and circulating immune complexes
Laboratory Findings	• Lymphocytopenia and/or granulocytopenia

Flat-type smallpox (also known as malignant smallpox) occurred in about 6% of cases in the pre-vaccination era, and more commonly in children. The lesions do not progress to the pustular stage, instead remaining soft and flattened. There tends to be more systemic toxicity and higher mortality (>90%), and may be related to impaired host cell-mediated immunity.

Hemorrhagic smallpox occurred in about 3% of cases. It presented with severe systemic toxicity and case-fatality rates >95%. The rash begins as a dusky erythema, followed by extensive petechiae, mucosal hemorrhage, and intense toxemia. Thrombocytopenia and coagulopathy may be present. These patients usually died during week 1 of illness, often before the development of the typical pox lesions.

Two additional forms, **modified smallpox** and **variola without eruption**, were milder forms of disease that occurred in persons with some immunity from past infection or vaccination.

Variola Minor

Variola minor is a milder form of smallpox caused by distinct strains of variola virus. In the early 20th century, it was the most prevalent form of smallpox in the USA. Compared with variola major, the disease results in milder constitutional symptoms, typically discrete lesions that evolve a bit more rapidly, lower rates of hemorrhagic disease, and only rarely fatal (<1%) outcomes. The illness may be difficult to distinguish clinically from modified smallpox and variola without eruption.

DIFFERENTIAL DIAGNOSIS

The characteristic features of smallpox need to be differentiated from other illnesses that present with vesicular or pustular rash. The one disease that is most likely to be misidentified as smallpox in the setting of an outbreak is chicken pox. These may be differentiated clinically, as follows:

CLINICAL DIFFERENTIATION OF VARIOLA VS. VARICELLA

Feature	Variola	Varicella
Prodrome	• Lasts 2-4 days • High fever, headache, backache, severe prostration	• Often absent • If present, mild and brief (1 day)
Rash Distribution	• Begins on oropharyngeal mucosa • Expands to face • Then expands centrifugally – most dense on distal extremities • Commonly affects palms and soles • More involvement of back than abdomen	• Begins on trunk • Expands centripetally – most dense on trunk • Spares palms and soles • Back and abdomen equally involved
Lesion Evolution	• Emerge widely over 1-2 days, then progress at same rate • Progress slowly (7-14 days) from macules to papules to vesicles to pustules to scabs	• Emerge in crops, often at different stages of evolution at any given time • Progress quickly (1-2 days) from macules to papules to vesicles to scabs
Lesion Attributes	• May be semiconfluent or confluent • May be umbilicated • Often painful; pruritic only as scabs	• Usually discrete • Do not umbilicate or dimple • Typically painless; intensely pruritic

CDC has developed criteria for determining the risk of smallpox when evaluating patients with generalized vesicular or pustular rash. An online version of the algorithm is available at: www.bt.cdc.gov/agent/smallpox/diagnosis/riskalgorithm/index.asp

Risk of Smallpox in Patients with Generalized Vesicular or Pustular Rash	
High	All 3 'major criteria' present: a) Febrile prodrome 1-4 days before rash onset, with fever >101°F, plus 1 or more of the following: Prostration, headache, backache, chills, vomiting, severe abdominal pain b) Classic smallpox lesions present (vesicles or pustules that are deep-seated, firm or hard, round, and well-circumscribed; sharply raised and feel like 'BB pellets' under the skin; may become umbilicated or confluent as they evolve) c) Lesions on any one part of the body are in the same stage of development
Moderate	Febrile prodrome as in (a) above, plus either (b) or (c) above *OR* Febrile prodrome as in (a) above, plus at least 4 of the following 'minor criteria': • Centrifugal distribution • First lesions appeared on the oral mucosa/palate, face, or forearms • Patient appears toxic or moribund • Slow evolution of lesions from macules to papules to pustules over several days • Lesions on the palms and soles
Low	No viral prodrome *OR* Febrile prodrome as in (a) above, plus < 4 'minor criteria' above
Source: CDC (www.bt.cdc.gov/agent/smallpox/diagnosis/rashtestingprotocol.asp)	

Additional considerations in the differential diagnosis of smallpox include:

- Disseminated herpes zoster
- Hand, foot & mouth disease - (Coxsackie virus)
- Disseminated herpes simplex
- Molluscum contagiosum
- Human monkey pox*
- Erythema multiforme major - (Stevens-Johnson syndrome)
- Bullous pemphigoid
- Miscellaneous drug eruptions
- Impetigo (*Strep, Staph*)
- Secondary syphilis

Hemorrhagic smallpox may resemble:

- Meningococcemia
- Rocky Mountain spotted fever
- Ehrlichiosis

* In June 2003, an outbreak of monkeypox virus occurred among 71 persons in several Midwestern US states. There were no fatalities. The outbreak was traced to contact with prairie dogs, which had been infected through contact with rodents from Ghana. Monkeypox in humans is similar to discrete or semiconfluent ordinary smallpox, but is generally milder than smallpox, and is distinguished by the presence of prominent lymphadenopathy.

- Gram-negative septicemia

LABORATORY DIAGNOSIS

Laboratory diagnosis is confirmatory, as smallpox can most often be diagnosed clinically. Once smallpox has been confirmed in a geographic area, additional cases can be diagnosed clinically, and specimen testing can be reserved for specific cases in which the clinical presentation is unclear, to identify an index case, or to assist with law enforcement activities.

If you consider testing for Smallpox, you should IMMEDIATELY notify YCHD (24/7 (530) 666-8645) to facilitate specimen processing and public health response.

Per CDC guidelines, only personnel vaccinated within 3 years, wearing appropriate barrier protection (gloves, gown, shoe covers, and face shields) should be involved in specimen collection for suspected Smallpox.

If vaccinated personnel are not available, only those without contraindications to vaccination should be utilized as they would require immediate vaccination if the diagnosis of Smallpox is confirmed. Appropriate respiratory as well as barrier protection should be worn.

Basic confirmation relies upon electron microscopic examination of vesicular or pustular fluid or scabs, which can rapidly confirm the presence of *Orthopoxvirus* in the specimen but does not prove that *variola* is the species. Definitive laboratory identification and characterization of the variola virus requires several days, and involves growth of the virus in cell culture or on chorioallantoic egg membrane and characterization of strains by use of various biologic assays (including PCR techniques) and restriction fragment-length polymorphisms.

Specimen Collection from Patients with Vesicles or Pustules

Use the protective equipment described above.

Lesion Specimens. Sanitize skin with an alcohol wipe and allow it to dry. Unroof the lesion with a sterile scalpel and place the skin into a dry, sterile, capped plastic tube. Scrape the base of the vesicle or pustule with the blunt edge of the scalpel. Apply a microscope slide to the vesicular fluid multiple times, with progressive movement of the slide, to make a touch prep. Allow the fluid to air-dry 10 minutes without smearing. Store the dried slide in a plastic slide container. If available, lightly touch an electron microscope grid to the unroofed base of the lesion and allow to air dry. Repeat this procedure two more times, varying the pressure applied to the unroofed lesion (lighter or firmer pressure). Place in gridbox and record which slot is used for each patient specimen. Biopsy vesicles (2) with 3.5- or 4-mm punch biopsy kit. Place one biopsy in formalin and the other in a dry, screw-capped container.

Blood Samples. Draw 10 cc of blood into a plastic marble-topped tube or plastic yellow-topped serum separator tube. If plastic tubes are not available, glass tubes may be used, but should be placed in Styrofoam protector for packaging and shipping.

Labeling and Shipping. Label all specimens with patient name, date of collection, and specimen source. Place specimens from a single patient into a biohazard bag labeled with the above information. Ship all specimens, packaged to avoid shocks and breakage, within 24 hours of collection. All samples should be stored at 4°C, except formalin-fixed biopsy (room temperature) and non-formalin fixed biopsy (dry ice).

Specimen Collection from Patients with Scab Lesions

Use the protective equipment described above.

Scab Specimens. Sanitize skin with an alcohol wipe and allow it to dry. Use a 26-gauge needle to pry off as many scabs as possible (at least four). Place two scabs in each of two dry, screw-capped plastic vials. Biopsy lesions (2) with 3.5- or 4-mm punch biopsy kit. Place one biopsy in formalin and the other in a dry, screw-capped container.

Blood Specimens. As above.

Labeling and Shipping. As above.

TREATMENT AND PROPHYLAXIS

These recommendations are current as of this document date. YCHD will provide periodic updates as needed and situational guidance in response to events (www.yolohealth.org).

Treatment

The management of confirmed or suspected cases consists of supportive care, with careful attention to electrolyte and volume status, and ventilatory and hemodynamic support. General supportive measures include ensuring adequate fluid intake (difficult because of the enanthem), alleviation of pain and fever, and keeping skin lesions clean to prevent bacterial superinfection.

Currently there are no antivirals with proven activity against smallpox in humans, though several agents have shown *in vitro* activity and are undergoing testing in animal models.

Vaccine Supply, Administration, and Efficacy

The smallpox vaccine used in the US (Dryvax) is a lyophilized (freeze-dried) preparation of live attenuated Vaccinia virus, an *Orthopoxvirus* closely related to cowpox that induces antibodies that are protective against smallpox. The preparation also contains the antibiotics polymyxin B, streptomycin, tetracycline and neomycin. The diluent used to reconstitute the vaccine is 50% glycerin and a small amount of phenol as a preservative. The vaccine vial stopper contains natural rubber.

The Dryvax vaccine was produced by Wyeth in the 1970's and existing supplies have been maintained in storage since that time. Evaluation has shown that the vaccine is still potent. Although there are about 15 million full-strength doses remaining, studies have shown that the vaccine is capable of eliciting adequate immune responses in most vaccinees at dilutions of up to 1:10 (Frey, JAMA 2003). It is licensed by the FDA and distributed by the CDC.

An additional 85 million doses of a similar smallpox vaccine produced by Aventis were stored frozen. This preparation is not currently licensed, but has shown >99% vaccination success rates at 1:10 dilution (Talbot, JAMA 2004). Efforts to develop new smallpox vaccines are in progress.

Technique. Dryvax vaccine is administered using a droplet of the vaccine applied to a bifurcated needle. The needle is dipped into the vaccine vial and stroked against the skin with sufficient vigor that a trace of blood appears at the vaccination site. The site is then covered with sterile gauze dressing underneath a semipermeable dressing. Since the vaccine contains live Vaccinia virus, vaccinees must be instructed to keep the site dry and covered, to avoid touching the site, and to thoroughly launder or carefully discard any materials that come into contact with the site. (**Note: vaccine should be administered by persons trained in its administration, who have themselves been successfully vaccinated. Should smallpox vaccination be necessary in Yolo County, it will be coordinated by YCHD.)** For additional information on vaccine administration, see www.bt.cdc.gov/agent/smallpox/vaccination.

Assessment. Under optimal conditions, Dryvax vaccinees must return 6-8 days after vaccination for a "take check." Successful primary vaccination is demonstrated by occurrence of a pustular or vesicular skin lesion at the site of vaccination. Successful revaccination (in persons who received ≥1 prior dose of vaccine) is indicated by palpable inflammation at the site. The presence of a successful "take" correlates with the development of neutralizing antibody, which appears about 10 days after primary vaccination and about 7 days after revaccination.

Protection. Antibody titers of 1:10 or higher develop in 95% of primary vaccinees after a single inoculation, a level believed to confer adequate protection. Protection against smallpox persists for 5 to 10 years after primary vaccination. Antibody titers of 1:10 or higher are found in 75% of persons up to 10 years after receiving two doses of vaccine and up to 30 years after receiving three doses. Probably fewer than 20% of persons vaccinated before the early 1970s have immunologic protection today. It is not clear whether a remote history of receiving one dose of smallpox vaccine will modulate disease severity in the event that infection occurs.

Smallpox Vaccination in the Pre-Event and Post-Exposure Settings

Routine vaccination of the US population ended in the 1970's. Vaccination is currently required for most military personnel and is recommended for select health care and emergency workers, described below. Due to the relative frequency and seriousness of vaccine-related complications and the low risk of smallpox outbreak in the US, routine vaccination is not recommended for the vast majority of healthcare workers or for the general US population.

In 2002, the CDC recommended pre-event vaccination for local smallpox response teams, consisting of public health, medical, nursing, and public safety personnel, who would conduct investigation and management of initial smallpox cases.

Immunity to variola virus generally develops within 8 to 11 days after vaccination. Since the incubation period for smallpox averages about 12 days, vaccination within 4 days may confer some immunity to exposed persons and reduce the likelihood of a fatal outcome. Post-exposure vaccination may be particularly important for those vaccinated in the past, provided that revaccination is able to boost the anamnestic immune response.

An exposed person is defined as one 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, once the case has developed febrile illness.

Vaccine Contraindications and Complications

The Dryvax vaccine does have serious complications with up to 3 in 100,000 vaccinees reporting significant adverse reactions and nearly 1 in 1,000,000 deaths. Likelihood of adverse effects is 3- to 4-fold higher in infants and in primary vaccinees.

Vaccination during the pre-exposure period is contraindicated for certain persons. **During a smallpox emergency, however, all contraindications would be reviewed in the context of the risk of smallpox exposure, and updated recommendations would be issued by YCHD and other public health authorities.** Contraindications to vaccination are as follows (see www.bt.cdc.gov/agent/smallpox/vaccination for further description):

- Past or present eczema or atopic dermatitis (risk of eczema vaccinatum)
- Other acute or chronic exfoliative skin conditions (e.g. burns, impetigo, chicken pox, contact dermatitis, shingles, herpes, severe acne, psoriasis), until the condition resolves
- Immunodeficiency states, due to disease or treatment of disease
- Pregnancy or breastfeeding
- Hypersensitivity to vaccine components
- Under 18 years of age in nonemergency situations
- Household contacts who are immunodeficient, who have past or present eczema or atopic dermatitis, or who have an acute, chronic, or exfoliative skin condition
- Physician-diagnosed cardiac disease, or $\geq$3 major risk factors for cardiac disease

Well-documented adverse reactions to vaccination are listed below (photos of vaccine adverse events at www.bt.cdc.gov/training/smallpoxvaccine/reactions):

- Tenderness, erythema at the injection site, other localized reactions (including allergic reactions to tape adhesives and “robust takes”), and secondary bacterial infections
- Systemic reactions: fever of at least 100°F, malaise, myalgias, local lymphadenopathy
- Dermatologic reactions, including erythema multiforme and Stevens Johnson syndrome, urticaria, exanthems, contact dermatitis, and erythematous papules

- Focal and generalized suppurative folliculitis (without evidence of viral infection; may be mistaken for generalized vaccinia)
- Inadvertent autoinoculation of another body site (25-529 cases per 1M* primary vaccinees)
- Generalized vaccinia (GV): vesicles or pustules appearing on normal skin distant from the vaccination site (23-241 cases per 1M primary vaccinees)
- Eczema vaccinatum (EV): localized or systemic spread of vaccinia virus; may be severe and can be fatal; (10-38 cases per 1M primary vaccinees)
- Vaccinia keratitis
- Progressive vaccinia (PV): progressive necrosis in vaccination area, often with spread to other sites; can be severe and fatal; (0.9-1.5 cases per 1M primary vaccinees)
- Postvaccinial encephalitis (PVEM) (2.9-12.3 cases per 1M primary vaccinees)
- Fetal vaccinia: occurs after primary inoculation of the mother during pregnancy; usually results in stillbirth or death of the infant soon after birth
- Myopericarditis, identified among military personnel vaccinated 12/2002-12/2003 (124 cases per 1M vaccinees)
- Death: 1.1 deaths per 1M primary vaccinees
- Contact vaccinia: transmission of vaccinia virus from newly vaccinated persons to susceptible unvaccinated contacts (61-81 cases per 1M primary vaccinees; higher rates of transmission likely with immunocompromised contacts)

The primary therapy for adverse reactions to smallpox vaccination is vaccinia immunoglobulin (VIG). VIG is manufactured from plasma of persons vaccinated with vaccinia vaccine. An intravenous preparation (VIGIV) was recently licensed by the FDA. Antiviral agents with activity against vaccinia virus include cidofovir (a nucleotide analogue of cytosine), which may also be available from the CDC under an investigational protocol, and topical ophthalmic antiviral drugs (trifluridine or vidarabine) for vaccinia ocular involvement.

INFECTION CONTROL†

These recommendations are current as of this document date. YCHD will provide periodic updates as needed and situational guidance in response to events (www.yolohealth.org).

Smallpox is transmissible from person-to-person by exposure to respiratory secretions, particularly during coughing, by contact with pox lesions, and by fomites. **Airborne and Contact Precautions in addition to Standard Precautions** should be implemented for patients with suspected smallpox. Healthcare workers caring for patients with suspected smallpox should be vaccinated immediately.

Standard disinfection/sterilization methods are deemed to be adequate for medical equipment used with smallpox patients. Standard hospital disinfectants or hypochlorite are adequate for cleaning

* 1M = 1 million

† For description of Precautions, see chapter on Infection Control

surfaces potentially contaminated with the virus. Bedding and clothing of smallpox patients should be minimally handled to prevent re-aerosolization, and autoclaved or laundered in hot water to which bleach has been added. Since variola virus is rapidly inactivated in the environment, standard terminal cleaning practices are considered adequate for rooms that have housed smallpox patients. Airspace decontamination (fumigation) is not required.

Detailed instructions on infection control practices for smallpox have been prepared by the CDC and may be found at: www.bt.cdc.gov/agent/smallpox/response-plan/files/guide-f.doc.

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TULAREMIA 2006

Outline

By law, health care providers must report suspected or confirmed Tularemia to the local health department immediately (within 1 hr).

Even a single case of Tularemia is considered an outbreak and is a public health emergency.

To report: call YCHD (24/7 (530) 666-8645).

Upon receipt, YCHD will initiate the public health response and can facilitate lab testing.

AGENT

Tularemia is a zoonotic disease caused by *Franciscella tularensis*, a non-sporulating, non-motile, aerobic gram-negative coccobacillus. The organism has a thin, lipid-rich capsule. It grows on commercial blood culture media, but does not grow reliably on most other standard media. *F. tularensis* strains are generally resistant to beta-lactam antibiotics. Organisms can persist for long periods of time in water, mud, and decaying animal carcasses.

There are several subspecies of *F. tularensis*. The most common naturally occurring isolate in the US is the subspecies *tularensis* (type A), which typically results in a more severe illness. *F. tularensis* is a facultative intracellular pathogen that multiplies predominantly within macrophages. Its virulence factors are not well characterized.

EPIDEMIOLOGY

Tularemia as a Biological Weapon

Weaponized *F. tularensis* was developed and stockpiled by the US military, though the supply was destroyed in the 1970's. The Soviet Union is reported to have developed antibiotic- and vaccine-resistant strains of weaponized *F. tularensis.*

The most likely form of intentional release for *F. tularensis* organisms would be via infectious aerosols. An aerosol release is likely to cause several clinical syndromes:

- Primary pneumonic tularemia in the majority of patients
- Nonspecific febrile illness of varying severity (i.e. typhoidal tularemia) in some
- Oculoglandular tularemia could occur from eye contamination
- Glandular or ulceroglandular disease following exposure of broken skin to infectious aerosols
- Oropharyngeal disease also could occur through inhalation of organisms

An intentional outbreak of tularemia would be expected to have the following features:

- **Short incubation period (shorter incubation correlates with virulence of the infecting strain, and in a bioterrorist attack a highly virulent strain is likely)**
- **Illness onset 3 to 5 days after the initial release (range 1-14 days)**
- **Outbreak in an urban area, where naturally occurring tularemia is not endemic**
- **Patients lack risk factors for tularemia exposure (e.g. outdoor field work or recreational activity, contact with tissues of potentially infected animals).**

In the event of a bioterrorist attack, use of *F. tularensis* strains with enhanced virulence or antimicrobial resistance may be encountered.

Naturally Occurring Tularemia

The natural reservoirs for *F. tularensis* are small and medium-sized mammals. In the US these are primarily lagomorphs (rabbits, hares) but may include aquatic rodents (beaver, muskrats), field voles, water and wood rats, and squirrels. Humans, other mammalian species (e.g. cats, dogs, cattle), and some species of birds, fish, and amphibians are incidental hosts.

The primary vectors for infection in the US are ticks (dog ticks, wood ticks) and flies such as the deerfly. Humans have become infected by several mechanisms:

- Bites by infected arthropods (majority of cases)
- Handling of infectious animal tissues or fluids, *e.g.*, during hunting or butchering
- Ingestion of contaminated food or water
- Inhalation of infectious aerosols, including dust from contaminated hay and aerosols generated by lawn mowing and brush cutting
- Exposure in the laboratory setting during specimen handling

Nationwide, reported cases have declined from about 2,000 annually during the 1930s, to a mean of 124 per year during the 1990's. Most cases have occurred in rural or semi-rural environments, during the summer months. In California, there were 21 total cases reported during the period 1994-2003.

In 2002, tularemia was responsible for a die-off of several hundred prairie dogs caught in the wild in South Dakota and then commercially distributed widely throughout the US. One human case occurred in an animal handler who cared for the infected animals.

In 2003, low levels of *F. tularensis* were identified in a biodetection air-monitoring system in Houston, Texas. No human cases occurred. An investigation supported contamination of the filters by naturally occurring *F. tularensis* organisms, although the environmental reservoir was not definitively identified.

CLINICAL FEATURES

Human tularemia occurs in 6 recognized forms, determined primarily by route of infection. Clinically, tularemia can range from a mild infection to a severe life-threatening illness. Overall case-fatality rates have declined from 7% in the pre-antibiotic era to approximately 2% currently. Mortality was historically much higher with pulmonic infection. Most patients respond rapidly to appropriate antibiotic therapy, with fever and generalized symptoms improving in 24-48 hours. Recognition of tularemia as a potential etiologic agent is critical, as poor outcomes have been associated with delays in seeking care and/or instituting effective antimicrobial treatment.

Pneumonic Tularemia

Pneumonic tularemia occurs after inhalation of the organism, or as the result of secondary hematogenous spread to the lung. The infectious dose is thought to be as low as 10 organisms. It is only rarely acquired naturally, but is associated with the most severe disease. Pneumonic tularemia would present as a non-specific febrile illness with progression to pleuropneumonitis and systemic infection.

PNEUMONIC TULAREMIA: CLINICAL FEATURES	
Incubation Period	3-5 days (range 1-14 days)
Signs & Symptoms	• Initial presentation as atypical community-acquired pneumonia (CAP) unresponsive to typical antibiotic therapy for CAP • Illness may progress rapidly to severe disease OR may be indolent with progressive debilitation over several months • Prominent symptoms: abrupt onset of fever, nonproductive cough, dyspnea, pleuritic chest pain, myalgias • Hilar adenopathy, pleural effusion, pleural adhesions, bronchiolitis, and/or pharyngitis may be present • Nausea, vomiting, diarrhea may occur • 20% may have generalized maculopapular rash with progression to pustules or erythema-nodosum type rash
Complications	• Severe pneumonia • Lung abscess or cavitary lesions • Respiratory failure, ARDS • Sepsis
Laboratory Findings	• Lobar, segmental, or sub-segmental opacities on CXR, often with pleural involvement • Leukocytosis; differential may be normal • Liver enzymes and/or CK may be abnormal • Sputum gram stain is often not helpful

Glandular and Ulceroglandular Tularemia

Glandular and ulceroglandular tularemia account for the majority of naturally-occurring cases of tularemia. In both these forms, organisms enter the skin through the bite of infective arthropods,

direct contact with infectious materials (such as contaminated carcasses), or percutaneous inoculation with a sharp object (such as a bone fragment from a contaminated carcass).

In the ulceroglandular form, an ulcer is formed at the site of inoculation, with subsequent lymphadenopathy in the proximal draining lymph nodes. Occasionally, lymphadenopathy occurs without an ulcer leading to the designation of glandular disease.

GLANDULAR AND ULCEROGLANDULAR TULAREMIA: CLINICAL FEATURES	
Incubation Period	3-5 days (range 1-14 days)
Signs & Symptoms	• Ulceroglandular form – begins as local painful cutaneous lesion at inoculation site (papule that ulcerates in a few days) • Glandular form – no cutaneous lesion • Tender regional lymphadenopathy • Fever, chills, malaise, myalgias, arthralgias, headache, anorexia, GI symptoms are common • Lymphadenopathy may persist for months
Complications	• Lymph node suppuration • Secondary pneumonia • Hematogenous spread to other organs • Sepsis
Laboratory Findings	• Leukocytosis; differential may be normal • Liver enzymes and/or CK may be abnormal

Oculoglandular Tularemia

In oculoglandular tularemia, organisms gain entry via the conjunctiva. Oculoglandular tularemia might occur in a bioterrorist setting as a result of an aerosol exposure or from direct or indirect contact with contaminated water or food. Organisms spread from the conjunctiva to the preauricular, submandibular, or cervical lymph nodes, where they cause focal necrosis and lesions similar to those noted with ulceroglandular tularemia.

After an incubation period of 3-5 (range 1-14) days, oculoglandular tularemia presents as a painful "red eye" with purulent exudation and painful preauricular and/or cervical lymphadenopathy. Additional signs and symptoms may include photophobia, lacrimation, itching, local edema, and changes in visual acuity. There is a potential for lymph node suppuration, hematogenous dissemination, and development of sepsis.

Laboratory values are generally unremarkable, and gram stain of conjunctival scrapings may or may not demonstrate organisms.

Oropharyngeal Tularemia

Oropharyngeal or gastrointestinal tularemia occurs via ingestion of contaminated food, undercooked meat, contaminated water or droplets, and oral inoculation from the hands after contact with contaminated material.

After an incubation period of 3-5 (range 1-14) days, oropharyngeal tularemia presents either as acute pharyngitis with cervical lymphadenopathy or as 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. A large inoculum (approximately 100,000,000 organisms) is required to transmit disease orally. There is a potential for lymph node suppuration, hematogenous dissemination, and development of sepsis. Laboratory values are generally unremarkable, although leukocytosis may be present.

Typhoidal Tularemia

Typhoidal (septicemic) tularemia is an acute, nonspecific febrile illness associated with *F. tularensis* that is not associated with prominent lymphadenopathy.

TYPHOIDAL TULAREMIA: CLINICAL FEATURES	
Incubation Period	3-5 days (range 1-14 days)
Signs & Symptoms	• Fever, chills, malaise, weakness, myalgias, arthralgias • Prostration, dehydration • GI symptoms (watery diarrhea, vomiting, abdominal pain) • Skin findings may include generalized maculopapular rash with progression to pustules or erythema-nodosum type rash
Complications	• Secondary pneumonia (50-80%) • Hematogenous spread to other organs – osteomyelitis, pericarditis, peritonitis, endocarditis, meningitis • Sepsis • Rhabdomyolysis • Renal failure • Debilitating illness lasting several months
Laboratory Findings	• Leukocytosis; differential may be normal • Liver enzymes and/or CK may be abnormal • Sterile pyuria may occur

DIFFERENTIAL DIAGNOSIS

A high index of suspicion is required to diagnose tularemia as there are no readily available rapid and specific confirmatory tests. In addition, the various forms of tularemia can have a nonspecific appearance and/or resemble a wide range of much more common illnesses.

Pneumonic Tularemia: Differential

Key features that could help identify intentional aerosol release of tularemia:

- **Cluster of acute, severe respiratory illness in an urban, non-agricultural setting**
- **Unexpected, severe respiratory illness in otherwise healthy persons**
- **Findings of atypical pneumonia, pleuritis, and hilar lymphadenopathy**
- **Community-acquired atypical pneumonia unresponsive to typical antimicrobials**

Other conditions to consider:

- Community-acquired bacterial pneumonia (*Mycoplasma, Staph, Strep, Haemophilus, Klebsiella, Moraxella)*
- *Chlamydia psittaci* or *pneumoniae*
- Inhalational anthrax
- Pneumonic plague
- Q fever
- Tuberculosis
- Fungal pulmonary disease (histoplasmosis, coccidiodomycosis)
- Viral pneumonia (influenza, hantavirus, RSV, CMV)

Glandular Tularemia: Differential

- Bubonic plague
- Cat-scratch disease
- Mycobacterial infection
- Sporotrichosis
- *Staph* or *Strep* Adenitis
- Chancroid
- Lymphogranuloma venereum
- Primary genital herpes
- Syphilis

Ulceroglandular Tularemia: Differential

- Anthrax
- Pasteurella infections
- Primary syphilis
- Rat-bite fever
- Rickettsial pox
- Scrub typhus
- *Staph* or *Strep* cellulitis
- Orf virus

Oculoglandular Tularemia: Differential

- Adenoviral infection
- Cat-scratch disease
- Coccidiodomycosis
- Herpes simplex or Herpes zoster
- Pyogenic bacterial infections
- Sporotrichosis
- Syphilis
- Tuberculosis

Oropharyngeal Tularemia: Differential

- *Strep* pharyngitis
- GI anthrax
- Diphtheria
- Infectious mononucleosis
- Adenoviral infection

Typhoidal Tularemia: Differential

- Brucellosis
- Disseminated mycobacterial or fungal infection
- Endocarditis
- Leptospirosis
- Malaria
- Q fever
- Typhoid fever
- Meningococcemia
- Septicemic plague
- Septicemia caused by other gram-negative bacteria
- *Staph* or *Strep* toxic shock syndrome
- Rocky Mountain spotted fever
- Ehrlichiosis

LABORATORY DIAGNOSIS

The diagnosis of tularemia requires a high index of suspicion since the disease often presents with non-specific symptoms. Since the organism is hard to isolate, diagnosis often rests on serologic evidence of infection in a patient with a compatible clinical syndrome.

If you consider testing for Tularemia, you should:

- **IMMEDIATELY notify YCHD (24/7 (530) 666-8645) to facilitate specimen processing and public health response.**
- **Notify the lab that Tularemia is suspected, as *F. tularensis* may pose a risk to lab personnel.**

Antibody detection assays include tube agglutination, microagglutination, and ELISA. Significant antibodies appear around the end of the 2nd week of illness, peak at 4-5 weeks, and can persist indefinitely. A single titer of $\geq$1:160 (by tube agglutination) or $\geq$1:128 (by microagglutination) is a presumptive positive; a four-fold rise in titer is required for definitive serologic diagnosis.

Gram stain may be of little value, as *F. tularensis* is a small, weakly staining pleomorphic gram-negative coccobaccilus that cannot readily be distinguished from the background. Culture and isolation of *F. tularensis* are difficult and often not fruitful. Some strains may require up to a week to develop visible colonies, especially if the patient has been placed on bacteriostatic antibiotic therapy. A positive DFA test on a culture isolate confirms the identification.

TREATMENT AND PROPHYLAXIS

These recommendations are current as of this document date. YCHD will provide periodic updates as needed and situational guidance in response to events (www.yolohealth.org).

Treatment

The treatment of choice for all forms of tularemia is streptomycin. Gentamicin, which is more widely available, is an acceptable alternative. Tetracycline and chloramphenicol have been used to

treat tularemia, however as these drugs are bacteriostatic, relapses occur more often than with the aminoglycosides. Bioterrorist use of an *F. tularensis* strain resistant to conventional antibiotic therapy is of concern and should be considered, particularly if patients deteriorate despite early initiation of antibiotic therapy.

TABLE 1. TREATMENT OF TULAREMIA IN THE CONTAINED CASUALTY SETTING

Patient Category	Therapy Recommendation*
Adults: Preferred Choices	Streptomycin, 1 gm IM BID for 10 days‡†§ ***OR*** Gentamicin, 5 mg/kg IM or IV QD for 10 days‡†
Adults: Alternative Choices	Doxycycline, 100 mg IV BID for 14-21 days† ***OR*** Chloramphenicol, 15 mg/kg IV QID for 14-21 days** ***OR*** Ciprofloxacin, 400 mg IV BID for 10 days†
Children: Preferred Choices	Streptomycin, 15 mg/kg IM BID (max 2 gm/day) for 10 days‡ ***OR*** Gentamicin, 2.5 mg/kg IM or IV TID for 10 days‡
Children: Alternative Choices	Doxycycline, >45 kg, give adult dosage for 14-21 days <45 kg, give 2.2 mg/kg IV BID for 14-21 days ***OR*** Chloramphenicol, 15 mg/kg IV QID for 14-21 days** ***OR*** Ciprofloxacin, 15 mg/kg IV BID (max 1 gm/day) for 10 days

* These treatment recommendations reflect those of the Working Group on Civilian Biodefense and may not necessarily be approved by the Food and Drug Administration.
† Acceptable for pregnant women.
§ Streptomycin is not as acceptable as gentamicin for use in pregnant women because irreversible deafness in children exposed *in utero* has been reported with streptomycin use.
‡ Aminoglycosides must be adjusted according to renal function.
** Concentration should be maintained between 5 and 20 цg/mL; concentrations >25 цg/mL can cause reversible bone marrow suppression.

Source: Working Group on Civilian Biodefense. Dennis DT, JAMA 2001 285(21):2763-2773.

Supportive care of patients is also critical, including fluid management and hemodynamic monitoring as indicated. Some patients may require intensive care with respiratory support owing to complications of gram-negative sepsis.

In a contained casualty setting where the medical care delivery system can effectively manage the number of patients, parenteral antibiotics should be administered **(Table 1, above)**. Therapy may be switched to oral antimicrobials when clinically indicated.

In a mass casualty setting where the medical care delivery system is not able to meet the demands for patient care, use of oral antibiotics may be necessary **(Table 2, below)**.

TABLE 2. TREATMENT OF TULAREMIA IN THE MASS CASUALTY SETTING AND FOR POST-EXPOSURE PROPHYLAXIS*	
Patient Category	**Therapy Recommendation***
Adults (Including Pregnant Women)	Doxycycline, 100 mg PO BID for 14 days‡ ***OR*** Ciprofloxacin, 500 mg PO BID for 14 day‡
Children	Doxycycline, >45 kg, give adult dosage for 14 days <45 kg, give 2.2 mg/kg PO BID for 14 days ***OR*** Ciprofloxacin, 15 mg/kg PO BID (max 1 gm/day) for 10 days
* These treatment recommendations reflect those of the Working Group on Civilian Biodefense and may not necessarily be approved by the Food and Drug Administration. ‡ Although fetal toxicity may occur with doxycycline use, the Working Group recommended doxycycline or ciprofloxacin for postexposure prophylaxis of pregnant women or for treatment of infection of pregnant women in the mass casualty setting.	
Source: Working Group on Civilian Biodefense. Dennis DT, JAMA 2001 285(21):2763-2773.	

Post-Exposure Prophylaxis

Antibiotic prophylaxis should begin as soon as possible and preferably within 24 hours after exposure to an infectious aerosol containing *F. tularensis* **(Table 2)**. Post-exposure prophylactic antibiotic treatment of close contacts of tularemia patients is not recommended since human-to-human transmission of *F. tularensis* is not known to occur.

Vaccination

A live, attenuated vaccine was used in the US until recently to protect laboratory workers at high risk for *F. tularensis* exposure. However the vaccine currently is unavailable and is under review by the FDA.

INFECTION CONTROL*

These recommendations are current as of this document date. YCHD will provide periodic updates as needed and situational guidance in response to events (www.yolohealth.org).

Person-to-person transmission of tularemia has not been documented; therefore, **Standard Precautions** are considered adequate for patients with tularemia. Commercially available bleach or a 1:10 dilution of household bleach and water is considered adequate for disinfecting contaminated surfaces. After direct exposure to powder or liquid aerosols containing *F. tularensis*, body surfaces and clothing should be washed with soap and water.

* For description of Precautions, see Chapter on Infection Control

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VIRAL HEMORRHAGIC FEVER (VHF) 2006

Outline

By law, health care providers must report suspected or confirmed VHF to the local health department immediately (within 1 hr).

Even a single case of VHF is considered an outbreak and is a public health emergency.

To report: call YCHD (24/7 (530) 666-8645).

Upon receipt, YCHD will initiate the public health response and can facilitate lab testing.

AGENT

Hemorrhagic fever viruses are a diverse group of RNA viruses that cause viral hemorrhagic fever (VHF) in humans. Hemorrhagic fever viruses 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

EPIDEMIOLOGY

VHF as a Biological Weapon

Several countries, including the US and Russia, have conducted research on weaponizing VHF. Aerosolized VHF preparations are considered potentially suitable as biological weapons because they would have a low infectious dose, would cause high morbidity and mortality, would have the potential for person-to-person transmission, and because effective therapy and vaccines are not always available.

The two families of viruses of most concern based on mortality and feasibility of production are the filoviruses and the arenaviruses.

Several species of hemorrhagic fever viruses (dengue, hantavirus, and Crimean-Congo hemorrhagic fever) are not considered to represent a significant bioterror threat.

Naturally Occurring Viral Hemorrhagic Fever

All of the VHF agents cause sporadic disease or epidemics in areas of endemicity. The routes of transmission are variable, but most are zoonotic with spread via arthropod bites or contact with infected animals. Person-to-person spread is a major form of transmission for many of the viruses.

Ebola hemorrhagic fever (Central Africa) exhibits case-fatality rates of 50-90%. An outbreak among primates occurred in 1991 at a laboratory in Reston, Virginia. The natural reservoirs and exact patterns of transmission of Ebola virus are not known.

Marburg virus (sub-Saharan Africa) has caused outbreaks in Angola resulting in 451 cases (312 fatal) as of July 10, 2005. As with Ebola, the natural reservoirs and exact patterns of transmission of Marburg virus are not known.

Rodents are the primary reservoir for **Lassa** virus (West Africa). Case-fatality rates are lower for Lassa fever than for Ebola and Marburg, and ribavirin has been effective in treating some cases.

A number of uncommon viruses comprise **New World** hemorrhagic fever (South America), which appears to be transmitted via contact with rodents or rodent excreta. Three cases of imported **Whitewater Arroyo** virus were reported in California in 1999-2000; all were fatal.

Rift Valley fever (sub-Saharan and North Africa) is a mosquito-borne disease of mammals that primarily causes mild illnesses in humans, although meningoencephalitis and retinitis can occur.

Yellow fever (sub-Saharan Africa and tropical South America) is transmitted by a mosquito vector and causes an estimated 200,000 cases and 30,000 deaths each year in endemic areas. Urban outbreaks with vector-borne transmission have not occurred in the Americas since the 1940's due to public health programs aimed at eliminating the mosquito vector. Illness ranges from mild to severe, with an overall case-fatality rate of 5% to 7%. A vaccine against yellow fever is available.

CLINICAL FEATURES

The clinical features of VHF vary according to the virus. Virus enters the body through mucosal surfaces in contact with infectious fluids, needlesticks or via inhalation. Common presenting complaints are fever, myalgia, and prostration. Clinical examination may initially reveal only as of conjunctival injection, mild hypotension, flushing, and petechial hemorrhages.

In all VHF syndromes the target organ is the vascular bed, and the dominant clinical features result from microvascular damage and changes in vascular permeability. Disease can range from minimally symptomatic to fulminant, and symptomatology varies depending on the specific virus. However, all share the potential for the development of a bleeding diathesis manifested by severe hemorrhage from mucosal surfaces and petechiae. Full-blown VHF typically evolves to shock and

generalized bleeding from the mucous membranes, often accompanied by severe neurological, hematopoietic, or pulmonary involvement.

EBOLA AND MARBURG VIRUS HEMORRHAGIC FEVERS: COMMON CLINICAL FEATURES	
Incubation Period	2-21 days
Signs & Symptoms	Prodrome (<1 week): Abrupt onset fever, severe prostration, headache, myalgias Syndrome • Maculopapular nonpruritic rash • Jaundice and pancreatitis often occur • Bleeding manifestations (mucous membrane hemorrhages, bloody diarrhea and/or vomiting, petechiae, ecchymoses, oozing of blood at puncture sites) in 30-40% • Shock (with DIC and end-organ failure) often during 2nd week of illness Complications (≥ 2 weeks after onset) • Migratory arthralgias • Ocular disease (unilateral vision loss, uveitis) • Orchitis, suppurative parotitis • Pericarditis • Illness-induced abortion among pregnant women
Laboratory Findings	• Leukopenia and thrombocytopenia early in course; leukocytosis late • Elevated amylase and hepatic enzymes, laboratory manifestations of DIC as disease progresses

LASSA VIRUS HEMORRHAGIC FEVER: CLINICAL FEATURES	
Incubation Period	5-16 days
Signs & Symptoms	Prodrome (< 1 week): Gradual onset fever, weakness, malaise, arthralgias Syndrome • Exudative pharyngitis • Severe prostration • Faint maculopapular rash • Neurological involvement common (encephalopathy, coma, seizures) • Bleeding manifestations in 15-20% • Shock (with DIC and end-organ failure) uncommon Complications (≥ 2 weeks after onset) • 8th cranial nerve damage with hearing loss • Pericarditis • Illness-induced abortion among pregnant women
Laboratory Findings	• Leukocyte & platelet counts often normal • Elevated hepatic enzymes may occur

YELLOW FEVER: CLINICAL FEATURES	
Incubation Period	3-6 days
Signs & Symptoms	Prodrome (< 1 week): Fever, headache, myalgias, facial flushing, conjunctival injection Syndrome • Subclinical or mild infections predominate (80%) • 'Moderately severe' form includes high fever, jaundice, vomiting, bleeding manifestations • 'Malignant' form includes fulminant infection with severe hepatic involvement, bleeding manifestations, shock, renal failure, and death
Laboratory Findings	• Leukopenia early, leukocytosis later • Thrombocytopenia • Elevated hepatic enzymes & bilirubin

DIFFERENTIAL DIAGNOSIS

Most clinicians in the US have little or no clinical experience with the syndromes associated with VHF. The variable clinical presentation of VHF adds to the challenge.

With VHF used as a biological weapon, patients are less likely to have risk factors for natural VHF infection such as travel to Africa, Asia, or South America, handling of animal carcasses, contact with sick animals or people, or arthropod bites within 21 days of symptom onset. The observation of a severe illness with bleeding manifestations as its primary feature, which develops as a point-source epidemic with simultaneous presentation of many cases, should be highly suspicious for VHF.

The diagnosis of VHF should be considered for any patient who presents with:

- Acute onset of fever (<3 weeks duration)
- Severe prostrating or life-threatening illness
- Bleeding manifestations (at least two of the following: hemorrhagic or purpuric rash, epistaxis, hematemesis, hemoptysis, blood in stool, or other bleeding)
- No predisposing factors for a bleeding diathesis

The differential diagnosis includes:

<u>Bacterial and Rickettsial Infections</u>

- Gram-negative bacterial septicemia
- Staphylococcal or streptococcal toxic shock syndrome
- Meningococcemia
- Secondary syphilis
- Septicemic plague
- Typhoid fever
- Rocky Mountain spotted fever
- Ehrlichiosis
- Leptospirosis

Viral and Parasitic Infections

- Malaria
- African trypanosomiasis
- Hemorrhagic smallpox
- Measles
- Hemorrhagic varicella
- Rubella
- Viral hepatitis

Other Conditions

- Thrombotic or Idiopathic thrombocytopenic purpura
- Acute leukemia
- Hemolytic uremic syndrome

LABORATORY DIAGNOSIS

The diagnosis of VHF is based initially on clinical criteria and judgment, with laboratory testing used to confirm or exclude this clinical diagnosis. Laboratory testing requires time and, in the event of an attack, may be delayed or impossible given current laboratory capacities.

If you consider testing for VHF, you should:

- **IMMEDIATELY notify YCHD (24/7 (530) 666-8645) to facilitate specimen processing & proper specimen transport, and to initiate the public health response.**
- **Notify the laboratory that VHF is suspected, so that they may follow established biosafety procedures.**

A number of test methods can be used to diagnose VHF. These include: antigen-capture testing by ELISA, IgM antibody testing, paired acute-convalescent serum serologies, PCR, immunohistochemistry methods, and electron microscopy. Viral identification in cell culture is the 'gold standard' of viral detection, however this technique is time consuming and extremely dangerous, and should only be attempted by labs with high-level biosafety facilities.

Diagnosis is via blood or serum testing. For serological testing, avoid collection tubes with citrate, oxalate, or EDTA. For PCR tests, use an EDTA tube. Collect acute-phase specimens within 7 days of illness onset. Collect convalescent-phase specimens 7-20 days later, and at least 14 days after illness onset.

Marburg and Ebola viruses may be recovered from soft tissue effusions, semen, and anterior eye fluid, especially during later stages of illness. Lassa virus often can be recovered from throat swabs, pleural effusions, placental tissue, and urine and has been demonstrated in CSF of patients with fever and neurologic signs.

TREATMENT AND PROPHYLAXIS

These recommendations are current as of this document date. YCHD will provide periodic updates as needed and situational guidance in response to events (www.yolohealth.org).

Treatment

Supportive care is essential for patients with all types of VHF and includes maintenance of fluid and electrolyte balance, active hemodynamic monitoring, mechanical ventilation, dialysis, and appropriate therapy for secondary infections. Treatment of other suspected causes of disease, such as bacterial sepsis, should not be withheld while awaiting confirmation or exclusion of the diagnosis of VHF. Anticoagulant therapies, aspirin, nonsteroidal anti-inflammatory medications, and intramuscular injections are contraindicated.

Ribavirin has shown *in vitro* and *in vivo* activity against Arenaviruses (Lassa fever, New World hemorrhagic fevers) and Bunyaviruses (Rift Valley fever and others). Ribavirin has shown no activity against, and is not recommended for Filoviruses (Ebola and Marburg hemorrhagic fever) or Flaviviruses (Yellow fever, Kyasanur Forest disease, Omsk hemorrhagic fever).

Recommendations for IV ribavirin therapy are shown below. However in a mass casualty situation where the number of persons requiring therapy overwhelms the resources available to deliver IV agents, an oral regimen of ribavirin is recommended.

RIBAVIRIN THERAPY FOR PATIENTS WITH VHF OF UNKNOWN CAUSE OR KNOWN TO BE CAUSED BY AN ARENAVIRUS OR BUNYAVIRUS*

Patient Group	Contained-Casualty Setting	Mass-Casualty Setting†
Adults (Including Pregnant Women‡)	• Loading dose of 30 mg/kg (max 2 gm) IV, then: • 16 mg/kg (max 1 gm) IV q6 hr for 4 days, then: • 8 mg/kg (max 500 mg) IV q8 hr for 6 days	• Loading dose of 2000 mg PO, then: • (Weight >75 kg): 1200 mg/day PO in 2 divided doses for 10 days§ • (Weight <75 kg): 1000 mg/day PO in divided doses (400 mg in am and 600 mg in pm) for 10 days§
Children	Same as for adults	• Loading dose of 30 mg/kg PO, then: 15 mg/kg/d PO in 2 divided doses for 10 days

* Ribavirin is not approved by the US Food and Drug Administration for treatment of VHF and must be used under an Investigational New Drug (IND) protocol, although in a mass-casualty setting, this requirement may need to be modified.
† The decision to use oral rather than parenteral medication will depend on available resources.
‡ Generally, ribavirin is contraindicated in pregnant women; however, the benefits may outweigh the fetal risk of ribavirin therapy.
§ The current available formulation of ribavirin is 200-mg capsules, which cannot be broken open.

Source: Working Group on Civilian Biodefense. Borio et al, JAMA 2002; 287(18):2391-2405.

Post Exposure Prophylaxis

According to the Working Group on Civilian Biodefense, exposure is defined as proximity to an initial release of VHF, or close or high-risk contact with a patient suspected of having VHF during the 21 days following onset of symptoms. High risk is defined as having mucous membrane contact or having percutaneous injury involving contact with secretions, excretions, or blood from a patient with VHF. Close contact is defined as those who live with, shake hands with, hug, process laboratory specimens from, or care for a patient with VHF.

Previous CDC recommendations (MMWR, 1988) state that prophylaxis with ribavirin should be given to persons exposed to Lassa virus. However, the efficacy of ribavirin prophylaxis for Lassa virus is not well documented and CDC may be reconsidering this recommendation. Instead, the Working Group recommends that persons exposed to VHF be placed under medical surveillance until 21 days after the last exposure, and that if symptoms suggestive of VHF occur or if a temperature of $\geq$101°F (38.3°C) is documented, ribavirin therapy should be initiated unless another diagnosis is confirmed (or the etiologic agent is known to be a filovirus or flavivirus). **In the event of an outbreak, YCHD will provide situational guidance on prophylaxis (www.yolohealth.org).**

Vaccine

Yellow fever live attenuated 17D vaccine is effective when administered to travelers to endemic areas. However this vaccine would not be useful in preventing disease if given in the post-exposure setting because yellow fever has a short incubation period of 3 to 6 days, and neutralizing antibodies take longer to appear following vaccination.

There is no licensed vaccine for any of the other hemorrhagic fever viruses, though research is underway on several candidates.

INFECTION CONTROL*

These recommendations are current as of this document date. YCHD will provide periodic updates as needed and situational guidance in response to events (www.yolohealth.org).

Filoviruses and arenaviruses are highly infectious after direct contact with infected blood and bodily secretions, and person-to-person transmission has been documented. In Africa, transmission of VHF in healthcare settings has been associated with provision of patient care without appropriate barrier precautions to prevent exposure to virus-containing blood and other body fluids. The risk for person-to-person transmission of VHF is greatest during the latter stages of illness when virus loads are highest. No VHF infection has been reported in persons whose contact with an infected person occurred only during the incubation period (i.e., before onset of fever).

* For description of Precautions, see chapter on Infection Control

Preventing the transmission of VHF infection relies on meticulous compliance with strict infection control measures. The most recent CDC recommendations (MMWR, 2005) for isolation of patients with VHF are as follows:

- Patients who are hospitalized or treated in an outpatient setting should be placed in a private room and **Standard, Contact, and Droplet Precautions** should be initiated. Patients with respiratory symptoms also should wear **a face mask** to contain respiratory droplets prior to placement in their hospital or examination room and during transport.
- Caretakers should use barrier precautions to prevent skin or mucous membrane exposure with patient blood, other body fluids, secretions (including respiratory droplets), or excretions. All persons entering the patient's room should wear gloves and gowns to prevent contact with items or environmental surfaces that may be soiled. In addition, face shields or surgical masks and eye protection (e.g., goggles or eyeglasses with side shields) should be worn by persons coming within approximately 3 feet of the patient.
- Additional barriers may be needed depending on the likelihood and magnitude of contact with body fluids. For example, if copious amounts of any body fluids or feces are present in the environment, plastic apron, leg, and shoe coverings also may be needed.
- Nonessential staff and visitors should be restricted from entering the room of patients with suspected VHF. Maintain a log of persons entering the patient's room.
- Before exiting the room of a patient with suspected VHF, safely remove and dispose of all protective gear, and clean and disinfect shoes that are soiled with body fluids as described in the section on environmental infection control below.
- To prevent percutaneous injuries, needles and other sharps should be used and disposed of in accordance with recommendations for Standard Precautions.
- If the patient requires a surgical or obstetric procedure, consult with YCHD regarding appropriate precautions for these invasive procedures.
- Although transmission by the airborne route has not been established, hospitals may choose to use **Airborne Precautions** for patients with suspected VHF who have severe pulmonary involvement or who undergo procedures that stimulate coughing and promote the generation of aerosols.

Decontamination

Persons with percutaneous or mucocutaneous exposures to blood, body fluids, secretions, or excretions from a patient with suspected VHF should immediately wash the affected skin surfaces with soap and water. Mucous membranes should be irrigated with copious amounts of water or eyewash solution. Exposed persons should receive medical evaluation and monitoring.

Hemorrhagic fever viruses have lipid envelopes and are not environmentally stable; therefore, these viruses would not be expected to persist in the environment following a bioterrorist attack. Decisions about decontamination of the environment following an intentional release would depend upon the specific events surrounding the attack.

In the healthcare setting, environmental surfaces, inanimate contaminated objects, or contaminated equipment should be disinfected with an approved hospital disinfectant or a 1:100 dilution of household bleach using standard procedures. For grossly soiled surfaces, (e.g., vomitus or stool), a 1:10 dilution of household bleach should be used. Contaminated linens should be incinerated, autoclaved, or placed in labeled, leak-proof bags at the site of use and washed without sorting in a normal hot water cycle with bleach. Hospital housekeeping staff and linen handlers should wear appropriate personal protective equipment (as outlined in the section on isolation practices above) when handling or cleaning potentially contaminated material or surfaces. Contaminated stool, fluids, and secretions can be managed per standard procedures, since hemorrhagic fever viruses are not likely to survive standard US sewage treatment.

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CHEMICAL AGENTS 2006

Outline

Health care providers are required to report suspected or confirmed Pesticide-Related Illness to the local health department within 24 hours.

Health care providers are encouraged to report all other suspected or confirmed Chemical Agent exposures immediately (within 1 hour).

To report: call YCHD (24/7 (530) 666-8645).

INTRODUCTION

Chemical warfare agents were used in World War I causing over one million casualties. After World War II, Egypt allegedly used chemicals in Yemen, and Iraq used them against Iran and Iraqi Kurds. In 1994, the cult Aum Shinrikyō manufactured and released sarin (GB) in Matsumoto, Japan resulting in 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, and 5,500 who sought medical care. Over 80% of the injured found their own transportation to medical facilities. One hundred thirty-five first responders (police, fire, EMS) were injured.

First responders are often secondary victims of a chemical exposure. Chemical cross-contamination of ambulances and hospitals could cripple the capacity of the local pre-hospital and hospital system. Convergent casualties, those who leave the incident site without pre-hospital care and then seek hospital care, also pose a serious threat to the hospital and to health care providers.

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% 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 or incapacitating agents, 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.

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 health care providers performing decontamination procedures.

Dermal Protection: Latex examination gloves provide little protection from most chemical agents. Chemical resistant suits, nitrile, butyl or neoprene gloves and boots provide splash protection and should be worn when performing decontamination.

Charteristics of the following agents, their clinical effects and medical management are discussed further in this chapter:

Agent	Name
Nerve Agents	Sarin, Soman, Tabun, VX
Vesicants	Mustard, Lewisite
Blood Agents	Cyanide, Hydrogen Cyanide, Cyanogen
Pulmonary Intoxicants	Phosgene, Chlorine, Ammonia
Riot Control Agents	Mace7, Pepper Spray

NERVE AGENTS: SARIN, SOMAN, TABUN, VX

Nerve agents are the most toxic of the known chemical warfare agents. They are chemically similar to organophosphate pesticides and exert their biological effects by inhibiting acetylcholinesterase. G-type agents are clear, colorless, and tasteless liquids that are miscible in water and most organic solvents. GB is odorless and is the most volatile nerve agent; however, it evaporates at about the same rate as water. GA has a slightly fruity odor, and GD has a slight camphor-like odor. VX is a clear, amber-colored, odorless, oily liquid. It is miscible with water and soluble in all solvents. It is the least volatile nerve agent.

Clinical Effects – Nerve Agents

Vapor exposure (inhalation)

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. 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. 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.

- Moderate dose - 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
- Large dose - 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.

Liquid exposure

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.

- Small 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 nausea, vomiting, and diarrhea. Generally, there will be no pinpoint pupils.
- Large dose - A droplet the size of the LD50 or larger on the skin will cause sudden loss of consciousness, seizures, flaccid paralysis, and apnea within minutes.

Medical Management– Nerve Agents

Decontamination

Although liquid-contaminated casualties are unlikely to present directly to the hospital ED prior to decontamination by emergency responders, medical personnel should always assume the presence of liquid contamination. Areas of liquid contamination should be decontaminated prior to patient handling. Minimum decontamination should include removal of patients' clothing and jewelry to prevent secondary chemical exposure due to off-gassing. If the patient has been exposed to a liquid nerve

agent, survivors will require complete decontamination of skin and hair with water, soap and water, and water rinse at the scene prior to evacuation. 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.

NERVE AGENT PROTOCOL (CDC 4/6/05)

1. Severe respiratory distress?
   YES:
   - Intubate and ventilate
   - ATROPINE
     Adults: 6 mg IM or IV
     Inf/ped: 0.05 mg/kg IV
   - 2-PAM C1
     Adults: 600-1000 mg IM or slow IV
     Inf/ped: 15 mg/kg slow IV

2. Major secondary symptoms?
   NO: Go to 6.
   YES:
   - ATROPINE
     Adults: 4 mg IM or IV
     Inf/ped: 0.02 - 0.05 mg/kg IV
   - 2-PAM C1
     Adults: 600-1000 mg IM or slow IV
     Inf/ped: 15 mg/kg
   - OPEN IV LINE

3. Repeat atropine as needed until secretions decrease and breathing easier
   Adults: 2 mg IV or IM
   Inf/ped: 0.02 - 0.05 mg/kg IV

4. Repeat 2-PAM C1 as needed
   Adults: 1.0 gm IV over 20-30 min - Repeat q lh x 3 prn
   Inf/ped: 15 mg/kg slow IV

5. Convulsions?
   NO: Go to 6.
   YES: DIAZEPAM 10 mg slow IV
   Inf/ped: 0.2 mg/kg IV

6. Reevaluate q 3-5 minutes, IF SIGNS WORSEN, repeat from 3.

Note: Warn hospital pharmacy that unusual amounts of atropine and 2-PAM may be needed

Source: from CDC Environmental Public Health Readiness Branch Chemical Weapons Eliminiation Team, www.cdc.gov/nceh/demil/articles/initialtreat.htm 4/6/05

VESICANTS: MUSTARD, LEWISITE

Vesicants discussed here are blistering agents developed for chemical warfare, namely mustard and Lewisite.

MUSTARD

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 airway injury, sepsis as a result of bone marrow damage, and impairment of the immune system. There is no specific therapy.

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 is typically not volatile, however at temperatures above 100 ºF it is a 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 concern for cross contamination.

Mustard is absorbed and causes 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 casualty 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. It alkylates DNA and clings 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.

Clinical Effects – Mustard

Eyes: Eye lesions may range from mild conjunctivitis to severe conjunctivitis, lid inflammation and edema, blepharospasm, and corneal roughening with greater exposure. Larger exposures, particularly if by liquid, may also produce corneal opacification, corneal ulceration, or corneal perforation.

Skin: 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.

Pulmonary: Mucosal 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. If the exposure is large, the agent may cause dyspnea and productive cough. At this stage, there may be hemorrhagic pulmonary edema, but otherwise, pulmonary edema is rare.

Gastrointestinal: Gastrointestinal effects within the first 24 hours following exposure include nausea and vomiting.

Hematopoietic System: Absorption of significant amounts of mustard produces damage to stem cells. If this occurs, the white blood cell count 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 prognosis for survival is poor

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 is largely supportive since there is no antidote for the effects of sulfur mustard (see below).

LEWISITE

Lewisite is a vesicant that has been used militarily, but there have been few human exposures to the chemical.

Clinical Effects - Lewisite

Lewisite is rapidly absorbed by the eyes, skin, and lungs and produces blisters similar to mustard. In contrast to mustard, lewisite is highly irritating on initial exposure, produces visible lesions more quickly, and it does not damage the bone marrow. Lewisite is an arsenical compound, thus a heavy metal poison.

Skin: Lewisite causes greater skin damage than 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. Pseudomembrane formation is common.

Cardiovascular: Lewisite causes increased capillary permeability, leading to volume depletion, hypotension, hepatic and renal injury.

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.

Medical Management & Treatment

MUSTARD PROTOCOL	LEWISITE PROTOCOL
1. Airway obstruction? **YES:** Tracheostomy 2. If there are large burns: • Establish IV line - do not push fluids as for thermal burns. • Drain vesicles - unroof large blisters and irrigate area with topical antibiotics. 3. Treat other symptoms appropriately: • Antibiotic eye ointment • Sterile precautions prn • Morphine prn (generally not needed in emergency treatment; might be appropriate for in-patient treatment.) Source: CDC Environmental Public Health Readiness Branch Chemical Weapons Eliminiation Team, www.cdc.gov/nceh/demil/articles/initialtreat.htm 4/6/05	1. Survey extent of injury. 2. Treat affected skin with British Anti-Lewisite (BAL) ointment (if available). 3. Treat affected eyes with BAL ophthalmic ointment (if available). 4. Treat pulmonary/severe effects • BAL in oil, 0.5 ml/25 lbs body wt. deep IM to max of 4.0 ml. Repeat q 4 h x 3 (at 4, 8, and 12 hours). • Morphine prn 5. Severe poisoning? **YES:** Shorten interval for BAL injections to q 2 h. Source: CDC Environmental Public Health Readiness Branch Chemical Weapons Eliminiation Team, www.cdc.gov/nceh/demil/articles/initialtreat.htm 4/6/05

BLOOD AGENTS: CYANIDE, HYDROGEN CYANIDE, CYANOGEN

Cyanide is a chemical that is widely utilized, manufactured, and transported in the US. 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. 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.

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 hyperventilate, and typically develops a headache with dizziness, nausea 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 seen. If a victim is exposed to a low concentration of vapor and removed from the source of the cyanide, the symptoms should not progress.

Severe cyanide exposures require rapid intervention. About 15 seconds after inhaling a large amount of cyanide, victims become anxious and start to hyperventilate. Thirty seconds after exposure, the patient may begin to convulse. In 3 to 5 minutes, breathing ceases. Asystole 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 may be noted when using a pulse oximeter, despite the fact that the patient may be in severe respiratory distress. Metabolic acidosis may also be present. 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 no value in the initial management of acute severe poisoning.

Medical Management & Treatment

Decontamination

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.

Treatment

For mild exposures, if conscious and breathing, give O_2 and IV fluids. Observe and monitor no antidotes are necessary.

For severe exposures, if unconscious, whether breathing or not, give O_2, and bag-mask ventilate with 100% O_2. Cardiac monitor. Oxygen saturation may or may not be normal. Administer amyl nitrate (if indicated), sodium nitrite, sodium thiosulfate (the "Cyanide Antidote Kit" - formerly known as the Lily Cyanide Kit and now produced by Taylor Pharmaceuticals).

- **Amyl nitrite** ampules 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 should be used only until the IV drugs can be given.
- **Sodium nitrite** is available for IV use in a dose of 300 mg (10 cc ampule) over 5 minutes in adults. For children, use 0.22 to 0.33 ml/kg of the 3 percent solution. Watch for 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 0.12 – 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. If the patient is still apneic after antidote administration, consider sodium bicarbonate for severe acidosis. If sodium nitrite is unavailable, administer amyl nitrite by inhalation from crushable ampules.
- **Sodium thiosulfate** 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 25% solution over 10-20 minutes. For children, use 1.65 ml/kg of the 25% solution over 10-20 minutes.

PULMONARY INTOXICANTS: PHOSGENE, CHLORINE, AMMONIA

Pulmonary intoxicants cause severe life-threatening lung injury after inhalation. These effects are generally delayed several hours after exposure.

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. Phosgene has a characteristic odor of freshly mown hay and is four times heavier than air. It is a gas above 47 ºF, and is principally a hazard by inhalation. 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.

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 destruction of 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.)

There is a symptom-free period of 2 to 24 hours. Over the first several hours, the patient develops a severe non-cardiogenic pulmonary edema. Treatment is usually supportive and may require advanced intensive care.

PHOSGENE PROTOCOL

1. Restrict fluids; chest x-ray, blood gas results consistent with phosgene poisoning?
   YES: Go to 4

2. Dyspnea?
   YES: OXYGEN, positive end-expiratory pressure

3. Observe closely for at least 6 hours.
   - IF SEVERE DYSPNEA develops, go to 4.
   - IF MILD DYSPNEA develops after several hours, go to 1.

4. Severe dyspnea develops or x-ray or blood gases consistent with phosgene poisoning:
   - Admit
   - Oxygen under positive end-expiratory pressure
   - Restrict fluids
   - Chest x-ray
   - Blood gases
   - Seriously ill list

Source: CDC Environmental Public Health Readiness Branch Chemical Weapons Eliminiation Team, www.cdc.gov/nceh/demil/articles/initialtreat.htm 4/6/05

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. 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. Chlorine injures cells by reacting with water, producing hydrochloric acid and free oxygen radicals. It is toxic to mucosal surfaces including the eyes, skin, respiratory tract, and GI tract. Chlorine gas is 30 times more irritating to the respiratory mucosa than HCl.

Within seconds of 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 noncardiogenic pulmonary edema. Sudden death is usually due to severe hypoxia and cardiac arrest.

Victims should be moved away from the source of exposure. If the victim has no complaints, it is unlikely any treatment will be necessary.

CHLORINE PROTOCOL

1. Dyspnea?
   - Try bronchodilators
   - Admit
   - Oxygen by mask
   - Chest X-ray
2. Treat other problems and reevaluate (consider phosgene).
3. Respiratory system OK?

   YES: Go to 5.
4. Is phosgene poisoning possible?

   YES: Go to PHOSGENE PROTOCOL
5. Supportive therapy; treat other problems or discharge.

Source: CDC Environmental Public Health Readiness Branch Chemical Weapons Eliminiation Team, www.cdc.gov/nceh/demil/articles/initialtreat.htm 4/6/05

AMMONIA

Ammonia is a colorless, highly water-soluble, alkaline gas with a characteristic 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.

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: Ammonia

Eyes: 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.

Skin: 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: Ammonia

After the patient has been removed from the area of exposure, decontamination should be started immediately in the field. 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. 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: CN (MACE), PEPPER SPRAY, ADAMSITE, CS (TEAR GAS)

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. The deleterious effect is usually transient, lasting about 30 minutes. These agents include: CN (Mace7), OC (oleoresin capsicum or pepper spray), Adamsite, CS (tear gas). 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, adamsite does not cause skin irritation.

Clinical Effects

Symptoms include blepharospasm, tearing, conjunctival injection, nasal discharge, sneezing, coughing, shortness of breath, wheezing, burning and redness of skin. 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.

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% will have eye, airway, or skin complaints severe enough to be medically assessed.

There is no antidote available for these agents. Treatment is supportive and directed towards alleviating symptoms which are not usually severe. Treatment may include: decontamination of skin with soap and water or a solution containing a carbonate and/or a bicarbonate; irrigation of eyes; bronchodilators or steroids for wheezing if standard bronchodilators fail and oxygen therapy if indicated. Delayed onset dermatitis should be managed with frequent irrigation and soothing ointments or creams.

ANTIDOTE AND DECONTAMINATION SUMMARY TABLE

Antidote Therapy & Decontamination for Chemical Agent Exposures

Chemical	Antidote	Decontamination (Including removal of clothing)	Other
Nerve Agents	Atropine, 2-PAM	Soap and Water	Diazepam
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, NA Nitrite, Amyl Nitrite, NA Thiosulfate	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 (Teflon)	None, Supportive		Monitor, O_2, watch for pulmonary edema
Ammonia	None, Supportive	Irrigate eyes – water only Soap and Water	Milk, bronchodilators, watch for mediastinitis, liquefactive necrosis
Chlorine	None, Supportive	Irrigate eyes – water only Soap and Water	Bronchodilators, steroids, intubation, bronchoscopy
CN (Mace)	None, Supportive	Irrigate eyes – water only Soap and Water	Remove foreign body from eye, watch for bronchospasm
CS (Tear gas)	None, Supportive	Irrigate eyes – water only Soap and Water	
Oleoresin (Pepper Spray)	None, Supportive	Irrigate eyes – water only Soap and Water	From chili pepper, dermatitis, eye injury

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MEDICAL EFFECTS OF RADIATION EXPOSURE 2006

ALPHA radiation cannot penetrate the outer layer of skin. It can be stopped by thin layers of light materials such as paper or a few centimeters of air, and pose no threat when the radioactive material is outside the human body; however, **alpha poses a serious health threat if ingested.**

BETA radiation is more penetrating than alpha with a range in air of up to 10 feet. It can only penetrate the skin to a depth of a few centimeters. Beta particles are a skin hazard when outside the body. Beta radiation can be lethal, depending on the **dose** and length of **time** of exposure. A thin sheet of aluminum or wood can shield it. Initial symptoms are itching and burning of skin with later symptoms including reddening of skin, changes in pigmentation, and sores. It is also an inhalation/ingestion hazard.

GAMMA, X-RAY, and NEUTRON radiation can penetrate the entire thickness of a human body and represent a great hazard to the body, whether internal or external. For comparison, this radiation has a range in air of up to several hundred feet. These forms of radiation have high energy. Shielding against them requires thick layers of dense materials such as lead, concrete or lots of water.

Medical Effects of Radiation Exposure*

0-75 Rad No overt effect. Possible increase in lifetime cancer risk depending on dose and time.

75-150 Rad Approximately 4 hours after exposure, 5 to 30% will suffer mild nausea for about 12 hours. Symptoms should decline and end but may be accompanied by upset stomach, clammy and sweaty skin, and mouth watering. No deaths are expected.

150-300 Rad Approximately 4 hours after exposure, 30 to 70% will suffer mild to moderate nausea. It will progress fairly rapidly to vomiting in 20 to 50%. Appetite will disappear in 50 to 90%. At the same time, 30 to 60% will complain of mild to moderate fatigue, with accompanying weakness. After 8 weeks, 10 to 50% will have a mild fever and 10% will experience mild bleeding.

300-530 Rad Approximately 2 hours after exposure, 70 to 90% will have upset stomach, clammy and sweaty skin. 90 to 100% will lose all appetite. After 4 hours, over half will begin vomiting. Moderate diarrhea may occur in 8 hours. Skin reddening may begin with 8 hours. Hair loss by the 2nd week. Moderate infections and fevers begin in 10 to 80% after 2 – 3 weeks and moderate bleeding in 10 – 50%. Deaths, when they occur, are usually from hemorrhage or infection.

530-830 Rad Nausea arises rapidly at 1 hour after exposure with vomiting to severe vomiting after 4 hours. At the high end of the dose range, almost all will die at 2 to 4 weeks, 50% dies in 5 to 6 at low end of dosage range.

830+ Rad Death is likely for at 2 – 3 weeks. Symptoms begin with nausea, vomiting and considerable sweating within 2 hours.

* Rad: **R**adiation **A**bsorbed **D**ose – The stronger the source, the shorter the distance to the source, and the longer the time of exposure all increase the Rads received.

Source: Yolo County Environmental Health

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).
  - 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).
  - 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).
  - 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]
  - 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).
  - 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]
  - 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.

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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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  - 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.
  - 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} ‡ is 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 $LD_{50/60}$ is the dose necessary to kill 50% of the exposed population in 60 days.
‡ The LD_{100} 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.

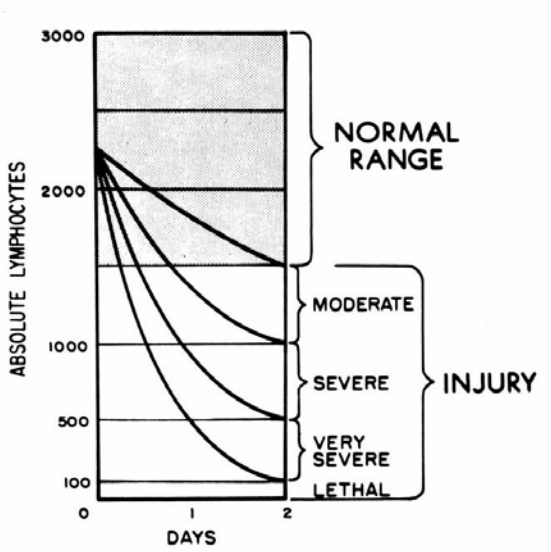
If a patient is known to have been or suspected of having been exposed to a large radiation dose, draw blood for CBC analysis with special attention to the lymphocyte count, every 2 to 3 hours during the first 8 hours after exposure (and every 4 to 6 hours for the next 2 days). Observe the patient during 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.

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.

(continued from previous page)

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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Medical Management of the Acute Radiation Syndrome: Recommendations of the Strategic National Stockpile Radiation Working Group

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Physicians, hospitals, and other health care facilities will assume the responsibility for aiding individuals injured by a terrorist act involving radioactive material. Scenarios have been developed for such acts that include a range of exposures resulting in few to many casualties. This consensus document was developed by the Strategic National Stockpile Radiation Working Group to provide a framework for physicians in internal medicine and the medical subspecialties to evaluate and manage large-scale radiation injuries.

Individual radiation dose is assessed by determining the time to onset and severity of nausea and vomiting, decline in absolute lymphocyte count over several hours or days after exposure, and appearance of chromosome aberrations (including dicentrics and ring forms) in peripheral blood lymphocytes. Documentation of clinical signs and symptoms (affecting the hematopoietic, gastrointestinal, cerebrovascular, and cutaneous systems) over time is essential for triage of victims, selection of therapy, and assignment of prognosis.

Recommendations based on radiation dose and physiologic response are made for treatment of the hematopoietic syndrome. Therapy includes treatment with hematopoietic cytokines; blood transfusion; and, in selected cases, stem-cell transplantation. Additional medical management based on the evolution of clinical signs and symptoms includes the use of antimicrobial agents (quinolones, antiviral therapy, and antifungal agents), antiemetic agents, and analgesic agents. Because of the strong psychological impact of a possible radiation exposure, psychosocial support will be required for those exposed, regardless of the dose, as well as for family and friends. Treatment of pregnant women must account for risk to the fetus. For terrorist or accidental events involving exposure to radioiodines, prophylaxis against malignant disease of the thyroid is also recommended, particularly for children and adolescents.

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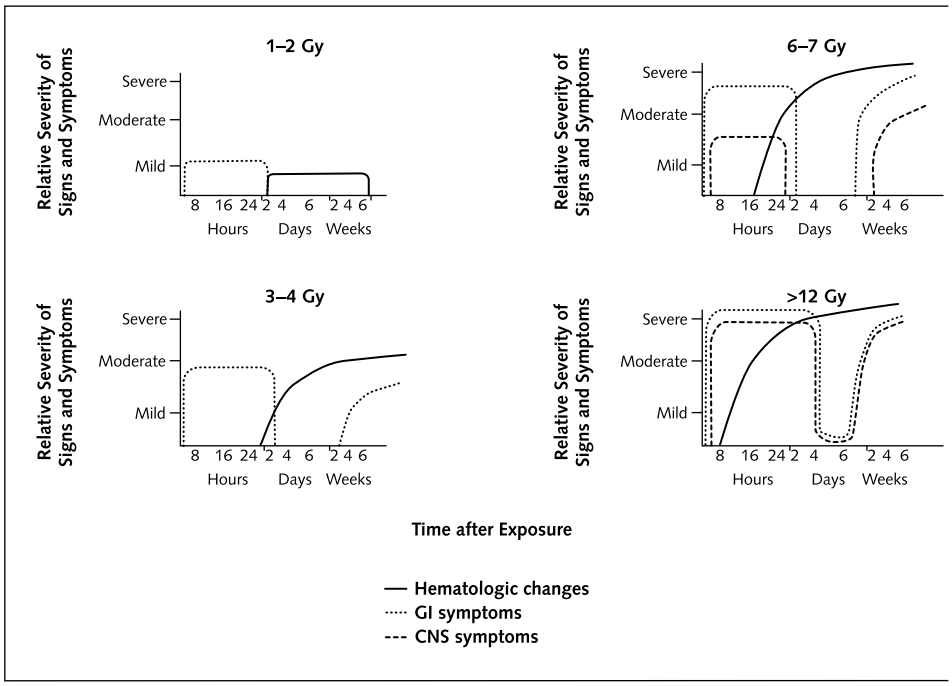
The events of September 11, 2001, confirmed the vulnerability of the United States and other nations to acts of terrorism. While our ability to react to and treat victims of biological terrorism has significantly improved, a terrorist event involving radioactive material remains a threat for which improved preparation is requisite. Several international conferences on treatment of acute radiation injury have been held in the past 2 decades (1–8). The conclusions of these conferences, together with mounting preclinical data showing the benefit of early cytokine use in combination with aggressive clinical support in irradiated animals (9–13), provide valuable information to clinicians faced with treating the acute radiation syndrome.

Scenarios for terrorist acts involving radioactive material have been developed, some of which indicate that mass casualties can occur. However, little information is currently available in the medical literature concerning guidelines for the medical management of large-scale, complex radiation injuries, such as those that might occur in an urban area (14–17). Therefore, this consensus document was created to help physicians who may be involved in evaluation, triage, or medical management of victims with acute radiation injury.

Methods

The Strategic National Stockpile (SNS) convened the SNS Radiation Working Group (Appendix, available at www.annals.org) to address issues of medical management and stockpiling of pharmaceutical agents in case of a significant radiologic event. Participants were selected on the basis of their established expertise in the field. The deliberations of the SNS Radiation Working Group during a series of 4 consensus meetings beginning in August 2002 and 4 additional conference calls were used as a basis to create this document. The group reviewed the available information for cases recorded in the radiation accident registries maintained by the Radiation Emergency Assistance Center/Training Site (REAC/TS), Oak Ridge, Tennessee, and the University of Ulm, Germany (6). This information was supplemented by outcomes of clinical management and therapy for cases reported in the scientific literature. Since no prospective, controlled clinical trials have been conducted in patients with acute radiation injury, the SNS Radiation Working Group reviewed management strategies used in accidental exposures of humans and evaluated results of prospective, controlled studies of acutely irradiated animals. In some cases, recommendations for therapy are based on results of animal studies. For radiologic terrorism events, definitive studies are required in animals to demonstrate impact on mortality and other clinical end points, according to requirements for licensure under the U.S. Food and Drug Administration's Animal Rule. In cases where the members of the SNS Radiation Working Group failed to achieve consensus, the alternatives are presented with relevant reference to the published

Figure 1. **Approximate time course of clinical manifestations.**



Shown are approximate times for hematopoietic, gastrointestinal (*GI*), and central nervous system (*CNS*) symptoms at different ranges of dose of whole-body radiation for exposed, living persons. Hematopoietic changes include development of lymphopenia, granulocytopenia, or thrombocytopenia. Gastrointestinal symptoms include headache, nausea, vomiting, or diarrhea. Cerebrovascular signs and symptoms include headache, impaired cognition, disorientation, ataxia, seizures, prostration, and hypotension. Note that the signs and symptoms of different organ systems significantly overlap at each radiation dose and that cerebrovascular symptoms do not appear until exposure to a high whole-body dose. The relative severity of signs and symptoms is measured on an arbitrary scale. Prepared from data in reference 16.

literature. The Centers for Disease Control and Prevention provided funding to some of the participants for attendance at meetings. This support played no role in the composition, deliberations, or report of the SNS Radiation Working Group. Because new approaches to individual biodosimetry and therapy that will apply to treatment of acutely irradiated persons are likely to emerge, the SNS Radiation Working Group will review scientifically based guidance annually.

Defining the Threat and Public Health Response

The lethality of a nuclear device was demonstrated when a 15-kiloton improvised nuclear device was detonated over Hiroshima, Japan, in 1945, resulting in approximately 150 000 casualties and 75 000 fatalities (18). Virtually all survivors of Hiroshima had estimated exposure of less than 3 Gy (19). Recent review of data suggests that the mean lethal dose of radiation required to kill 50% of humans at 60 days ($LD_{50/60}$) of whole-body radiation is between 3.25 Gy and 4 Gy in persons managed without supportive care and 6 to 7 Gy when antibiotics and transfusion support are provided (20).

Although most radiation injuries in the past 50 years have been due to accidents, society must be prepared for the intentional detonation of nuclear or radiologic devices. Modern nuclear threats can be divided into 5 general categories: 1) an attack on nuclear power plants, 2) a malevolent act using simple radiologic devices, 3) terrorist use of a radiologic dispersal device or "dirty bomb," 4) detonation of an improvised nuclear device, and 5) detonation of a sophisticated nuclear weapon (21). Whereas incidents involving simple devices and radiologic dispersal devices would probably cause a limited number of casualties, those involving improvised nuclear devices and small nuclear weapons would result in mass casualties.

The Joint Commission on Accreditation of Healthcare Organizations and government leaders have mandated that the health care system develop plans to prepare for response to a radiologic terrorist event. The Hospital Emergency Incident Command System (22) provides a command and coordination approach that is useful for radiation response planning. Emergency plans should clarify authority, command, and control; define organizational responsibilities; develop procedures that integrate efforts of all response agencies; identify logistic support, supplies, and equipment; and assess incident conditions and consequences (23). Given the devastation that would accompany a nuclear detonation, plans should incorporate contingency planning for significant loss of infrastructure and health care personnel in the radiation field and its environs. Contingency planning should include relocation of victims to nearby operational hospitals and medical centers and acti-

vation of regional and state disaster plans that are coordinated with federal agencies. Approaches to radiologic monitoring, triage, and therapy for exposed populations will vary, depending on the number of casualties and resources available on the scene and in emergency treatment centers and hospitals. Although disaster planning is beyond the scope of this document, it is hoped that this clinical guideline defines a need for formalization and coordinated testing of such plans by hospitals and government agencies (see www.ncrp.com).

Barriers to the provision of optimal medical care include limitation of resources, loss of infrastructure, a high volume of victims, and presence of combined injury. Allocation of potentially limited resources should be determined by the number of victims and their long-term prognosis. Estimation of individual radiation dose is recommended for determining survivability of patients in a range of doses that indicate predisposition to the acute radiation syndrome. Treatment recommendations are based on this dose range, which becomes increasingly narrower as the number of casualties increases and with the occurrence of combined injuries.

Essentials of Radiation Exposure and Injury

Radiation injury can occur from external irradiation; external contamination with radioactive materials; and internal contamination by inhalation, ingestion, or transdermal absorption with incorporation of radiologic materials into the body's cells and tissues. These 3 types of exposure can occur in combination and can be associated with thermal burns and traumatic injuries.

Injury from a nuclear detonation varies, depending on the location of the victim relative to the hypocenter and the consequent exposure to different types of energy. Three forms of energy are released from a nuclear detonation: heat, accounting for approximately 35% of total energy; shock or bomb blast, accounting for approximately 50% of total energy; and radiation, accounting for the remaining 15% of total energy. Heat and light cause thermal injury, including flash burns, flame burns, flash blindness (due to temporary depletion of photopigment from retinal receptors), and retinal burns. The blast wave results in fractures, lacerations, rupture of viscera, and pulmonary hemorrhage and edema. Radiation causes the acute radiation syndrome; cutaneous injury and scarring; chorioretinal damage from exposure to infrared energy; and, depending on radiation dose and dose rate, increased long-term risk for cancer, cataract formation (particularly with neutron irradiation), infertility, and fetal abnormalities (that is, growth retardation, fetal malformations, increased teratogenesis, and fetal death). We refer the reader to several excellent in-depth reviews of radiation effects (21, 23–25).

The Acute Radiation Syndrome

Studies in animals and humans exposed to radiation have allowed researchers to describe the acute radiation syndrome, also known as radiation sickness. The acute radiation syndrome occurs after whole-body or significant partial-body irradiation of greater than 1 Gy delivered at a relatively high-dose rate. The most replicative cells are the most sensitive to the acute effects of radiation, particularly spermatocytes, lymphohematopoietic elements, and intestinal crypt cells. The inherent sensitivity of these cells results in a constellation of clinical syndromes that predominates within a predictable range of doses of whole-body or significant partial-body exposure. Clinical components of the acute radiation syndrome include the hematopoietic, gastrointestinal, and cerebrovascular syndromes. The time course and severity of clinical signs and symptoms for the component syndromes at different dose ranges are reviewed in **Figure 1**. Each syndrome can be divided into 4 phases: prodromal, latent, manifest illness, and recovery or death.

Depending on the absorbed dose, symptoms appear within hours to weeks, following a predictable clinical course. The *prodromal phase* of the acute radiation syndrome usually occurs in the first 48 hours but may develop up to 6 days after exposure. The *latent phase* is a short period characterized by improvement of symptoms, as the person appears to have recovered. Unfortunately, this effect is transient, lasting for several days to a month. Symptoms of *manifest illness* then appear and may last for weeks. This stage is characterized by intense immunosuppression and is the most difficult to manage. If the person survives this stage, recovery is likely. Individuals exposed to a supralethal dose of radiation may experience all of these phases

Table 1. **Phases of Radiation Injury***

Dose Range, *Gy*	Prodrome	Manifestation of Illness	Prognosis (without Therapy)
0.5–1.0	Mild	Slight decrease in blood cell counts	Almost certain survival
1.0–2.0	Mild to moderate	Early signs of bone marrow damage	Highly probable survival (>90% of victims)
2.0–3.5	Moderate	Moderate to severe bone marrow damage	Probable survival
3.5–5.5	Severe	Severe bone marrow damage; slight GI damage	Death within 3.5–6 wk (50% of victims)
5.5–7.5	Severe	Pancytopenia and moderate GI damage	Death probable within 2–3 wk
7.5–10.0	Severe	Marked GI and bone marrow damage, hypotension	Death probable within 1–2.5 wk
10.0–20.0	Severe	Severe GI damage, pneumonitis, altered mental status, cognitive dysfunction	Death certain within 5–12 d
20.0–30.0	Severe	Cerebrovascular collapse, fever, shock	Death certain within 2–5 d

* Modified from Walker RI, Cerveny RJ, eds. (21). GI = gastrointestinal.

over a period of hours, resulting in early death. **Table 1** summarizes these responses as a function of dose delivered at a high exposure rate.

The Hematopoietic Syndrome

Irradiation of bone marrow stem and progenitor cells at increasing doses results in exponential cellular death (21). The hematopoietic syndrome is seen with significant partial-body or whole-body radiation exposures exceeding 1 Gy and is rarely clinically significant below this level (21). Mitotically active hematopoietic progenitors have a limited capacity to divide after a whole-body radiation dose greater than 2 to 3 Gy (26). In the ensuing weeks after exposure, a hematologic crisis occurs, characterized by hypoplasia or aplasia of the bone marrow. These changes result in pancytopenia predisposition to infection, bleeding, and poor wound healing, all of which contribute to death.

While most bone marrow progenitors are susceptible to cell death after sufficiently intense radiation doses, subpopulations of stem cells or accessory cells are selectively more radioresistant, presumably because of their largely noncycling (Go) state (27, 28). These radioresistant cells may play an important role in recovery of hematopoiesis after exposure to doses as high as 6 Gy, albeit with a reduced capacity for self-renewal (29). Another critical determinant for reconstitution is inhomogeneity of the dose with sparing of marrow sites that become foci of hematopoietic activity (Appendix, available at www.annals.org).

Lymphopenia is common and occurs before the onset of other cytopenias. A predictable decline in lymphocytes occurs after irradiation. In fact, a 50% decline in absolute lymphocyte count within the first 24 hours after exposure, followed by a further, more severe decline within 48 hours, characterizes a potentially lethal exposure. The predictability of the rate of lymphocytic depletion count has led to the development of a model using lymphocyte depletion kinetics as an element of biodosimetry (30, 31). Patients with burns (32–34) and trauma (35) may develop lymphopenia as a result of these injuries alone. Although currently available predictive models based on absolute lymphocyte count have been validated (and include patients with these injuries), it is important to examine more than one element of biodosimetry whenever possible.

The onset of other cytopenias varies, depending on both dose and dose rate (36). Granulocyte counts may transiently increase before decreasing in patients with exposure to less than 5 Gy (36) (**Appendix Figure 2**, available at www.annals.org). This transient increase before decline, termed an *abortive rise*, may indicate a survivable exposure.

Additional injuries, such as mechanical trauma or burns (the combined injury syndrome), are expected to occur in 60% to 70% of patients after detonation of an improvised nuclear device (19, 21). These injuries significantly complicate the management of patients with the hematopoietic syndrome and significantly lower the $LD_{50/60}$. Prognosis is grave in patients with the combined injury syndrome and radiation exposure (31).

The Gastrointestinal Syndrome

Radiation induces loss of intestinal crypts and breakdown of the mucosal barrier. These changes result in abdominal pain, diarrhea, and nausea and vomiting and predispose patients to infection. At doses exceeding 12 Gy, the mortality rate of the gastrointestinal syndrome exceeds that of the hematopoietic syndrome. Severe nausea, vomiting, watery diarrhea, and cramps occur within hours after high-dose (>10 Gy) irradiation. This is followed by a latent period lasting 5 to 7 days, during which symptoms abate. Vomiting and severe diarrhea associated with high fever make up the manifest illness. Systemic effects may include malnutrition from malabsorption; bowel obstruction from ileus; dehydration, cardiovascular collapse, and electrolyte derangements from fluid shifts; anemia from damage to the intestinal mucosa and microcirculation and subsequent gastrointestinal bleeding; and sepsis and acute renal failure (21).

The Cerebrovascular Syndrome

The cerebrovascular syndrome is less well defined than other syndromes, and its stages are compressed. Individuals presenting with fever, hypotension, and major impairment of cognitive function will most likely have had a supralethal exposure (26). These symptoms may be observed in those receiving more than 20 to 30 Gy of radiation (21). The prodromal phase is characterized by disorientation, confusion, and prostration and may be accompanied by loss of balance and seizures. The physical examination may show papilledema, ataxia, and reduced or absent deep tendon and corneal reflexes. During the latent period, apparent improvement occurs for a few hours and is followed by severe manifest illness. Within 5 to 6 hours, watery diarrhea, respiratory distress, hyperpyrexia, and cardiovascular shock can occur. This rapid decline mimics the clinical course of acute sepsis and septic shock, both of which must be considered. The ensuing circulatory complications of hypotension, cerebral edema, increased intracranial pressure, and cerebral anoxia can bring death within 2 days.

The Cutaneous Syndrome

Cutaneous injury from thermal or radiation burns is characterized by loss of epidermis and, at times, dermis. Injuries to the skin may cover small areas but extend deeply into the soft tissue, even reaching underlying muscle and bone (37). They may be accompanied by profound local edema and place the patient at risk for a compartment syndrome. Patients presenting with burns immediately after exposure have thermal rather than radiation burns. Significant injuries to the integument decrease the $LD_{50/60}$ and amplify the risk for death at any radiation exposure dose. Patients with the hematopoietic syndrome have a more complicated course of the cutaneous syndrome as a result of bleeding, infection, and poor wound healing (37). For a more thorough discussion, readers are directed to

Table 2. **Grading System for Response of Neurovascular, Gastrointestinal, and Cutaneous Systems***

Symptom	Degree 1	Degree 2	Degree 3	Degree 4
Neurovascular system				
Nausea	Mild	Moderate	Intense	Excruciating
Vomiting	Occasional (once per day)	Intermittent (2–5 times per day)	Persistent (6–10 times per day)	Refractory (>10 times per day)
Anorexia	Able to eat	Intake decreased	Intake minimal	Parenteral nutrition
Fatigue syndrome	Able to work	Impaired work ability	Needs assistance for ADLs	Cannot perform ADLs
Temperature, °C	<38	38–40	>40 for <24 h	>40 for >24 h
Headache	Minimal	Moderate	Intense	Excruciating
Hypotension	Heart rate >100 beats/min; blood pressure >100/170 mm Hg	Blood pressure <100/70 mm Hg	Blood pressure <90/60 mm Hg; transient	Blood pressure <80/? mm Hg; persistent
Neurologic deficits†	Barely detectable	Easily detectable	Prominent	Life-threatening, loss of consciousness
Cognitive deficits†	Minor loss	Moderate loss	Major impairment	Complete impairment
Gastrointestinal system				
Diarrhea				
Frequency, stools/d	2–3	4–6	7–9	≥10
Consistency	Bulky	Loose	Loose	Watery
Bleeding	Occult	Intermittent	Persistent	Persistent with large amount
Abdominal cramps or pain	Minimal	Moderate	Intense	Excruciating
Cutaneous system				
Erythema§	Minimal, transient	Moderate (<10% body surface area)	Marked (10%–40% body surface area)	Severe (>40% body surface area)
Sensation or itching	Pruritus	Slight and intermittent pain	Moderate and persistent pain	Severe and persistent pain
Swelling or edema	Present, asymptomatic	Symptomatic, tension	Secondary dysfunction	Total dysfunction
Blistering	Rare, sterile fluid	Rare, hemorrhage	Bullae, sterile fluid	Bullae, hemorrhage
Desquamation	Absent	Patchy dry	Patchy moist	Confluent moist
Ulcer or necrosis	Epidermal only	Dermal	Subcutaneous	Muscle or bone involvement
Hair loss	Thinning, not striking	Patchy, visible	Complete, reversible	Complete, irreversible
Onycholysis	Absent	Partial	Partial	Complete

* Modified from Fliedner TM, Friesecke I, Beyrer K (39). ADL = activity of daily living.
† Reflex status (including corneal reflexes), papilledema, seizures, ataxia, and other motor signs or sensory signs.
‡ Impaired memory, reasoning, or judgment.
§ The extent of involvement is decisive and should be documented for all skin changes.

excellent reviews on the acute radiation syndrome with the cutaneous syndrome (37, 38).

Management

Table 2 summarizes the clinical responses for all of these syndromes, and **Table 3** presents a grading system based on severity of hematologic change. The presence of nausea, vomiting, fatigue, and anorexia may indicate exposure to a significant radiation dose, particularly if onset is within hours of exposure. The physical examination should focus on documentation of vital signs (presence of fever, hypotension, and orthostasis), skin examination (erythema, blistering, onycholysis, edema, desquamation, and petechiae), neurologic examination (presence of motor or sensory deficits, papilledema, ataxia, and assessment of mental status and cognition), and abdominal examination (presence of pain or tenderness).

PSYCHOLOGICAL IMPACT OF RADIATION EXPOSURE

Psychosocial issues must be addressed in the potentially exposed population (40). Since a primary objective of terrorism is to elicit psychological shock, many persons requiring medical treatment will develop psychosocial symptoms even in the setting of no radiation exposure or

Table 3. **Levels of Hematopoietic Toxicity***

Symptom or Sign	Degree 1	Degree 2	Degree 3	Degree 4
Lymphocyte changes†	$\geq 1.5 \times 10^9$ cells/L	$1–1.5 \times 10^9$ cells/L	$0.5–1 \times 10^9$ cells/L	$<0.5 \times 10^9$ cells/L
Granulocyte changes‡	$\geq 2 \times 10^9$ cells/L	$1–2 \times 10^9$ cells/L	$0.5–1 \times 10^9$ cells/L	$<0.5 \times 10^9$ cells/L
Thrombocyte changes§	$\geq 100 \times 10^9$ cells/L	$50–100 \times 10^9$ cells/L	$20–50 \times 10^9$ cells/L	$<20 \times 10^9$ cells/L
Blood loss	Petechiae, easy bruising, normal hemoglobin level	Mild blood loss with <10% decrease in hemoglobin level	Gross blood loss with 10%–20% decrease in hemoglobin level	Spontaneous bleeding or blood loss with >20% decrease in hemoglobin level

* Modified from Dainiak N (24).
† Reference value, $1.4–3.5 \times 10^9$ cells/L.
‡ Reference value, $4–9 \times 10^9$ cells/L.
§ Reference value, $140–400 \times 10^9$ cells/L.

Table 4. **Mass Casualty Scenario for a Nuclear Detonation***

Patient Category	Radiation Dose, *Gy*	Patients, *n*	
		1-kiloton Detonation	10-kiloton Detonation
Combined injuries (minimal to intensive care)	All doses	1000–3000	15 000–24 000
Immediate fatalities	All doses	>7000	>13 000
Radiation fallout			
Expectant care	≥10	18 000	45 000
Intensive care	5–10	19 500	79 400
Critical care	3–5	33 000	108 900
Normal care	1–3	66 000	70 000
Ambulatory monitoring	0.5–1	82 500	139 000
Epidemiologic monitoring	0.25–0.5	106 000	147 000
Monitoring for psychosocial well-being without other injury	<0.25	>150 000	>270 000

* The table depicts projected casualty estimates based on a 1- or 10-kiloton detonation. Assumptions include a city with a population of 2 million people and casualties estimated on the basis of the Hazard Prediction Assessment Capability Program (HPAC), version 3.21 (Defense Threat Reduction Agency, Fort Belvoir, Virginia). Combined injuries consist of radiation injuries in addition to burns or blunt trauma.

very-low-dose exposure. Accordingly, terrorists will exploit an inherent, widespread fear of radiation by the general public to achieve a psychological effect.

Approximately 75% of individuals exposed to nuclear weapon detonations exhibit some form of psychological symptoms, ranging from inability to sleep to difficulty concentrating and social withdrawal (21). Among those at highest risk for significant psychological effects are children, pregnant women, mothers of young children, participants in radiation cleanup, and people with a medical history of a psychiatric disorder (41–43). In addition, exposed individuals and their families and friends have a high rate of post-traumatic stress disorder (44). Symptoms associated with post-traumatic stress disorder include anxiety disorders, depression, and a recurrent sense of re-experiencing the traumatic event. Individuals may exhibit outbursts of anger, an exaggerated startle response, and increased irritability. Post-traumatic stress disorder can be diagnosed when these symptoms persist for more than 1 month (45).

To assess the potential impact on the response system of persons with little or no radiation exposure, we generated a scenario for 1-kiloton and 10-kiloton nuclear detonations (**Table 4**). The number of individuals without exposure (that is, <0.25 Gy) who require psychosocial support is far greater than the number of patients who would be physically injured (**Table 4**). Expeditious triage of the former victims is essential and provision of appropriate treatment in the ambulatory setting is required so that those with survivable injuries can receive supportive care.

Biological Dosimetry

Individual biodosimetry is essential for predicting the clinical severity, treatment, and survivability of exposed individuals and triaging those with minimal or no exposure. The 3 most useful elements for calculating the exposure dose are time to onset of vomiting, lymphocyte depletion kinetics, and the presence of chromosome dicentrics. A radiation casualty management software program, the Biological Assessment Tool, is available at the Armed Forces Radiobiology Research Institute's Web site (www.afrri.usuhs.mil). This tool was developed in collaboration with REAC/TS and others to facilitate medical recording and estimation of individual dose (46). In addition, the International Atomic Energy Agency has developed generic guidelines for recording clinical signs and symptoms for victims of a radiation incident (see www.iaea.org). Using a grading system for the severity of clinical signs and symptoms, the Medical Treatment Protocols team has also developed a quantitative system to assess individual biological response to radiation exposure when results of chromosomal analysis are not yet available (39).

Prodromal signs and symptoms must be recorded throughout the course of medical management after a radiation exposure. Body location of radioactivity and thermal and traumatic injuries, and the degree of erythema, must be recorded on medical cards or flow charts that document signs and symptoms as a function of time after exposure. Dose estimates derived from the use of personnel dosimeters (if available) or other radiation monitoring devices must be recorded as well. These data may then be entered into the Biological Assessment Tool (or similar recording devices) at set triage stations so that an exposure dose can be estimated and the patient can be triaged accordingly.

The rate of decline and nadir of the absolute lymphocyte count over the initial 12 hours to 7 days after exposure is a function of cumulative dose (47). Lymphocyte depletion kinetics predict dose assessment for a photon-equivalent dose range between 1 and 10 Gy with an exposure resolution of approximately 2 Gy. Ideally, a complete blood cell count with leukocyte differential should be obtained immediately after exposure, 3 times per day for the next 2 to 3 days, and then twice per day for the following 3 to 6 days. However, this will require that deployable hematology laboratory capabilities be established and exercised for potential mass-casualty scenarios. It is recommended that 6 (and a minimum of 3) complete blood

Table 5. **Biodosimetry Based on Acute Photon-Equivalent Exposures***

Dose Estimate	Victims with Vomiting	Time to Onset of Vomiting	Absolute Lymphocyte Count†						Rate Constant for Lymphocyte Depletion‡	Dicentrics in Human Peripheral Blood Lymphocytes§	
			Day 0.5	Day 1	Day 2	Day 4	Day 6	Day 8		Per 50 Cells	Per 1000 Cells
Gy	*%*	*h*	←			*×10⁹ cells/L*		→	*k*‡	*n*	
0	–	–	**2.45**	**2.45**	**2.45**	**2.45**	**2.45**	**2.45**	–	0.05–0.1	1–2
1	19		**2.30**	**2.16**	**1.90**	**1.48**	1.15	0.89	0.126	4	88
2	35	4.63	**2.16**	**1.90**	**1.48**	0.89	0.54	0.33	0.252	12	234
3	54	2.62	**2.03**	**1.68**	1.15	0.54	0.25	0.12	0.378	22	439
4	72	1.74	**1.90**	**1.48**	0.89	0.33	0.12	0.044	0.504	35	703
5	86	1.27	**1.79**	1.31	0.69	0.20	0.06	0.020	0.63	51	1024
6	94	0.99	**1.68**	1.15	0.54	0.12	0.03	0.006	0.756		
7	98	0.79	**1.58**	1.01	0.42	0.072	0.012	0.002	0.881		
8	99	0.66	**1.48**	0.89	0.33	0.044	0.006	<0.001	1.01		
9	100	0.56	1.39	0.79	0.25	0.030	0.003	<0.001	1.13		
10	100	0.48	1.31	0.70	0.20	0.020	0.001	<0.001	1.26		

* Depicted above are the 3 most useful elements of biodosimetry. Dose range is based on acute photon-equivalent exposures. The second column indicates the percentage of people who vomit, based on dose received and time to onset. The middle section depicts the time frame for development of lymphopenia. Blood lymphocyte counts are determined twice to predict a rate constant that is used to estimate exposure dose. The final column represents the current gold standard, which requires several days before results are known. Colony-stimulating factor therapy should be initiated when onset of vomiting or lymphocyte depletion kinetics suggests an exposure dose for which treatment is recommended (see Table 7). Therapy may be discontinued if results from chromosome dicentrics analysis indicate a lower estimate of whole-body dose.
† Normal range, 1.4–3.5 × 10^9 cells/L. Numbers in boldface fall within this range.
‡ The lymphocyte depletion rate is based on the model $Lt = 2.45 \times 10^9$ cells/L × e − k(D)t, where *Lt* equals the lymphocyte count (×10^9 cells/L), 2.45 × 10^9 cells/L equals a constant representing the consensus mean lymphocyte count in the general population, *k* equals the lymphocyte depletion rate constant for a specific acute photon dose, and *t* equals the time after exposure (days).
§ Number of dicentric chromosomes in human peripheral blood lymphocytes.

counts with differential be obtained within the initial 4 days after exposure to calculate a slope for lymphocyte decline that can be used to estimate exposure dose. Complete blood counts with differential should then be obtained weekly or twice weekly until a nadir in neutrophil count is defined.

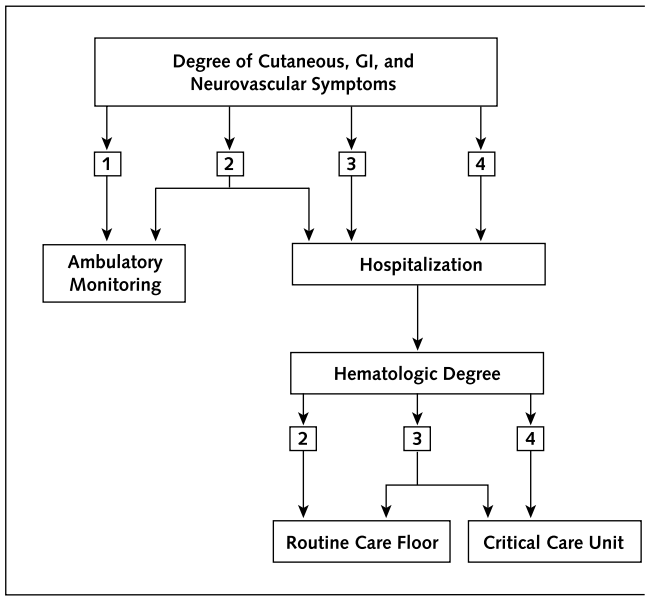
The chromosome-aberration cytogenetic bioassay, primarily the lymphocyte dicentrics assay introduced by Bender and Gooch (48), remains the gold standard for biodosimetry. The International Organization for Standardization recently proposed a standard to certify laboratories for performance of this bioassay (49). Rapid response is required from specialized cytogenetic biodosimetry laboratories in the case of a mass-casualty scenario (50, 51). A peripheral blood sample should be obtained at 24 hours after exposure (or later) in accordance with the policies of a qualified radiation cytogenetic biodosimetry laboratory. Because of incubation times, results will not be available for 48 to 72 hours after the sample has been submitted for analysis. Several cytogenetic biodosimetry laboratories use variations of interphase methods, such as the premature chromosome condensation bioassay, which permits dose assessment at higher doses (>5 Gy photon-equivalent and acute high-dose rate exposures) (52, 53). Although variations of the premature chromosome condensation assay (54) may provide dose estimates in less than 24 hours, this

Table 6. **Priorities in Triage of Patients with and without Combined Injury, Based on Dose of Radiation***

Conventional Triage Categories for Injuries without Exposure to Radiation	Changes in Expected Triage Categories after Whole-Body Radiation		
	<1.5 Gy	1.5–4.5 Gy	>4.5 but ≤10 Gy
Delayed	Delayed	Variable†	Expectant
Immediate	Immediate	Immediate	Expectant
Minimal	Minimal	Minimal‡	Minimal‡
Expectant	Expectant	Expectant	Expectant
Absent	Ambulatory monitoring	Ambulatory monitoring with routine care and hospitalization as needed	

* The military triage system was modified to develop priorities for therapy of individuals with radiation exposure and combined injury (i.e., significant mechanical trauma or burns). Priorities change as a function of radiation dose (range based on acute photon-equivalent exposures). At a whole-body dose <1.5 Gy, triage categories remain the same: 1) delayed treatment for those who are medically stable with significant injury but who may survive until definitive treatment is available; 2) immediate therapy for those with high survivability and significant injury, provided that immediate therapy is available; 3) minimal therapy for medically stable patients with minor injury; and 4) expectant therapy for patients who are seriously injured and in whom survivability is poor. All patients with the combined injury syndrome and an exposure dose >4.5 Gy should be treated expectantly, except for those with minimal or no injury. Patients with radiation injury alone (i.e., without combined injury) should be triaged to the ambulatory setting if dose <1.5 Gy. For those with a higher exposure dose, routine care should include therapy with cytokines, antimicrobial agents, blood transfusion, and frequent outpatient follow-up with laboratory monitoring. Hospitalization may be required, as indicated in Figure 2 and Table 7.
†Triage category depends on the nature and extent of physical injury.
‡ Although other injuries may be minimal, treatment guidelines in Figure 2 and Table 7 should be followed for patients receiving a whole-body radiation dose greater than 3 Gy.

Figure 2. **Approach to triage and therapy for persons exposed to radiation in a limited-casualty scenario.**



A numeric degree of severity is assigned for the cutaneous, gastrointestinal (*GI*), neurovascular, and hematopoietic systems, as defined in **Tables 2** and **3**. The highest degree of toxicity to an organ system indicates the physiologic "response category" (that is, 1, 2, 3, or 4). Modified with permission from reference 24.

method still requires validation. Other methods, such as messenger RNA biomarker assessment using gene profiling technology, are under development (55–58). **Table 5** compares dose estimates based on time to onset of vomiting, reduction in absolute lymphocyte count, and frequency of dicentric chromosomes.

Triage and Emergency Care

The goal of triage is to evaluate and sort individuals by immediacy of treatment needed to do the greatest good for the most people. Triage should include a radiologic survey to assess dose rate, documentation of prodromal symptoms, and collection of tissue samples for biodosimetry. Management of life-threatening injuries takes precedence over radiologic surveys and decontamination.

We present two triage systems. The first system is a modification of the military triage system used in mass-casualty scenarios (**Table 6**). Patients are categorized on the basis of the estimated range of exposure dose and the presence or absence of significant mechanical trauma or burns (that is, combined injury). Individuals requiring surgical intervention should undergo surgery within 36 hours (and not later than 48 hours) after the exposure (21). Additional surgery should not be performed until 6 weeks or later. Depending on the time elapsed after the exposure and availability of resources, patients may be re-triaged to another category. Additional information regarding this triage system is available elsewhere (21).

Alternatively, an individual physiologic "response category" based on grading of clinical signs and symptoms may be used in triage (24, 39) even before individual dose estimates are available to care providers. An initial response category is assigned by determining the degree of toxicity to the cutaneous, gastrointestinal, and neurovascular systems (**Figure 2**). Further categorization of patients based on hematologic degree of toxicity permits triage to an ambulatory setting, admission to a routine-care hospital floor, or admission to a critical care unit. While this system is very useful to the clinician in management of a small-volume radiologic event, it is time-consuming and may be impractical in a large-volume scenario.

Once patients have been triaged by biodosimetry assessment and presence of other injuries, they may be categorized into treatment groups according to general treatment guidelines on the basis of radiation exposure dose (**Table 7**). These guidelines are intended to complement clinical judgment on the basis of signs and symptoms of the exposed individual. Treatment of the acute radiation syndrome is not indicated when exposure dose is very low (<1 Gy) or very high (>10 Gy). Supportive and comfort care is indicated for people with an exposure dose greater than 10 Gy because their prognosis is grave.

Medical Management of the Hematopoietic Syndrome

Treatment of radiologic victims with the hematopoietic syndrome varies with dose estimates, exposure scenarios, and presenting symptoms. Short-term therapy with cytokines is appropriate when the exposure dose is relatively low (<3 Gy). Prolonged therapy with cytokines, blood component transfusion, and even stem-cell transplantation may be appropriate when exposure dose is high (>7 Gy) or when traumatic injury or burns are also present. If there are many casualties, treatment must be prioritized (**Table 7**).

Cytokine Therapy

Today, the only hematopoietic colony-stimulating factors (CSFs) that have marketing approval for the management of treatment-associated neutropenia are the recombinant forms of granulocyte macrophage colony-stimulating factor (GM-CSF), granulocyte colony-stimulating factor (G-CSF), and the pegylated form of G-CSF (pegylated G-CSF or pegfilgrastim). Currently, none of these cytokines have been approved by the U.S. Food and Drug Administration for the management of radiation-induced aplasia. The rationale for the use of CSFs in the radiation setting is derived from 3 sources: enhancement of neutrophil recovery in patients with cancer who are treated with CSFs, an apparently diminished period of neutropenia in a small number of radiation accident victims receiving CSFs, and improved survival in irradiated canines and nonhuman primates treated with CSFs.

The value of CSFs in the treatment of radiation-induced myelosuppression of the bone marrow lies in their ability to increase the survival, amplification, and differen-

tiation of granulocyte progenitors. Both GM-CSF and G-CSF activate or prime neutrophils to enhance their function, such as microbicidal activity (60–65). Both have been shown to hasten neutrophil recovery by approximately 3 to 6 days in humans after intensely myelotoxic therapies (66), including bone marrow and stem-cell transplantation (67, 68). In fact, neutrophil recovery times are similar for both early and delayed treatment with G-CSF after transplantation (69–71). In the REAC/TS registry, 25 of 28 patients treated with G-CSF and GM-CSF after radiation accidents appeared to have faster neutrophil recovery. In most instances, these persons received both G-CSF and GM-CSF concurrently for significant periods. However, there was considerable variation in when CSFs were used (often weeks after the incident) and how they were used. Some of these patients also received interleukin-3. A significant survival advantage has been demonstrated in irradiated animals treated with CSFs in the first 24 hours. Laboratory evidence for the efficacy of CSFs after irradiation is summarized in the Appendix (available at www.annals.org).

Table 8 summarizes recommendations for therapy based on radiation exposure dose. In any adult with a whole-body or significant partial-body exposure greater than 3 Gy, treatment with CSFs should be initiated as soon as biodosimetry results suggest that such an exposure has occurred or when clinical signs and symptoms indicate a level 3 or 4 degree of hematotoxicity. Doses of CSFs can be readjusted on the basis of other evidence, such as analysis for chromosome dicentrics. While there may be initial granulocytosis followed by significant neutropenia, CSF treatment should be continued throughout this entire period. The CSF may be withdrawn when the absolute neutrophil count reaches a level greater than 1.0×10^9 cells/L after recovery from the nadir. Reinstitution of CSF treatment may be required if the patient has a significant neutrophil decline ($<0.500 \times 10^9$ cells/L) after discontinuation. Although the benefit of epoetin and darbepoetin has not been established in radiologic events, these agents should be considered for patients with anemia. Response time is prolonged (that is, 3 to 6 weeks), and iron supplementation may be required.

People at the extremes of age (children $<$ 12 years and adults $>$ 60 years) may be more susceptible to irradiation and have a lower $LD_{50/60}$ (26). Therefore, a lower threshold exposure dose (2 Gy) for initiation of CSF therapy is appropriate in such persons and in those who have major trauma injuries or burns (**Table 7**). Individuals receiving an external radiation dose of at least 6 to 7 Gy from an incident involving more than 100 casualties due to detonation of an improvised nuclear device or small nuclear weapon will have a poor prognosis, particularly when additional injury is also present. Depending on the state of the health care infrastructure and availability of resources, it may be prudent to withhold CSF treatment from persons with significant burns or major trauma in a mass-casualty scenario (**Table 6**). Since CSFs are a critical resource that must be given for long durations, particularly in people with multiple injuries such as trauma and burns, difficult triage decisions may mean that CSFs may be preferentially used for people without additional injury because they may have a higher chance of survival (exposure dose of 3 to 7 Gy in adults $<$ 60 years of age and 2 to 7 Gy in children and in adults $\geq$ 60 years of age). The doses of

Table 7. **Guidelines for Treatment of Radiologic Victims***

Variable	Proposed Radiation Dose Range for Treatment with Cytokines	Proposed Radiation Dose Range for Treatment with Antibiotics†	Proposed Radiation Dose Range for Referral for SCT Consideration
	← Gy →		
Small-volume scenario (≤100 casualties)			
Healthy person, no other injuries	3–10‡	2–10§	7–10 for allogeneic SCT; 4–10 if previous autograft stored or syngeneic donor available
Multiple injuries or burns	2–6‡	2–6§	NA
Mass casualty scenario (>100 casualties)			
Healthy person, no other injuries	3–7‡	2–7§	7–10 for allogeneic SCT‖; 4–10 if previous autograft stored or syngeneic donor available‖
Multiple injuries or burns	2–6‖	2–6§‖	NA

* Consensus guidance for treatment is based on threshold whole-body or significant partial-body exposure doses. Events due to a detonation of a radiologic dispersal device resulting in ≤100 casualties and those due to detonation of an improvised nuclear device resulting in >100 casualties have been considered. These guidelines are intended to supplement (and not substitute for) clinical findings based on examination of the patient. NA = not applicable; SCT = stem-cell transplantation.

† Prophylactic antibiotics include a fluoroquinolone, acyclovir (if patient is seropositive for herpes simplex virus or has a medical history of this virus), and fluconazole when absolute neutrophil count is $<0.500 \times 10^9$ cells/L.

‡ Consider initiating therapy at lower exposure dose in nonadolescent children and elderly persons. Initiate treatment with granulocyte colony-stimulating factor or granulocyte-macrophage colony-stimulating factor in victims who develop an absolute neutrophil count $<0.500 \times 10^9$ cells/L and are not already receiving colony-stimulating factor.

§ Absolute neutrophil count $<0.500 \times 10^9$ cells/L. Antibiotic therapy should be continued until neutrophil recovery has occurred. Follow Infectious Diseases Society of America guidelines (59) for febrile neutropenia if fever develops while the patient is taking prophylactic medication.

‖ If resources are available.

Table 8. **Recommended Doses of Cytokines***

Cytokine	Adults	Children	Pregnant Women†	Precautions
G-CSF or filgrastim	Subcutaneous administration of 5 μg/kg of body weight per day, continued until ANC $>1.0 \times 10^9$ cells/L	Subcutaneous administration of 5 μg/kg per day, continued until ANC $>1.0 \times 10^9$ cells/L	Class C (same as adults)	Sickle-cell hemoglobinopathies, significant coronary artery disease, ARDS; consider discontinuation if pulmonary infiltrates develop at neutrophil recovery
Pegylated G-CSF or pegfilgrastim	1 subcutaneous dose, 6 mg	For adolescents >45 kg: 1 subcutaneous dose, 6 mg	Class C (same as adults)	Sickle-cell hemoglobinopathies, significant coronary artery disease, ARDS
GM-CSF or sargramostim	Subcutaneous administration of 250 μg/m^2 per day, continued until ANC $>1.0 \times 10^9$ cells/L	Subcutaneous administration of 250 μg/m^2 per day, continued until ANC $>1.0 \times 10^9$ cells/L	Class C (same as adults)	Sickle-cell hemoglobinopathies, significant coronary artery disease, ARDS; consider discontinuation if pulmonary infiltrates develop at neutrophil recovery

* ANC = absolute neutrophil count; ARDS = acute respiratory distress syndrome; G-CSF = granulocyte colony-stimulating factor; GM-CSF = granulocyte-macrophage colony-stimulating factor.
† Experts in biodosimetry must be consulted. Any pregnant patient with exposure to radiation should be evaluated by a health physicist and maternal–fetal specialist for an assessment of risk to the fetus. Class C refers to U.S. Food and Drug Administration Pregnancy Category C, which indicates that studies have shown animal, teratogenic, or embryocidal effects, but there are no adequate controlled studies in women; or no studies are available in animals or pregnant women.

CSFs recommended for use in radiologic incidents are based on the standard doses used in patients who have treatment-related neutropenia (**Table 7**).

Transfusion

Transfusion of cellular components, such as packed red blood cells and platelets, is required for patients with severe bone marrow damage. Fortunately, this complication does not typically occur for 2 to 4 weeks after the exposure, thereby permitting time for rapid mobilization of blood donors. Blood component replacement therapy is also required for trauma resuscitation. All cellular products must be leukoreduced and irradiated to 25 Gy to prevent transfusion-associated graft-versus-host disease in the irradiated (and therefore immunosuppressed) patient. It may be difficult to distinguish transfusion-associated graft-versus-host disease from radiation-induced organ toxicity, which may include fever, pancytopenia, skin rash, desquamation, severe diarrhea, and abnormalities on liver function tests (in particular, hyperbilirubinemia).

Leukoreduction is known to lessen febrile nonhemolytic reactions and the immunosuppressive effects of blood transfusion (72, 73). Moreover, leukoreduction helps protect against platelet alloimmunization and against acquiring cytomegalovirus infections (74, 75). Ideally, life-saving blood products should be leukoreduced and irradiated.

Stem-Cell Transplantation

Matched related and unrelated allogeneic stem-cell transplantations are life-saving and potentially curative treatments in patients with certain predominantly hematologic malignant conditions. A small number of radiation accident victims have undergone allogeneic transplantation from a variety of donors in an attempt to overcome radiation-induced aplasia. The initial experience with this method in an irradiated patient dates back to 1958 (76, 77). Many reports demonstrate transient engraftment with partial chimerism, with nearly all patients experiencing autologous reconstitution of hematopoiesis. However, despite the transient engraftment, outcomes have been poor, largely because of the impact of burns, trauma, or other radiation-related organ toxicity (78–80). In fact, in a recent review of the allogeneic transplant experience in 29 patients who developed bone marrow failure from previous radiation accidents (79), all patients with burns died and only 3 of the 29 lived beyond 1 year. It is unclear whether the transplants affected survival.

Similar results were observed in the 1999 radiation accident in Tokaimura, Japan (78), where 2 of the 3 victims were referred for allogeneic transplantation. Both patients demonstrated transient evidence of donor-cell engraftment followed by complete autologous hematopoietic recovery before eventually dying of radiation injuries to another organ system or infection. Survival may have been longer than expected in these patients.

If resources allow, transplantation should be considered in people with an exposure dose of 7 to 10 Gy who do not have significant burns or other major organ toxicity and who have an appropriate donor. Individuals with a granulocyte count exceeding 0.500×10^9 cells/L and a platelet count of more than 100×10^9 cells/L at 6 days after exposure appear to have evidence of residual hematopoiesis and may not be candidates for transplantation (81). In the unusual circumstance that a syngeneic donor may be available or previously harvested autologous marrow is available, a stem-cell infusion may be considered in patients with exposures exceeding 4 Gy (**Table 7**).

Medical Management of Other Complications and Special Considerations

The following treatment recommendations are defined by clinical and laboratory-based triage and observation of the clinical signs and symptoms associated with the acute radiation syndrome.

Supportive Care

Supportive care includes the administration of antimicrobial agents, antiemetic agents, antidiarrheal agents, fluids, electrolytes, analgesic agents, and topical burn creams. Experimental work performed more than 2 decades ago demonstrated the efficacy of supportive care, including the use of systemic antibiotics directed at gram-negative bacteria and transfusion with fresh, irradiated platelets (82–86).

Careful attention must be given to early fluid resuscitation of patients with significant burns, hypovolemia, hypotension, and multiorgan failure. Expectant care (treatment for comfort with psychosocial support) is recommended for patients who develop multiorgan failure within hours after exposure, as their radiation dose will have been high (>10 Gy). Resources permitting, routine critical care therapy should be provided to patients who develop multiorgan failure several days to weeks after exposure because their dose will have been in the moderate range. Therapy includes endotracheal intubation; administration of anticonvulsant agents; and the judicious use of parenteral analgesic agents, anxiolytic agents, and sedatives, as needed.

Infections

Susceptibility to infection results from a breech in the integument or mucosal barriers, as well as immune suppression consequent to a decline in lymphohematopoietic elements. Several studies have indicated that administration of antibiotics reduces mortality rates in irradiated dogs in the $LD_{50/30}$ range (84–87). Controlling infection during the critical neutropenic phase is a major limiting factor for successful outcome (85). In non-neutropenic patients, antibiotic therapy should be directed toward foci of infection and the most likely pathogens. Fluoroquinolones have been used extensively for prophylaxis in neutropenic patients (88–91). In patients who experience significant neutropenia (absolute neutrophil count $< 0.500 \times 10^9$ cells/L), broad-spectrum prophylactic antimicrobial agents should be given during the potentially prolonged neutropenia period. Prophylaxis should include a fluoroquinolone with streptococcal coverage or a fluoroquinolone without streptococcal coverage plus penicillin (or a congener of penicillin), antiviral drugs (acyclovir or one of its congeners), and antifungal agents (fluconazole). The efficacy of quinolones in irradiated animal models and guidelines for the use of acyclovir and fluconazole are reviewed in the Appendix (available at www.annals.org).

Antimicrobial agents should be continued until they are clearly not effective (for example, the patient develops neutropenic fever) or until the neutrophil count has recovered (absolute neutrophil count $\geq 0.500 \times 10^9$ cells/L). Focal infections developing during the neutropenic period require a full course of antimicrobial therapy. In patients who experience fever while receiving a fluoroquinolone, the fluoroquinolone should be withdrawn and therapy should be directed at gram-negative bacteria (in particular, *Pseudomonas aeruginosa*), since infections of this type may become rapidly fatal. Therapy for patients with neutropenia and fever should be guided by the recommendations of the Infectious Diseases Society of America (92–94). Use of additional antibiotics is based on treatment of concerning foci (that is, anaerobic cocci and bacilli that may occur in patients with abdominal trauma or infection with gram-positive bacteria such as *Staphylococcus* and *Streptococcus* species in addition to significant burns). Altering the anaerobic gut flora of irradiated animals may worsen outcomes (95). Therefore, we recommend that gut prophylaxis not be administered empirically unless clinically indicated (for example, in patients with an abdominal wound or *Clostridium difficile* enterocolitis).

Gastrointestinal Symptoms

Nausea and vomiting are common in patients exposed to radiation. The time to onset of vomiting has merit as a means of clinical dosimetry (96) but should be interpreted together with other forms of biodosimetric assessment. Given the importance of vomiting onset in determining individual radiation dose, prophylaxis against vomiting is not initially desired and would be impractical given the short time to onset with clinically significant exposures (96). At low exposure doses, vomiting usually abates after 48 to 72 hours; therefore, prolonged antiemetic therapy is not warranted in this situation. Serotonin receptor antagonists are very effective prophylaxis in patients who have received radiation therapy (97–100).

Supportive measures include fluid replacement, antibiotic therapy, and prophylaxis against ulceration of the gastrointestinal tract. Instrumentation of the gastrointestinal tract should be performed judiciously or not at all, since the intestinal mucosa is friable and prone to sloughing and bleeding after mechanical manipulation.

Comfort Measures

People with a high exposure dose whose outcome is grim must be identified for appropriate management. Since there is no chance for survival after irradiation with a dose of more than 10 to 12 Gy (**Table 1**), it is appropriate for definitive care to be withheld from such individuals. Rather than being treated aggressively, these patients should be provided with comfort measures. This includes attention to pain management and general comfort as well as administration of antiemetic and antidiarrheal agents. In this devastating situation, psychological support and pastoral care are essential not only for the patient but also for family and friends, who may experience traumatic grief.

Special Considerations

In pregnant women, the risk to the fetus must be assessed. Persons who have been exposed to radioiodines should receive prophylaxis with potassium iodide. Children and adolescents are particularly prone to developing malignant thyroid disease. Recommendations for treatment of victims who are pregnant and for prevention of thyroid cancer are provided in the Appendix (available at

Table 9. **Sources for Additional Information on Assessment, Triage, and Clinical Management of Radiologic Victims**

Source	Web Site
American Academy of Pediatrics	www.aap.org
American College of Radiology Disaster Planning Task Force, in collaboration with the American Society for Therapeutic Radiology and Oncology and the American Association of Physicists in Medicine	www.acr.org www.astro.org www.aapm.org
American Medical Association	www.ama-assn.org
Armed Forces Radiobiology Research Institute	www.afrri.usuhs.mil
Centers for Disease Control and Prevention	www.bt.cdc.gov
Health Physics Society	http://hps.org
Radiation Emergency Assistance Center/Training Site	www.orau.gov/reacts
Uniformed Services University of the Health Sciences Center for Disaster and Humanitarian Assistance Medicine	http://usuhs.mil
U.S. Army	www.nbc-med.org
U.S. Department of Homeland Security Working Group on Radiological Dispersal Device Preparedness	www1.va.gov
U.S. Food and Drug Administration	www.fda.gov
U.S. Nuclear Regulatory Commission	www.nrc.gov

www.annals.org). Table 9 lists Web sites providing more detailed information on radiation response.

Precautions for Health Care Workers

Guidelines have been established for the use of personal protective equipment by health care providers, as described elsewhere (23) and on the Oak Ridge Associated Universities Web site (www.orau.gov/reacts). Providers should use strict isolation precautions, including donning of gown, mask, cap, double gloves, and shoe covers, when evaluating and treating contaminated patients. Outer gloves should be changed frequently to avoid cross-contamination. No health care workers who have adhered to these guidelines have become contaminated from handling a contaminated patient. Radiation detection devices can readily locate contaminants in the hospital facility to allow decontamination to take place. Protective gear should be removed after use and placed in a clearly labeled, sealed plastic container.

Conclusion

Medical management of patients exposed to intentional or accidental radiation is complex and demands many resources. The primary responsibility for optimizing outcome resides with hospital staff and physicians and other health care facilities. Careful documentation of clinical signs and symptoms and estimation of individual radiation dose are required for medical triage. While loss of life in a nuclear detonation may be enormous, the survival benefit afforded those who receive modern supportive care is significant. Effective care requires implementation of well-organized disaster plans. Disaster planning should include contingency planning for a scenario that involves loss of infrastructure. Organizing as a nation will be instrumental in order to successfully combat a radiologic threat in the United States and across the globe.

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Appendix

Institutional and Committee Participants

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Hematopoietic Reconstitution

Hematopoietic reconstitution has been shown to be possible with partial-body radiation exposure of up to 10 to 12 Gy. Recovery may result from proliferation and differentiation of radioresistant stem cells or stem cells that are spared from radiation because the person's physical environment and proximity to the source may afford partial shielding. **Appendix Figure 1** summarizes the medical record of a radiation accident victim. Note that the lowest dose of 1.5 Gy is received in the right posterior pelvis. Hematopoietically active bone marrow predominates in the dorsal areas of the spine, ribs, and pelvis (21). Accordingly, the patient may have areas of viable marrow, and his injury is potentially survivable (26). Indeed, this individual survived the acute injuries and died 17 years later of radiation hepatitis (36).

Persons exposed to a radiation dose of less than 5 Gy may have a transient increase in granulocyte count. This abortive increase is followed by a nadir that occurs between 1 and 4 weeks (**Appendix Figure 2**) (26, 36). A longer time to nadir is seen with an exposure to a low dose or dose rate of radiation, but the duration of the nadir may be prolonged, requiring long-term therapy.

Experimental Evidence of Efficacy of CSFs

Several studies examining the role of G-CSF, GM-CSF, pegylated G-CSF, and a chimeric molecule in an irradiated rhesus macaque model (10, 101–106) demonstrated significant neutrophil enhancement when these agents were administered 1 day after exposure and were continued for 14 to 21 consecutive days. Studies performed in irradiated rhesus macaques also suggested that there is a survival benefit to initiation of G-CSF or GM-CSF therapy within 24 hours of exposure. However, another report suggested that there is no diminished efficacy when cytokine therapy is delayed (101). Therefore, there is no conclusive proof that early (that is, within 24 hours) administration is necessary and sufficient for optimal outcome in mammals. Nevertheless, CSF therapy should be initiated as early as possible for persons who have been exposed to a survivable whole-body dose of radiation and are at risk for the hematopoietic syndrome (>3 Gy but <10 Gy in adults <60 years of age; >2 Gy but <10 Gy in nonadolescent children and in adults ≥ 60 years of age). Those who become significantly neutropenic (absolute neutrophil count $<0.500 \times 10^9$ cells/L) should also receive CSFs.

Pegfilgrastim has recently received marketing approval in the United States and has efficacy similar to that of G-CSF in chemotherapy-induced myelosuppression (107, 108). Preclinical studies in irradiated rhesus macaques demonstrated that neutrophil recovery occurs after a single injection of pegfilgrastim and that the effect is equivalent to that observed with conventional, daily dosing with filgrastim (109).

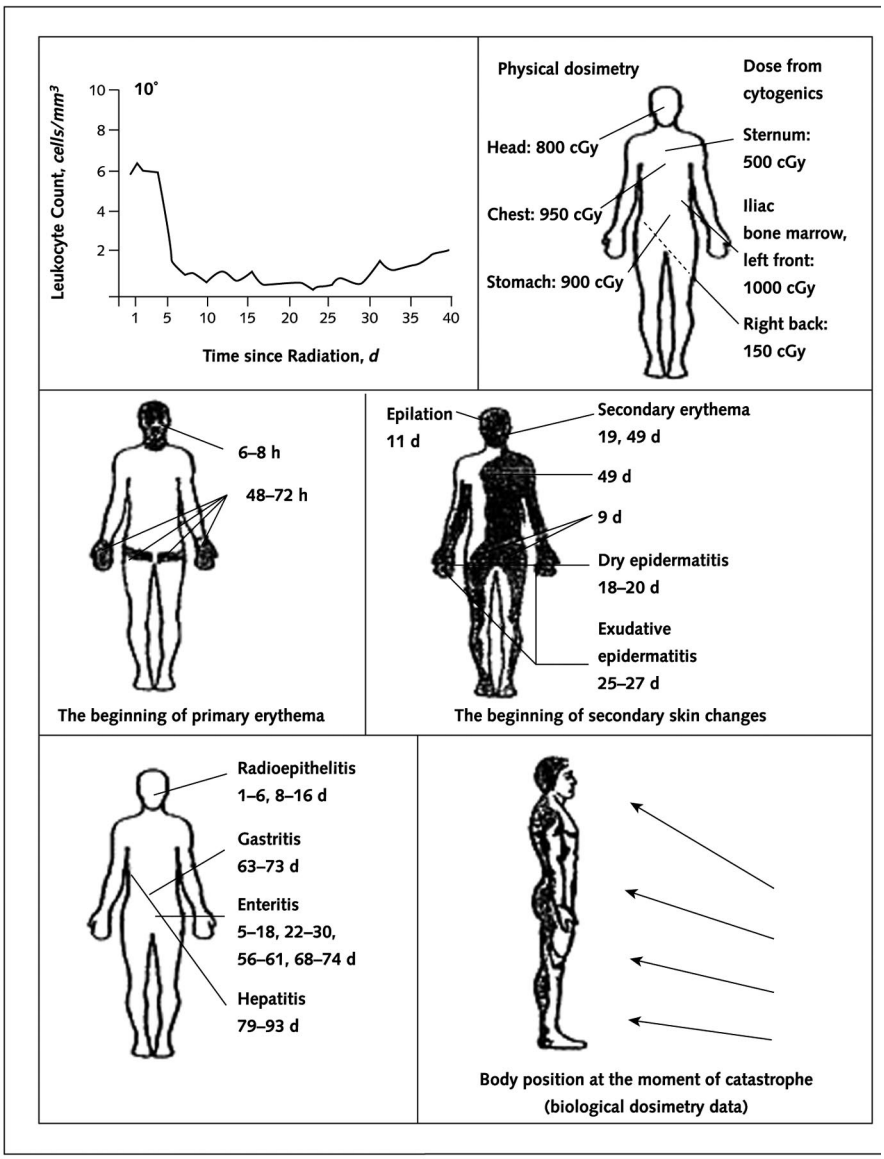
Rationale for Use of Antibiotics

Studies in irradiated mice demonstrated that the gut flora is dramatically altered soon after acute, high-dose exposure. The total mass of aerobes and anaerobes is reduced by several orders of magnitude, while Enterobacteriaceae increase at the expense of vital anaerobic species (95). In addition to breaks in the integrity of the gut wall, a dose-dependent reduction in number of stem cells in intestinal crypts occurs in the first 4 days after radiation (95, 110). Fatal bacteremia may result from bacterial outgrowth and translocation across damaged walls and interstitium of these organisms to the bloodstream. The use of quinolones was effective in controlling systemic endogenous gram-negative infections after radiation (110, 111). Supplementation with penicillin prevented treatment failures due to *Streptococci* infection and in patients with cancer who experienced treatment-related neutropenia (112). Quinolones were also effective in preventing endogenous infections with *Klebsiella* and *Pseudomonas* species (95, 111, 113).

If serologic tests for herpes simplex viruses (HSV-1 and HSV-2) are known to be positive, acyclovir or one of its congeners should be administered. Patients with positive serologic results are at high risk for reactivation of HSV infection during intense immunosuppression and may present with a clinical scenario that mimics radiation stomatitis. While patients undergoing local radiation therapy for head and neck cancer do not show a significant risk for HSV reactivation (114), patients who receive immunosuppressive therapies such as bone marrow transplantation have a high incidence of reactivation (115), which may add to the severity of mucosal injury. If serologic results are not known, it is reasonable to offer HSV prophylaxis on the basis of a medical history of oral or genital herpes infection. Individuals who experience severe mucositis should be assessed for possible reactivation of HSV.

Oral fluconazole, 400 mg/d, lessens the severity of invasive fungal infections and mortality rates in patients undergoing allogeneic bone marrow transplantation (116, 117). Data in patients receiving conventional forms of severely myelotoxic chemotherapy have also demonstrated benefit (59), although conflicting results exist (118, 119). Fluconazole prophylaxis is ineffective

Appendix Figure 1. **Summary of a medical record of a patient injured in a radiation accident.**



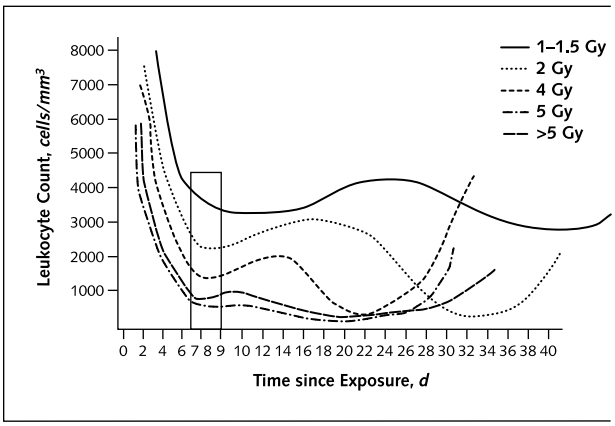
Shown are the absolute leukocyte count (*top left panel*), estimated organ dose (*top right panel*), areas of skin injury (*middle panels*), injury to oral cavity and gastrointestinal system (*bottom left panel*), and body position relative to the radioactive source (*bottom right panel*) as a function of time after the exposure. To convert cells/mm^3 to $\times 10^9$ cells/L, multiply by 0.001. Redrawn with permission from reference 29.

against aspergillus, molds, *Candida krusei*, and resistant *Candida* species.

Prolonged immune suppression from radiation may lead to reactivation of CMV and development of *Pneumocystis carinii* pneumonia. While the incidence of reactivation of CMV in patients with serologic evidence of previous infection after exposure to ionizing radiation is unknown, extrapolation from the marrow transplant literature indicates that the period of greatest risk is within the first 100 days of exposure. If resources allow, the serologic status of CMV should be determined and a sensitive test should be used to assay for reactivation of CMV (that is, antigen assessment or a polymerase chain reaction test) every 2 weeks for 30 days postexposure, up to day 100 in patients with documented previous CMV exposure. Subsequent examination may be necessary based on the clinical scenario because CMV infection may occur later.

An assessment of the absolute CD4 cell count should be considered at 30 days postexposure for patients who have had or currently have radiation-associated lymphopenia. Patients who are highly susceptible to *Pneumocystis carinii* pneumonia have an absolute CD4 cell count less than 0.200×10^9 cells/L. Trimethoprim–sulfamethoxazole should be avoided until the leukocyte count exceeds 3.0×10^9 cells/L or the absolute neutrophil count exceeds 1.5×10^9 cells/L. Alternative therapy includes atovaquone, dapsone, and aerosolized pentamidine. Prophylaxis should continue until the absolute CD4 cell count increases to a level of 0.200×10^9 cells/L or greater. This increase in CD4 cell count may not occur for several months.

Appendix Figure 2. **Leukocyte count based on exposure dose in patients exposed to radiation in Chernobyl.**



Note the abortive rise (transient increase before the fall) in counts of leukocytes, which are primarily composed of granulocytes, in doses less than 5 Gy. Neutropenia may not occur for weeks, especially with lower exposures, and its duration may be prolonged. To convert cells/mm^3 to $\times 10^9$ cells/L, multiply by 0.001. Redrawn with permission from reference 36.

Guidelines for Management of Pregnancy and Prevention of Thyroid Cancer

All hematopoietic cytokines and many antibiotics are class C drugs (**Table** 7). However, any pregnant woman who has been exposed to more than 0.25 Gy of radiation should have an estimate of fetal dose determined. The fetus's dose is often lower than that of the mother, except in the settings of radioiodine exposure (because the fetal thyroid gland is more iodine-avid than the adult thyroid gland) and internal contamination of the maternal urinary bladder (where increased exposure may occur because of proximity of the fetus to radioactivity). Consultation with a health physicist and a maternal–fetal medicine specialist is advised to assess risk to the fetus. The most important factor for ensuring fetal survival is survival of the mother. Pregnant women should receive the same supportive care as that provided to nonpregnant adults. Antibiotic use in pregnant women will require a review of safety in pregnancy. Risks and benefits to the mother and fetus must be explained before therapy is administered.

In the fetus, child, and adolescent, the thyroid gland is a radiosensitive organ that is at risk for malignant transformation. Because the thyroid gland concentrates iodine with great efficiency, exposure to radioiodines (^{131}I, ^{125}I) results in localization of radioactivity in the thyroid gland. This concentration of radioactivity can result in thyroid cancer, a delayed consequence that may be more aggressive than de novo forms of thyroid cancer (120). The main route of radioiodine exposure is inhalation by those in the near field and ingestion of contaminated food and drink (particularly milk) for those farther away (in the far field). Thyroid blocking with potassium iodide offers some protection (reduction of radioiodine uptake by 50% when administered within 4 hours of the exposure) by saturating the thyroid gland with nonradioactive iodine.

However, potassium iodide is not a generic antiradiation drug. If radioiodines are not part of the exposure, potassium iodide is not recommended. For example, because of their short half-life of 8.5 days, it is extremely unlikely that radioiodines will be incorporated into a radiologic dispersal device or "dirty bomb." In this scenario, potassium iodide will be of no clinical benefit but its potential toxicity (including life-threatening anaphylaxis) will be risked. Therefore, it is recommended that treatment with potassium iodide be avoided in victims of a "dirty bomb" explosion.

Dosing guidance for exposures involving radioiodines is reviewed in the **Appendix Table** and is also available online at www.bt.cdc.gov/radiation/ki.asp. Potassium iodide should be administered by mouth (tablets or Lugol solution) as soon as possible after the accident (≤6 hours). Caution should be taken in victims who have a personal history of allergy to iodine because severe allergic reactions have been reported. Thyroid protection for pregnant women exposed to radioiodine is critical for the mother and fetus. In the first trimester with a near-field exposure, stable iodine will protect the mother. Pregnant women with far-field exposure may be able to avoid contaminated foods and milk. The fetal thyroid gland normally does not begin to function until approximately the 12th week of gestation. Thus, pregnant women in the second and third trimesters should receive potassium iodide in both near- and far-field exposures to protect the maternal and fetal thyroid glands.

Appendix Table. **Threshold Dose and Recommended Doses of Potassium Iodide for Different Risk Groups***

Patients	Predicted Thyroid Dose	Daily Dose of Potassium Iodide	130-mg Tablets	65-mg Tablets
	Gy	*mg*	*n*	
Adults >40 y of age	≥5	130	1	2
Adults >18 through 40 y of age	≥0.1	130	1	2
Pregnant or lactating women	≥0.05	130	1	2
Adolescents >12 through 18 y of age†	≥5	65	1/2	2
Children >3 through 12 y of age	≥5	65	1/2	1
Children >1 mo through 3 y of age	≥5	32	1/4	1/2
Birth through 1 mo	≥5	16	1/8	1/4

* Based on reference 121. Potassium iodide tables or Lugol solution must be used within 4 to 6 hours of exposure to block uptake of radioiodines by the thyroid gland. If radioiodines are not part of the exposure, potassium iodide treatment is not indicated. Therapy should be continued for 7 to 10 days or as long as the exposure continues.
† Adolescents approaching adult size (≥70 kg) should receive the full adult dose (130 mg).

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BIOTERRORISM: EVENT DEFINITION

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 DEFINITION	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* www.dhs.ca.gov/ps/dcdc/bt/index.htm

Selected Biowarfare Agent Characteristics

Disease	Person-to Person Transmission	Infective Dose (Aerosol)	Incubation Period	Duration of Illness	Lethality	Persistence of Organism	Vaccine Efficacy (aerosol exposure)
Anthrax	No	8,000-50,000 spores	1-6 days	3-5 days (usually fatal if untreated)	High	Very stable - spores remain viable for > 40 years in soil	2 dose efficacy against up to 1,000 LD_{50} in monkeys
Brucellosis	No	10 -100 organisms	5-60 days (usually 1-2 months)	Weeks to months	<5% untreated	Very stable	No vaccine
Botulism	No	0.001 μg/kg is LD_{50} for type A	12 hours to 5 days	Death in 24-72 hours; lasts months if not lethal	High without respiratory support	For weeks in nonmoving water and food	3 dose efficacy 100% against 25-250 LD_{50} in primates
Cholera	Rare	10-500 organisms	4 hours - 5 days (usually 2-3 days)	≥ 1 week	Low with treatment, high without	Unstable in aerosols & fresh water; stable in salt water	No data on aerosol
Glanders	Low	Assumed low	10-14 days via aerosol	Death in 7-10 days in septicemic form	> 50%	Very stable	No vaccine
Melioidosis	Low	Assumed low	1-21 days (up to years)	Death in 2-3 days with septicemic form	19-50% for severe disease	Very stable; survives indefinitely in warm moist soil or stagnant water	No data on aerosol
Plague	Moderate, Pneumonic	100-500 organisms	1-7 days (usually 2-3 days)	1-6 days (usually fatal)	High unless treated within 12-24 hours	For up to 1 year in soil; 270 days in live tissue	3 doses not protective against 118 LD_{50} in monkeys
Q Fever	Rare	1-10 organisms	7-41 days	2-14 days	Very low	For months on wood and sand	94% protection against 3,500 LD_{50} in guinea pigs
Ricin	No	3-5 μg/kg is LD_{50} in mice	18-24 hours	Days (death within 10-12 days if ingested)	High	Stable	No vaccine
Smallpox	High	Assumed low (10-100 organisms)	7-17 days (average 12)	4 weeks	High to moderate	Very stable	Vaccine protects against large doses in primates
Staph Enterotoxin B	No	0.03 μg/person incapacitation	3-12 hours after inhalation	Hours	< 1%	Resistant to freezing	No vaccine
Tularemia	No	10-50 organisms	2-10 days (average 3-5)	≥ 2 weeks	Moderate if untreated	For months in moist soil or other media	80% protection against 1-10 LD_{50}
Venezuelan Equine Encephalitis	Low	10-100 organisms	2-6 days	Days to weeks	Low	Relatively unstable	TC 83 protects against 30-500 LD_{50} in hamsters
Viral Hemorrhagic Fevers	Moderate	1-10 organisms	4-21 days	Death between 7-16 days	High to moderate, depends on strain	Relatively unstable - depends on agent	No vaccine
T-2 Mycotoxins	No	Moderate	2-4 hours	Days to months	Moderate	For years at room temperature	No vaccine

LD_{50} = lethal dose (μg/kg)

Source: USAMRIID's Medical Management of Biological Casualties Handbook, 5th Ed., August 2004; www.usamriid.army.mil/education/bluebook.htm

Anthrax as a Biological Weapon, 2002
Updated Recommendations for Management

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Objective To review and update consensus-based recommendations for medical and public health professionals following a *Bacillus anthracis* attack against a civilian population.

Participants The working group included 23 experts from academic medical centers, research organizations, and governmental, military, public health, and emergency management institutions and agencies.

Evidence MEDLINE databases were searched from January 1966 to January 2002, using the Medical Subject Headings *anthrax*, *Bacillus anthracis*, *biological weapon*, *biological terrorism*, *biological warfare*, and *biowarfare*. Reference review identified work published before 1966. Participants identified unpublished sources.

Consensus Process The first draft synthesized the gathered information. Written comments were incorporated into subsequent drafts. The final statement incorporated all relevant evidence from the search along with consensus recommendations.

Conclusions Specific recommendations include diagnosis of anthrax infection, indications for vaccination, therapy, postexposure prophylaxis, decontamination of the environment, and suggested research. This revised consensus statement presents new information based on the analysis of the anthrax attacks of 2001, including developments in the investigation of the anthrax attacks of 2001; important symptoms, signs, and laboratory studies; new diagnostic clues that may help future recognition of this disease; current anthrax vaccine information; updated antibiotic therapeutic considerations; and judgments about environmental surveillance and decontamination.

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OF THE BIOLOGICAL AGENTS that may be used as weapons, the Working Group on Civilian Biodefense identified a limited number of organisms that, in worst case scenarios, could cause disease and deaths in sufficient numbers to gravely impact a city or region. *Bacillus anthracis*, the bacterium that causes anthrax, is one of the most serious of these.

Several countries are believed to have offensive biological weapons programs, and some independent terrorist groups have suggested their intent to use biological weapons. Because the possibility of a terrorist attack using bioweapons is especially difficult to predict, detect, or prevent, it is among the most feared terrorism scenarios.[1] In September 2001, *B anthracis* spores were sent to several locations via the US Postal Service. Twenty-two confirmed or suspect cases of anthrax infection resulted. Eleven of these were inhalational cases, of whom 5 died; 11 were cutaneous cases (7 confirmed, 4 suspected).[2] In this article, these attacks are termed *the anthrax attacks of 2001*. The consequences of these attacks substantiated many findings and recommendations in the Working Group on Civilian Biodefense's previous consensus statement published in 1999[3]; however, the new information from these attacks warrant updating the previous statement.

Before the anthrax attacks in 2001, modern experience with inhalational anthrax was limited to an epidemic in Sverdlovsk, Russia, in 1979 following an unintentional release of *B anthracis* spores from a Soviet bioweapons factory and to 18 occupational exposure cases in the United States during the 20th century. Information about the potential impact of a large, covert attack using *B anthracis* or the possible effi-

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cacy of postattack vaccination or therapeutic measures remains limited. Policies and strategies continue to rely partially on interpretation and extrapolation from an incomplete and evolving knowledge base.

CONSENSUS METHODS

The working group comprised 23 representatives from academic medical centers; research organizations; and government, military, public health, and emergency management institutions and agencies. For the original consensus statement,[3] we searched MEDLINE databases from January 1966 to April 1998 using Medical Subject Headings of *anthrax*, *Bacillus anthracis*, *biological weapon*, *biological terrorism*, *biological warfare*, and *biowarfare*. Reference review identified work published before 1966. Working group members identified unpublished sources.

The first consensus statement, published in 1999,[3] followed a synthesis of the information and revision of 3 drafts. We reviewed anthrax literature again in January 2002, with special attention to articles following the anthrax attacks of 2001. Members commented on a revised document; proposed revisions were incorporated with the working group's support for the final consensus document.

The assessment and recommendations provided herein represent our best professional judgment based on current data and expertise. The conclusions and recommendations need to be regularly reassessed as new information develops.

HISTORY OF CURRENT THREAT

For centuries, *B anthracis* has caused disease in animals and serious illness in humans.[4] Research on anthrax as a biological weapon began more than 80 years ago.[5] Most national offensive bioweapons programs were terminated following widespread ratification or signing of the Biological Weapons Convention (BWC) in the early 1970s[6]; the US offensive bioweapons program was terminated after President Nixon's 1969 and 1970 executive orders. However, some nations continued offensive bioweapons development programs despite ratification of the BWC. In 1995, Iraq acknowledged producing and weaponizing *B anthracis* to the United Nations Special Commission.[7] The former Soviet Union is also known to have had a large *B anthracis* production program as part of its offensive bioweapons program.[8] A recent analysis reports that there is clear evidence of or widespread assertions from nongovernmental sources alleging the existence of offensive biological weapons programs in at least 13 countries.[6]

The anthrax attacks of 2001 have heightened concern about the feasibility of large-scale aerosol bioweapons attacks by terrorist groups. It has been feared that independent, well-funded groups could obtain a manufactured weapons product or acquire the expertise and resources to produce the materials for an attack. However, some analysts have questioned whether "weapons grade" material such as that used in the 2001 attacks (ie, powders of *B anthracis* with characteristics such as high spore concentration, uniform particle size, low electrostatic charge, treated to reduce clumping) could be produced by those not supported by the resources of a nation-state. The US Department of Defense recently reported that 3 defense employees with some technical skills but without expert knowledge of bioweapons manufactured a simulant of *B anthracis* in less than a month for $1 million.[9] It is reported that Aum Shinrikyo, the cult responsible for the 1995 release of sarin nerve gas in a Tokyo subway station,[10] dispersed aerosols of anthrax and botulism throughout Tokyo at least 8 times.[11] Forensic analysis of the *B anthracis* strain used in these attacks revealed that this isolate most closely matched the Sterne 34F2 strain, which is used for animal vaccination programs and is not a significant risk to humans.[12] It is probable that the cult attacks produced no illnesses for this and other technical reasons. Al Quaeda also has sought to acquire bioweapons in its terrorist planning efforts although the extent to which they have been successful is not reported.[13]

In the anthrax attacks of 2001, *B anthracis* spores were sent in at least 5 letters to Florida, New York City, and Washington, DC. Twenty-two confirmed or suspected cases resulted. All of the identified letters were mailed from Trenton, NJ. The *B anthracis* spores in all the letters were identified as the Ames strain. The specific source (provenance) of *B anthracis* cultures used to create the spore-containing powder remains unknown at time of this publication.

It is now recognized that the original Ames strain of *B anthracis* did not come from a laboratory in Ames, Iowa, rather from a laboratory in College Station, Tex. Several distinct Ames strains have been recognized by investigating scientists, which are being compared with the Ames strain used in the attack. At least 1 of these comparison Ames strains was recovered from a goat that died in Texas in 1997.[14]

Sen Daschle's letter reportedly had 2 g of *B anthracis* containing powder; the quantity in the other envelopes has not been disclosed. The powder has been reported to contain between 100 billion to 1 trillion spores per gram[15] although no official analysis of the concentration of spores or the chemical composition of the powder has been published.

The anthrax attacks of 2001 used 1 of many possible methods of attack. The use of aerosol-delivery technologies inside buildings or over large outdoor areas is another method of attack that has been studied. In 1970, the World Health Organization[16] and in 1993 the Office of Technology Assessment[17] analyzed the potential scope of larger attacks. The 1979 Sverdlovsk accident provides data on the only known aerosol release of *B anthracis* spores resulting in an epidemic.[18]

An aerosol release of *B anthracis* would be odorless and invisible and would have the potential to travel many kilometers before dissipating.[16,19] Aerosol technologies for large-scale dissemination have been developed and tested

Figure 1. Gram Stain of Blood in Culture Media

Gram-positive bacilli in long chains (original magnification ×20). Enlargement shows typical "jointed bamboo-rod" appearance of *Bacillus anthracis* (original magnification ×100). Reprinted from Borio et al.[36]

by Iraq[7] and the former Soviet Union[8] Few details of those tests are available. The US military also conducted such trials over the Pacific Ocean in the 1960s. A US study near Johnston Atoll in the South Pacific reported a plane "sprayed a 32-mile long line of agent that traveled for more then 60 miles before it lost its infectiousness."[20]

In 1970, the World Health Organization estimated that 50 kg of *B anthracis* released over an urban population of 5 million would sicken 250000 and kill 100000.[16] A US Congressional Office of Technology assessment analysis from 1993 estimated that between 130000 and 3 million deaths would follow the release of 100 kg of *B anthracis*, a lethality matching that of a hydrogen bomb.[17]

EPIDEMIOLOGY OF ANTHRAX

Naturally occurring anthrax in humans is a disease acquired from contact with anthrax-infected animals or anthrax-contaminated animal products. The disease most commonly occurs in herbivores, which are infected after ingesting spores from the soil. Large anthrax epizootics in herbivores have been reported.[21] A published report states that anthrax killed 1 million sheep in Iran in 1945[22]; this number is supported by an unpublished Iranian governmental document.[23] Animal vaccination programs have reduced drastically the animal mortality from the disease.[24] However, *B anthracis* spores remain prevalent in soil samples throughout the world and cause anthrax cases among herbivores annually.[22,25,26]

Anthrax infection occurs in humans by 3 major routes: inhalational, cutaneous, and gastrointestinal. Naturally occurring inhalational anthrax is now rare. Eighteen cases of inhalational anthrax were reported in the United States from 1900 to 1976; none were identified or reported thereafter. Most of these cases occurred in special-risk groups, including goat hair mill or wool or tannery workers; 2 of them were laboratory associated.[27]

Cutaneous anthrax is the most common naturally occurring form, with an estimated 2000 cases reported annually worldwide.[26] The disease typically follows exposure to anthrax-infected animals. In the United States, 224 cases of cutaneous anthrax were reported between 1944 and 1994.[28] One case was reported in 2000.[29] The largest reported epidemic occurred in Zimbabwe between 1979 and 1985, when more than 10000 human cases of anthrax were reported, nearly all of them cutaneous.[30]

Although gastrointestinal anthrax is uncommon, outbreaks are continually reported in Africa and Asia[26,31,32] following ingestion of insufficiently cooked contaminated meat. Two distinct syndromes are oral-pharyngeal and abdominal.[31,33,34]Little information is available about the risks of direct contamination of food or water with *B anthracis* spores. Experimental efforts to infect primates by direct gastrointestinal instillation of *B anthracis* spores have not been successful.[35] Gastrointestinal infection could occur only after consumption of large numbers of vegetative cells, such as what might be found in raw or undercooked meat from an infected herbivore, but experimental data is lacking.

Inhalational anthrax is expected to account for most serious morbidity and most mortality following the use of *B anthracis* as an aerosolized biological weapon. Given the absence of naturally occurring cases of inhalational anthrax in the United States since 1976, the occurrence of a single case is now cause for alarm.

MICROBIOLOGY

B anthracis derives from the Greek word for coal, *anthrakis*, because of the black skin lesions it causes. *B anthracis* is an aerobic, gram-positive, spore-forming, nonmotile *Bacillus* species. The nonflagellated vegetative cell is large (1-8 µm long, 1-1.5 µm wide). Spore size is approximately 1 µm. Spores grow readily on all ordinary laboratory media at 37°C, with a "jointed bamboo-rod" cellular appearance (FIGURE 1) and a unique "curled-hair" colonial appearance. Experienced microbiologists should be able to identify this cellular and colonial morphology; however, few practicing microbiologists outside the veterinary community have seen *B anthracis* colonies beyond what they may have seen in published material.[37] *B anthracis* spores germinate when they enter an environment rich in amino acids, nucleosides, and glucose, such as that found in the blood or tissues of an animal or human host. The rapidly multiplying vegetative *B anthracis* bacilli, on the contrary, will only form spores after local nutrients are exhausted, such as when anthrax-infected body fluids are exposed to ambient air.[22] Vegetative bacteria have poor survival outside of an animal or human host; colony counts decline to being undetectable within 24 hours following inoculation into water.[22] This contrasts with the environmentally hardy properties of the *B anthracis* spore, which can survive for decades in ambient conditions.[37]

PATHOGENESIS AND CLINICAL MANIFESTATIONS

Inhalational Anthrax

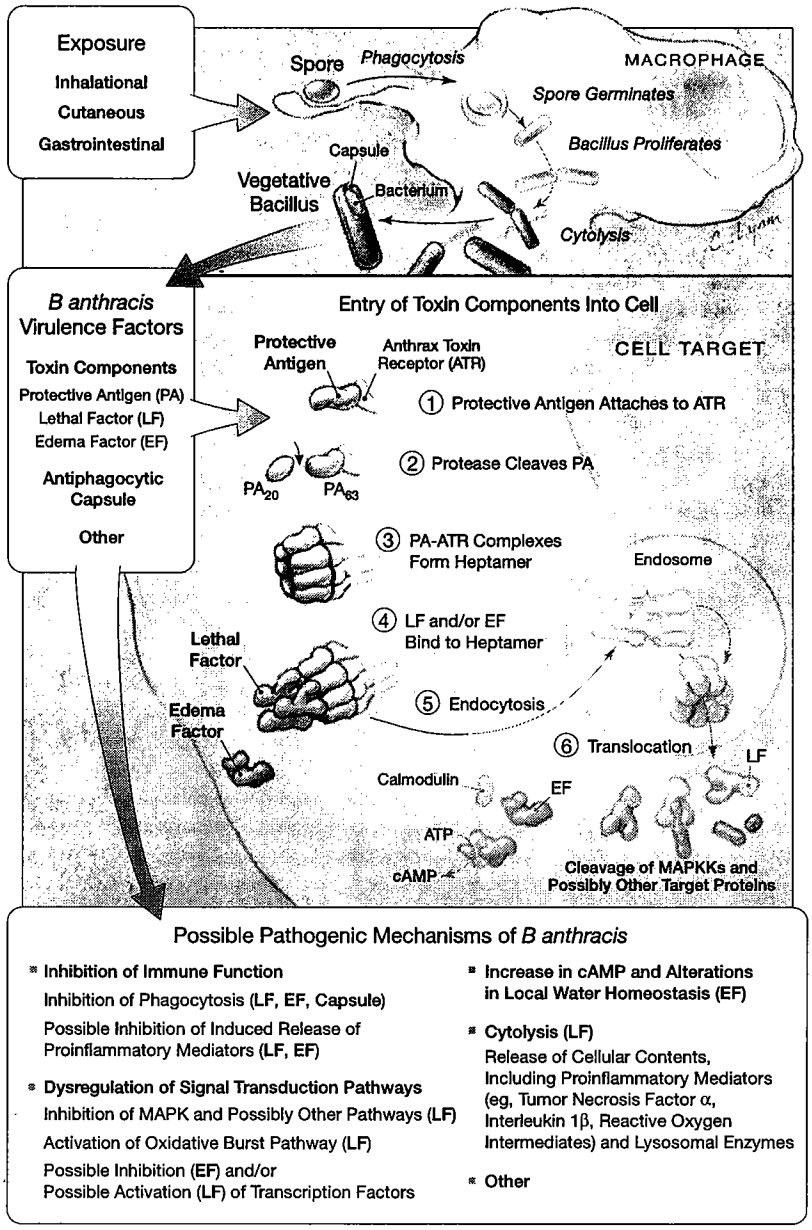
Inhalational anthrax follows deposition into alveolar spaces of spore-bearing particles in the 1- to 5-µm range.[38,39] Macrophages then ingest the spores, some of which are lysed and destroyed. Surviving spores are transported via lymphatics to mediastinal lymph nodes, where germination oc-

curs after a period of spore dormancy of variable and possibly extended duration.[35,40,41] The trigger(s) responsible for the transformation of *B anthracis* spores to vegetative cells is not fully understood.[42] In Sverdlovsk, cases occurred from 2 to 43 days after exposure.[18] In experimental infection of monkeys, fatal disease occurred up to 58 days[40] and 98 days[43] after exposure. Viable spores were demonstrated in the mediastinal lymph nodes of 1 monkey 100 days after exposure.[44]

Once germination occurs, clinical symptoms follow rapidly. Replicating *B anthracis* bacilli release toxins that lead to hemorrhage, edema, and necrosis.[32,45] In experimental animals, once toxin production has reached a critical threshold, death occurs even if sterility of the bloodstream is achieved with antibiotics.[27] Extrapolations from animal data suggest that the human LD_{50} (ie, dose sufficient to kill 50% of persons exposed to it) is 2500 to 55000 inhaled *B anthracis* spores.[46] The LD_{10} was as low as 100 spores in 1 series of monkeys.[43] Recently published extrapolations from primate data suggest that as few as 1 to 3 spores may be sufficient to cause infection.[47] The dose of spores that caused infection in any of the 11 patients with inhalational anthrax in 2001 could not be estimated although the 2 cases of fatal inhalational anthrax in New York City and Connecticut provoked speculation that the fatal dose, at least in some individuals, may be quite low.

A number of factors contribute to the pathogenesis of *B anthracis*, which makes 3 toxins—*protective antigen*, *lethal factor*, and *edema factor*—that combine to form 2 toxins: lethal toxin and edema toxin (FIGURE 2). The protective antigen allows the binding of lethal and edema factors to the affected cell membrane and facilitates their subsequent transport across the cell membrane. Edema toxin impairs neutrophil function in vivo and affects water homeostasis leading to edema, and lethal toxin causes release of tumor necrosis factor α and interleukin 1 β, factors that are believed to be linked to the sudden death in severe anthrax infection.[48] The molecular target of lethal and edema factors within the affected cell is not yet elucidated.[49] In addition to these virulence factors, *B anthracis* has a capsule that prevents phagocytosis. Full virulence requires the presence of both an antiphagocytic capsule and the

Figure 2. Pathogenesis of *Bacillus anthracis*



The major known virulence factors of *B anthracis* include the exotoxins edema toxin (PA and EF) and lethal toxin (PA and LF) and the antiphagocytic capsule. Although many exact molecular mechanisms involved in the pathogenicity of the anthrax toxins are uncertain, they appear to inhibit immune function, interrupt intracellular signaling pathways, and lyse cell targets causing massive release of proinflammatory mediators. ATP indicates adenosine triphosphate; cAMP, cyclic adenosine monophosphate; MAPKK, mitogen-activated protein kinase kinase; and MAPK, mitogen-activated protein kinase.

Table 1. Initial Symptoms, Physical Findings, and Test Results in Patients With Inhalational Anthrax Following US Anthrax Attacks in October and November 2001*

Symptoms (N = 10)	
Fever and chills	10
Sweats, often drenching	7
Fatigue, malaise, lethargy	10
Cough, minimal or nonproductive	9
Nausea or vomiting	9
Dyspnea	8
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	7
Tachycardia, heart rate >100/min	8
Hypotension, <110 mm Hg	1
Laboratory Results	
White blood cell count, median	9800 × 10^3/μL
Differential neutrophilia, >70%	7
Neutrophil band forms, >5%	4†
Elevated transaminases, SGOT or SPGT >40 U/L‡	9
Hypoxemia, alveolar-arterial oxygen gradient >30 mm Hg on room air oxygen saturation <94%	6
Metabolic acidosis	2
Elevated creatinine, >1.5 mg/dL (132.6 μmol/L)	1
Chest X-ray Film Findings	
Any abnormality	10
Mediastinal widening	7
Infiltrates or consolidation	7
Pleural effusion	8
Chest Computed Tomographic Findings§	
Any abnormality	8
Mediastinal lymphadenopathy, widening	7
Pleural effusion	8
Infiltrates or consolidation	6

*This table was adapted with permission from Jernigan, et al.[61]
†Five persons had laboratory results measuring neutrophil band forms.
‡SGOT indicates serum glutamic oxalacetic transaminase; SGPT, serum glutamic pyruvic transaminase.
§Eight persons had computed tomographic scan results.

3 toxin components.[37] An additional factor contributing to *B anthracis* pathogenesis is the high concentration of bacteria occurring in affected hosts.[49]

Inhalational anthrax reflects the nature of acquisition of the disease. The term *anthrax pneumonia* is misleading because typical bronchopneumonia does not occur. Postmortem pathological studies of patients from Sverdlovsk showed that all patients had hemorrhagic thoracic lymphadenitis, hemorrhagic mediastinitis, and pleural effusions. About half had hemorrhagic meningitis. None of these autopsies showed evidence of a bronchoalveolar pneumonic process although 11 of 42 patient autopsies had evidence of a focal, hemorrhagic, necrotizing pneumonic lesion analogous to the Ghon complex associated with tuberculosis.[50] These findings are consistent with other human case series and experimentally induced inhalational anthrax in animals.[40,51,52] A recent reanalysis of pathology specimens from 41 of the Sverdlovsk patients was notable primarily for the presence of necrotizing hemorrhagic mediastinitis; pleural effusions averaging 1700 mL in quantity; meningitis in 50%; arteritis and arterial rupture in many; and the lack of prominent pneumonitis. *B anthracis* was recovered in concentrations of up to 100 million colony-forming units per milliliter in blood and spinal fluid.[53]

In animal models, physiological sequelae of severe anthrax infection have included hypocalcemia, profound hypoglycemia, hyperkalemia, depression and paralysis of respiratory center, hypotension, anoxia, respiratory alkalosis, and terminal acidosis,[54,55] suggesting that besides the rapid administration of antibiotics, survival might improve with vigilant correction of electrolyte disturbances and acid-based imbalance, glucose infusion, and early mechanical ventilation and vasopressor administration.

Historical Data. Early diagnosis of inhalational anthrax is difficult and requires a high index of suspicion. Prior to the 2001 attacks, clinical information was limited to a series of 18 cases reported in the 20th century and the limited data from Sverdlovsk. The clinical presentation of inhalational anthrax had been described as a 2-stage illness. Patients reportedly first developed a spectrum of nonspecific symptoms, including fever, dyspnea, cough, headache, vomiting, chills, weakness, abdominal pain, and chest pain.[18,27] Signs of illness and laboratory studies were nonspecific. This stage of illness lasted from hours to a few days. In some patients, a brief period of apparent recovery followed. Other patients progressed directly to the second, fulminant stage of illness.[4,27,56]

This second stage was reported to have developed abruptly, with sudden fever, dyspnea, diaphoresis, and shock. Massive lymphadenopathy and expansion of the mediastinum led to stridor in some cases.[57,58] A chest radiograph most often showed a widened mediastinum consistent with lymphadenopathy.[57] Up to half of patients developed hemorrhagic meningitis with concomitant meningismus, delirium, and obtundation. In this second stage, cyanosis and hypotension progressed rapidly; death sometimes occurred within hours.[4,27,56]

In the 20th-century series of US cases, the mortality rate of occupationally acquired inhalational anthrax was 89%, but the majority of these cases occurred before the development of critical care units and, in most cases, before the advent of antibiotics.[27] At Sverdlovsk, it had been reported that 68 of the 79 patients with inhalational anthrax died.[18] However a separate report from a hospital physician recorded 358 ill with 45 dead; another recorded 48 deaths among 110 patients.[59] A recent analysis of available Sverdlovsk data suggests there may have been as many as 250 cases with 100 deaths.[60] Sverdlovsk patients who had onset of disease 30 or more days after release of organisms had a higher reported survival rate than those with earlier disease onset. Antibiotics, antianthrax globulin, corticosteroids, mechanical ventilation, and vaccine were used to treat some residents in the affected area after the accident, but how many were given vaccine and antibiotics is unknown, nor is it known which patients received these interventions or when. It is also uncertain if the *B anthracis* strain (or strains) to which patients was exposed were susceptible to the antibiotics used during the outbreak. However, a community-wide intervention about the 15th day after exposure did appear to diminish the projected attack rate.[60] In fatal cases, the

interval between onset of symptoms and death averaged 3 days. This is similar to the disease course and case fatality rate in untreated experimental monkeys, which have developed rapidly fatal disease even after a latency as long as 58 days.[40]

2001 Attacks Data. The anthrax attacks of 2001 resulted in 11 cases of inhalational anthrax, 5 of whom died. Symptoms, signs, and important laboratory data from these patients are listed in TABLE 1. Several clinical findings from the first 10 patients with inhalational anthrax deserve emphasis.[36,61-66] Malaise and fever were presenting symptoms in all 10 cases. Cough, nausea, and vomiting were also prominent. Drenching sweats, dyspnea, chest pain, and headache were also seen in a majority of patients. Fever and tachycardia were seen in the majority of patients at presentation, as were hypoxemia and elevations in transaminases.

Importantly, all 10 patients had abnormal chest x-ray film results: 7 had mediastinal widening; 7 had infiltrates; and 8 had pleural effusions. Chest computed tomographic (CT) scans showed abnormal results in all 8 patients who had this test: 7 had mediastinal widening; 6, infiltrates; 8, pleural effusions.

Data are insufficient to identify factors associated with survival although early recognition and initiation of treatment and use of more than 1 antibiotic have been suggested as possible factors.[61] For the 6 patients for whom such information is known, the median period from presumed time of exposure to the onset of symptoms was 4 days (range, 4-6 days). Patients sought care a median of 3.5 days after symptom onset. All 4 patients exhibiting signs of fulminant illness prior to antibiotic administration died.[61] Of note, the incubation period of the 2 fatal cases from New York City and Connecticut is not known.

Cutaneous Anthrax

Historically, cutaneous anthrax has been known to occur following the deposition of the organism into skin; previous cuts or abrasions made one especially susceptible to infection.[30,67] Areas of exposed skin, such as arms, hands, face, and neck, were the most frequently affected. In Sverdlovsk, cutaneous cases occurred only as late as 12 days after the original aerosol release; no reports of cutaneous cases appeared after prolonged latency.[18]

After the spore germinates in skin tissues, toxin production results in local edema. An initially pruritic macule or papule enlarges into a round ulcer by the second day. Subsequently, 1- to 3-mm vesicles may appear that discharge clear or serosanguinous fluid containing numerous organisms on Gram stain. As shown in FIGURE 3, development of a painless, depressed, black eschar follows, often associated with extensive local edema. The anthrax eschar dries, loosens, and falls off in the next 1 to 2 weeks. Lymphangitis and painful lymphadenopathy can occur with associated systemic symptoms. Differential diagnosis of eschars includes tularemia, scrub typhus, rickettsial spotted fevers, rat bite fever, and ecthyma gangrenosum.[68] Noninfectious causes of eschars include arachnid bites[63] and vasculitides. Although antibiotic therapy does not appear to change the course of eschar formation and healing, it does decrease the likelihood of systemic disease. Without antibiotic therapy, the mortality rate has been reported to be as high as 20%; with appropriate antibiotic treatment, death due to cutaneous anthrax has been reported to be rare.[4]

Following the anthrax attacks of 2001, there have been 11 confirmed or probable cases of cutaneous anthrax. One case report of cutaneous anthrax resulting from these attacks has been published (Figure 3).[63] This child had no reported evidence of prior visible cuts, abrasions, or lesions at the site of the cutaneous lesion that developed. The mean incubation period for cutaneous anthrax cases diagnosed in 2001 was 5 days, with a range of 1 to 10 days, based on estimated dates of exposure to *B anthracis*–contaminated letters. Cutaneous lesions occurred on the forearm, neck, chest, and fingers.[69]

Figure 3. Lesion of Cutaneous Anthrax Associated With Microangiopathic Hemolytic Anemia and Coagulopathy in a 7-Month-Old Infant

By hospital day 12, a 2-cm black eschar was present in the center of the cutaneous lesion. Reprinted from Freedman et al.[63]

The only published case report of cutaneous anthrax from the attacks of 2001 is notable for the difficulty in recognition of the disease in a previously healthy 7-month-old, the rapid progression to severe systemic illness despite hospitalization, and clinical manifestations that included microangiopathic hemolytic anemia with renal involvement, coagulopathy, and hyponatremia.[63] Fortunately, this child recovered, and none of the cutaneous cases of anthrax diagnosed after the 2001 attacks were fatal.

Gastrointestinal Anthrax

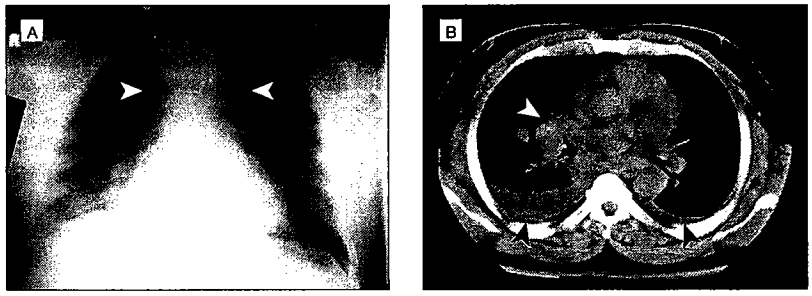
Some think gastrointestinal anthrax occurs after deposition and germination of spores in the upper or lower gastrointestinal tract. However, considering the rapid transit time in the gastrointestinal tract, it seems more likely that many such cases must result from the ingestion of large numbers of vegetative bacilli from poorly cooked infected meat rather than from spores. In any event, the oral-pharyngeal form of disease results in an oral or esophageal ulcer and leads to the development of regional lymphadenopathy, edema, and sepsis.[31,33] Disease in the lower gastrointestinal tract manifests as primary intestinal lesions occurring predominantly in the terminal ileum or cecum,[50] presenting initially with nausea, vomiting, and malaise and progressing rapidly to bloody diarrhea, acute abdomen, or sep-

Table 2. Diagnosis of Inhalational Anthrax Infection*

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 (eg, those in the 2001attacks: postal workers, members of the news media, and politicians and their staff)
Diagnostic tests	Chest radiograph: widened mediastinum, infiltrates, pleural effusion Chest computed tomographic scan: hyperdense hilar and mediastinal nodes, mediastinal edema, infiltrates, pleural effusion Thoracentesis: hemorrhagic pleural effusions
Microbiology	Peripheral blood smear: gram-positive bacilli on blood smear 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 1 for list of febrile illness symptoms and signs.
†Most rapid assays are available only at laboratories participating in the Laboratory Response Network.

Figure 4. Chest Radiograph and Computed Tomography (CT) Image



A, Portable chest radiograph of 56-year-old man with inhalational anthrax depicts a widened mediastinum (white arrowheads), bilateral hilar fullness, a right pleural effusion, and bilateral perihilar air-space disease. B, Noncontrast spiral CT scan depicts an enlarged and hyperdense right hilar lymph node (white arrowhead), bilateral pleural effusions (black arrowheads), and edema of the mediastinal fat. Reprinted from Mayer et al.[66]

sis. Massive ascites has occurred in some cases of gastrointestinal anthrax.[34] Advanced infection may appear similar to the sepsis syndrome occurring in either inhalational or cutaneous anthrax.[4] Some authors suggest that aggressive medical intervention as would be recommended for inhalational anthrax may reduce mortality. Given the difficulty of early diagnosis of gastrointestinal anthrax, however, mortality may be high.[4] Postmortem examinations in Sverdlovsk showed gastrointestinal submucosal lesions in 39 of 42 patients,[50] but all of these patients were also found to have definitive pathologic evidence of an inhalational source of infection. There were no gastrointestinal cases of anthrax diagnosed in either the Sverdlovsk series or following the anthrax attacks of 2001.

DIAGNOSIS

TABLE 2 lists the epidemiology, diagnostic tests, microbiology, and pathology for a diagnosis of inhalational anthrax infection. Given the rarity of anthrax infection, the first clinical or laboratory suspicion of an anthrax illness must lead to early initiation of antibiotic treatment pending confirmed diagnosis and should provoke immediate notification of the local or state public health department, local hospital epidemiologist, and local or state public health laboratory. In the United States, a Laboratory Response Network (LRN) has been established through a collaboration of the Association of Public Health Laboratories and the CDC (details are available at: http://www.bt.cdc.gov/LabIssues/index.asp). Currently 81 clinical laboratories in the LRN can diagnose bioweapons pathogens. Several preliminary diagnostic tests for *B anthracis* can be performed in hospital laboratories using routine procedures. *B anthracis* is a gram-positive, nonhemolytic, encapsulated, penicillin-sensitive, spore-forming bacillus. Confirmatory tests such as immuno-histochemical staining, gamma phage, and polymerase chain reaction assays must still be performed by special reference laboratories in the LRN.

The determination of individual patient exposure to *B anthracis* on the basis of environmental testing is complex due to the uncertain specificity and sensitivity of rapid field tests and the difficulty of assessing individual risks of exposure. A patient (or patients) seeking medical treatment for symptoms of inhalational anthrax will likely be the first evidence of a clandestine release of *B anthracis* as a biological weapon. The appearance of even a single previously healthy patient who becomes acutely ill with nonspecific febrile illness and symptoms and signs consistent with those listed in Table 1 and whose condition rapidly deteriorates should receive prompt consideration for a diagnosis of anthrax infection. The recognition of cutaneous cases of anthrax may also be the first evidence of an anthrax attack.[70]

The likely presence of abnormal findings on either chest x-ray film or chest CT scan is diagnostically important. Although anthrax does not cause a classic bronchopneumonia pathologically, it can cause widened mediastinum, massive pleural effusions, air bronchograms, necrotizing pneumonic lesions, and/or consolidation, as has been noted above.[36,55,56,61,64-66] The result can be hypoxemia and chest imaging abnormalities that may or may not be clinically distinguishable from pneumonia. In the anthrax attacks of 2001, each of the first 10 patients had abnormal chest x-ray film results and each of 8 patients for whom CT scans were obtained had abnormal results. These included widened mediastinum on chest radiograph and effusions on chest CT scan (FIGURE 4). Such findings in a previ-

ously healthy patient with evidence of overwhelming febrile illness or sepsis would be highly suggestive of advanced inhalational anthrax.

The bacterial burden may be so great in advanced inhalational anthrax infection that bacilli are visible on Gram stain of peripheral blood, as was seen following the 2001 attacks. The most useful microbiologic test is the standard blood culture, which should show growth in 6 to 24 hours. Each of the 8 patients who had blood cultures obtained prior to initiation of antibiotics had positive blood cultures.[61] However, blood cultures appear to be sterilized after even 1 or 2 doses of antibiotics, underscoring the importance of obtaining cultures prior to initiation of antibiotic therapy (J. Gerberding, oral communication, March 7, 2002). If the laboratory has been alerted to the possibility of anthrax, biochemical testing and review of colonial morphology could provide a preliminary diagnosis 12 to 24 hours after inoculation of the cultures. Definitive diagnosis could be promptly confirmed by an LRN laboratory. However, if the clinical laboratory has not been alerted to the possibility of anthrax, *B anthracis* may not be correctly identified. Routine procedures customarily identify a *Bacillus* species in a blood culture approximately 24 hours after growth, but some laboratories do not further identify *Bacillus* species unless specifically requested. This is because the isolation of *Bacillus* species most often represents growth of the common contaminant *Bacillus cereus*.[71] Given the possibility of future anthrax attacks, it is recommended that routine clinical laboratory procedures be modified, so *B anthracis* is specifically excluded after identification of a *Bacillus* species bacteremia unless there are compelling reasons not to do so. If it cannot be excluded then the isolate should be transferred to an LRN laboratory.

Sputum culture and Gram stain are unlikely to be diagnostic of inhalational anthrax, given the frequent lack of a pneumonic process.[37] Gram stain of sputum was reported positive in only 1 case of inhalational anthrax in the 2001 series. If cutaneous anthrax is suspected, a Gram stain and culture of vesicular fluid should be obtained. If the Gram stain is negative or the patient is taking antibiotics already, punch biopsy should be performed, and specimens sent to a laboratory with the ability to perform immunohistochemical staining or polymerase chain reaction assays.[69,70] Blood cultures should be obtained and antibiotics should be initiated pending confirmation of the diagnosis of inhalational or cutaneous anthrax.

Nasal swabs were obtained in some persons believed to be at risk of inhalational anthrax following the anthrax attacks of 2001. Although a study has shown the presence of *B anthracis* spores in nares of some monkeys following experimental exposure to *B anthracis* spores for some time after exposure,[72] the predictive value of the nasal swab test for diagnosing inhalational anthrax in humans is unknown and untested. It is not known how quickly antibiotics make spore recovery on nasal swab tests impossible. One patient who died from inhalational anthrax had a negative nasal swab.[36] Thus, the CDC advised in the fall of 2001 that the nasal swab should not be used as a clinical diagnostic test. If obtained for an epidemiological purpose, nasal swab results should not be used to rule out infection in a patient. Persons who have positive nasal swab results for *B anthracis* should receive a course of postexposure antibiotic prophylaxis since a positive swab would indicate that the individual had been exposed to aerosolized *B anthracis*.

Antibodies to the protective antigen (PA) of *B anthracis*, termed *anti-PA IgG*, have been shown to confer immunity in animal models following anthrax vaccination.[73,74] Anti-PA IgG serologies have been obtained from several of those involved in the 2001 anthrax attacks, but the results of these assays are not yet published. Given the lack of data in humans and the expected period required to develop an anti-PA IgG response, this test should not be used as a diagnostic test for anthrax infection in the acutely ill patient but may be useful for epidemiologic purposes.

Postmortem findings are especially important following an unexplained death. Thoracic hemorrhagic necrotizing lymphadenitis and hemorrhagic necrotizing mediastinitis in a previously healthy adult are essentially pathognomonic of inhalational anthrax.[50,58] Hemorrhagic meningitis should also raise strong suspicion of anthrax infection.[32,50,58,75] However, given the rarity of anthrax, a pathologist might not identify these findings as caused by anthrax unless previously alerted to this possibility.

If only a few patients present contemporaneously, the clinical similarity of early inhalational anthrax infection to other acute febrile respiratory infections may delay initial diagnosis although probably not for long. The severity of the illness and its rapid progression, coupled with unusual radiological findings, possible identification of *B anthracis* in blood or cerebrospinal fluid, and the unique pathologic findings should serve as an early alarm. The index case of inhalational anthrax in the 2001 attacks was identified because of an alert clinician who suspected the disease on the basis of large gram-positive bacilli in cerebrospinal fluid in a patient with a compatible clinical illness, and as a result of the subsequent analysis by laboratory staff who had recently undergone bioterrorism preparedness training.[65]

VACCINATION

The US anthrax vaccine, named anthrax vaccine adsorbed (AVA), is an inactivated cell-free product, licensed in 1970, and produced by Bioport Corp, Lansing, Mich. The vaccine is licensed to be given in a 6-dose series. In 1997, it was mandated that all US military active- and reserve-duty personnel receive it.[76] The vaccine is made from the cell-free filtrate of a nonencapsulated attenuated strain of *B anthracis*.[77] The principal antigen responsible for inducing immunity is the PA.[26,32] In the rabbit model, the quantity of antibody to PA has been corre-

lated with the level of protection against experimental anthrax infection.[78]

Preexposure vaccination with AVA has been shown to be efficacious against experimental challenge in a number of animal studies.[78-80] A similar vaccine was shown in a placebo-controlled human trial to be efficacious against cutaneous anthrax.[81] The efficacy of postexposure vaccination with AVA has been studied in monkeys.[40] Among 60 monkeys exposed to 8 LD_{50} of *B anthracis* spores at baseline, 9 of 10 control animals died, and 8 of 10 animals treated with vaccine alone died. None of 29 animals died while receiving doxycycline, ciprofloxacin, or penicillin for 30 days; 5 developed anthrax once treatment ceased. The remaining 24 all died when rechallenged. The 9 receiving doxycycline for 30 days plus vaccine at baseline and day 14 after exposure did not die from anthrax infection even after being rechallenged.[40]

The safety of the anthrax vaccine has been the subject of much study. A recent report reviewed the results of surveillance for adverse events in the Department of Defense program of 1998-2000.[82] At the time of that report, 425 976 service members had received 1 620 793 doses of AVA. There were higher rates of local reactions to the vaccine in women than men, but "no patterns of unexpected local or systemic adverse events" were identified.[82] A recent review of safety of AVA anthrax vaccination in employees of the United States Army Medical Research Institute of Infectious Diseases (USAMRIID) over the past 25 years reported that 1583 persons had received 10 722 doses of AVA.[83] One percent of these inoculations (101/10 722) were associated with 1 or more systemic events (defined as headache, malaise, myalgia, fever, nausea, vomiting, dizziness, chills, diarrhea, hives, anorexia, arthralgias, diaphoresis, blurred vision, generalized itching, or sore throat). The most frequently reported systemic adverse event was headache (0.4% of doses). Local or injection site reactions were reported in 3.6%. No long-term sequelae were reported in this series.

The Institute of Medicine (IOM) recently published a report on the safety and efficacy of AVA,[84] which concluded that AVA is effective against inhalational anthrax and concluded that if given with appropriate antibiotic therapy, it may help prevent the development of disease after exposure. The IOM committee also concluded that AVA was acceptably safe. Committee recommendations for new research include studies to describe the relationship between immunity and quantitative antibody levels; further studies to test the efficacy of AVA in combination with antibiotics in preventing inhalational anthrax infection; studies of alternative routes and schedules of administration of AVA; and continued monitoring of reported adverse events following vaccination. The committee did not evaluate the production process used by the manufacturer.

A recently published report[85] analyzed a cohort of 4092 women at 2 military bases from January 1999 to March 2000. The study compared pregnancy rates and adverse birth outcomes between groups of women who had been vaccinated with women who had not been vaccinated and the study found that anthrax vaccination with AVA had no effect on pregnancy or adverse birth outcomes.

A human live attenuated vaccine has been produced and used in countries of the former Soviet Union.[86] In the Western world, live attenuated vaccines have been considered unsuitable for use in humans because of safety concerns.[86]

Current vaccine supplies are limited, and the US production capacity remains modest. Bioport is the single US manufacturing facility for the licensed anthrax vaccine. Production has only recently resumed after a halt required the company to alter production methods so that it conformed to the US Food and Drug Administration (FDA) Good Manufacturing Practice standard. Bioport has a contract to produce 4.6 million doses of vaccine for the US Department of Defense that cannot be met until at least 2003 (D. A. Henderson, oral communication, February 2002).

The use of AVA was not initiated immediately in persons believed to have been exposed to *B anthracis* during the 2001 anthrax attacks for a variety of reasons, including the unavailability of vaccine supplies. Subsequently, near the end of the 60-day period of antibiotic prophylaxis, persons deemed by investigating public health authorities to have been at high risk for exposure were offered postexposure AVA series (3 inoculations at 2-week intervals, given on days 1, 14, and 28) as an adjunct to prolonged postexposure antibiotic prophylaxis. This group of affected persons was also offered the alternatives of continuing a prolonged course of antibiotics or of receiving close medical follow-up without vaccination or additional antibiotics.[87] This vaccine is licensed for use in the preexposure setting, but because it had not been licensed for use in the postexposure context, it was given under investigational new drug procedures.

The working group continues to conclude that vaccination of exposed persons following a biological attack in conjunction with antibiotic administration for 60 days following exposure provide optimal protection to those exposed. However, until ample reserve stockpiles of vaccine are available, reliance must be placed on antibiotic administration. To date, there have been no reported cases of anthrax infection among those exposed in the 2001 anthrax attacks who took prophylactic antibiotics, even in those persons not complying with the complete 60-day course of therapy.

Preexposure vaccination of some persons deemed to be in high-risk groups should be considered when substantial supplies of vaccine become available. A fast-track program to develop recombinant anthrax vaccine is now under way. This may lead to more plentiful vaccine stocks as well as a product that requires fewer inoculations.[88] Studies to evaluate intramuscular vs subcutaneous routes of administration and less frequent dosing of AVA are also under way. (J. Hughes, oral communication, February 2002.)

THERAPY

Recommendations for antibiotic and vaccine use in the setting of an aerosolized *B anthracis* attack are conditioned by a very small series of cases in humans, a limited number of studies in experimental animals, and the possible necessity of treating large numbers of casualties. A number of possible therapeutic strategies have yet to be explored experimentally or to be submitted for approval to the FDA. For these reasons, the working group offers consensus recommendations based on the best available evidence. The recommendations do not necessarily represent uses currently approved by the FDA or an official position on the part of any of the federal agencies whose scientists participated in these discussions and will need to be revised as further relevant information becomes available.

Given the rapid course of symptomatic inhalational anthrax, early antibiotic administration is essential. A delay of antibiotic treatment for patients with anthrax infection may substantially lessen chances for survival.[89,90] Given the difficulty in achieving rapid microbiologic diagnosis of anthrax, all persons in high-risk groups who develop fever or evidence of systemic disease should start receiving therapy for possible anthrax infection as soon as possible while awaiting the results of laboratory studies.

There are no controlled clinical studies for the treatment of inhalational anthrax in humans. Thus, antibiotic regimens commonly recommended for empirical treatment of sepsis have not been studied. In fact, natural strains of *B anthracis* are resistant to many of the antibiotics used in empirical regimens for sepsis treatment, such as those regimens based on the extended-spectrum cephalosporins.[91,92] Most naturally occurring *B anthracis* strains are sensitive to penicillin, which historically has been the preferred anthrax therapy. Doxycycline is the preferred option among the tetracycline class because of its proven efficacy in monkey studies[56] and its ease of administration. Other members of this class of antibiotics are suitable alternatives. Although treatment of anthrax infection with ciprofloxacin has not been studied in humans, animal models suggest excellent efficacy.[40,56,93] In vitro data suggest that other fluoroquinolone antibiotics would have equivalent efficacy although no animal data using a primate model of inhalational anthrax are available.[92] Penicillin, doxycycline, and ciprofloxacin are approved by the FDA for the treatment of inhalational anthrax infection,[56,89,90,94] and other antibiotics are under study. Other drugs that are usually active in vitro include clindamycin, rifampin, imipenem, aminoglycosides, chloramphenicol, vancomycin, cefazolin, tetracycline, linezolid, and the macrolides.

Reports have been published of a *B anthracis* strain that was engineered to resist the tetracycline and penicillin classes of antibiotics.[95] Balancing considerations of treatment efficacy with concerns regarding resistance, the working group in 1999 recommended that ciprofloxacin or other fluoroquinolone therapy be initiated in adults with presumed inhalational anthrax infection.[3] It was advised that antibiotic resistance to penicillin- and tetracycline-class antibiotics should be assumed following a terrorist attack until laboratory testing demonstrated otherwise. Once the antibiotic susceptibility of the *B anthracis* strain of the index case had been determined, the most widely available, efficacious, and least toxic antibiotic was recommended for patients requiring treatment and persons requiring postexposure prophylaxis. Since the 1999 consensus statement publication, a study[96] demonstrated the development of in vitro resistance of an isolate of the Sterne strain of *B anthracis* to ofloxacin (a fluoroquinolone closely related to ciprofloxacin) following subculturing and multiple cell passage.

Following the anthrax attacks of 2001, the CDC[97] offered guidelines advocating use of 2 or 3 antibiotics in combination in persons with inhalational anthrax based on susceptibility testing with epidemic strains. Limited early information following the attacks suggested that persons with inhalational anthrax treated intravenously with 2 or more antibiotics active against *B anthracis* had a greater chance of survival.[61] Given the limited number of persons who developed inhalational anthrax, the paucity of comparative data, and other uncertainties, it remains unclear whether the use of 2 or more antibiotics confers a survival advantage, but combination therapy is a reasonable therapeutic approach in the face of life-threatening illness. Another factor supporting the initiation of combination antibiotic therapy for treatment of inhalational anthrax is the possibility that an engineered strain of *B anthracis* resistant to 1 or more antibiotics might be used in a future attack. Some infectious disease experts have also advocated the use of clindamycin, citing the theoretical benefit of diminishing bacterial toxin production, a strategy used in some toxin-mediated streptococcal infections.[98] There are no data as yet that bear specifically on this question. Central nervous system penetration is another consideration; doxycycline or fluoroquinolone may not reach therapeutic levels in the cerebrospinal fluid. Thus, in the aftermath of the anthrax attacks, some infectious disease authorities recommended preferential use of ciprofloxacin over doxycycline, plus augmentation with chloramphenicol, rifampin, or penicillin when meningitis is established or suspected.

The *B anthracis* isolate recovered from patients with inhalational anthrax was susceptible to all of the antibiotics expected in a naturally occurring strain.[97] This isolate showed an inducible β-lactamase in addition to a constitutive cephalosporinase. The importance of the inducible β-lactamase is unknown; these strains are highly susceptible to penicillin in vitro, with minimum inhibiting concentrations less than .06 μg/mL. A theoretical concern is that this sensitivity could be overcome with a large bacterial burden. For this reason, the CDC advised that patients with inhalational anthrax should not be treated with penicillin or amoxicillin as monotherapy and that ciprofloxacin or doxycycline be considered the standards based on in vitro activ-

Table 3. Recommended Therapy for Inhalational Anthrax Infection in the Contained Casualty Setting[a,b]

Category	Initial IV Therapy [c,d]	Duration
Adults	Ciprofloxacin, 400 mg every 12 h or Doxycycline, 100 mg every 12 h[f] and 1 or 2 Additional antimicrobials[d]	IV treatment initially[e] before switching to oral antimicrobial therapy when clinically appropriate: Ciprofloxacin 500 mg twice daily or Doxycycline 100 mg twice daily Continue oral and IV treatment for 60 d[j]
Children	Ciprofloxacin, 10-15 mg/kg every 12 h[g,h] or Doxycycline[f,i] for those aged >8 y and weight >45 kg: 100 mg every 12 h; >8 y and weight ≤45 kg: 2.2 mg/kg every 12 h; ≤8 y: 2.2 mg/kg every 12 h and 1 or 2 Additional antimicrobials[d]	IV treatment initially[e] before switching to oral antimicrobial therapy when clinically appropriate: Ciprofloxacin 10-15 mg/kg every 12 h[h] or Doxycycline[i] for those aged >8 y and weight >45 kg: 100 mg twice daily >8 y and weight ≤45 kg: 2.2 mg/kg twice daily ≤8 y: 2.2 mg/kg 2 daily Continue oral and IV treatment for 60 d[j]
Pregnant women[k]	Same for nonpregnant adults	IV treatment initially before switching to oral antimicrobial therapy when clinically appropriate[b]; oral therapy regimens are the same for nonpregnant adults
Immunocompromised persons	Same for nonimmunocompromised adults and children	

[a]This table is adapted with permission from *Morbidity and Mortality Weekly Report*.[97] For gastrointestinal and oropharyngeal anthrax, use regimens recommended for inhalational anthrax.
[b]Ciprofloxacin or doxycycline should be considered an essential part of first-line therapy for inhalational anthrax.
[c]Steroids may be considered as an adjunct therapy for patients with severe edema and for meningitis based on experience with bacterial meningitis of other etiologies.
[d]Other agents with in vitro activity include rifampin, vancomycin, penicillin, ampicillin, chloramphenicol, imipenem, clindamycin, and clarithromycin. Because of concerns of constitutive and inducible β-lactamases in *Bacillus anthracis*, penicillin and ampicillin should not be used alone. Consultation with an infectious disease specialist is advised.
[e]Initial therapy may be altered based on clinical course of the patient; 1 or 2 antimicrobial agents may be adequate as the patient improves.
[f]If meningitis is suspected, doxycycline may be less optimal because of poor central nervous system penetration.
[g]If intravenous (IV) ciprofloxacin is not available, oral ciprofloxacin may be acceptable because it is rapidly and well absorbed from the gastrointestinal tract with no substantial loss by first-pass metabolism. Maximum serum concentrations are attained 1 to 2 hours after oral dosing but may not be achieved if vomiting or ileus is present.
[h]In children, ciprofloxacin dosage should not exceed 1 g/d.
[i]The American Academy of Pediatrics recommends treatment of young children with tetracyclines for serious infections (ie, Rocky Mountain spotted fever).
[j]Because of the potential persistence of spores after an aerosol exposure, antimicrobial therapy should be continued for 60 days.
[k]Although tetracyclines are not recommended during pregnancy, their use may be indicated for life-threatening illness. Adverse effects on developing teeth and bones of fetus are dose related; therefore, doxycycline might be used for a short time (7-14 days) before 6 months of gestation. The high death rate from the infection outweighs the risk posed by the antimicrobial agent.

ity, efficacy in the monkey model, and FDA approval.

In the contained casualty setting (a situation in which a modest number of patients require therapy), the working group supports these new CDC antibiotic recommendations[97] (TABLE 3) and advises the use of intravenous antibiotic administration. These recommendations will need to be revised as new data become available.

If the number of persons requiring therapy following a bioterrorist attack with anthrax is sufficiently high (ie, a mass casualty setting), the working group recognizes that combination drug therapy and intravenous therapy may no longer be possible for reasons of logistics and/or exhaustion of equipment and antibiotic supplies. In such circumstances, oral therapy may be the only feasible option (TABLE 4). The threshold number of cases at which combination and parenteral therapy become impossible depends on a variety of factors, including local and regional health care resources.

In experimental animals, antibiotic therapy during anthrax infection has prevented development of an immune response.[40,95] This suggests that even if the antibiotic-treated patient survives anthrax infection, the risk of recurring disease may persist for a prolonged period because of the possibility of delayed germination of spores. Therefore, we recommend that antibiotic therapy be continued for at least 60 days postexposure, with oral therapy replacing intravenous therapy when the patient is clinically stable enough to take oral medication.

Cutaneous anthrax historically has been treated with oral penicillin. For reasons articulated above, the working group recommends that oral fluoroquinolone or doxycycline in the adult dosage schedules described in TABLE 5 be used to treat cutaneous anthrax until antibiotic susceptibility is proven. Amoxicillin is a suitable alternative if there are contraindications to fluoroquinolones or doxycycline such as pregnancy, lactating mother, age younger than 18 years, or antibiotic intolerance. For cutaneous lesions associated with extensive edema or for cutaneous lesions of the head and neck, clinical management should be conservative as per inhalational anthrax treatment guidelines in Table 3. Although previous guidelines have suggested treating cutaneous anthrax for 7 to 10 days,[32,71] the working group recommends treatment for 60 days postexposure in the setting of bioterrorism, given the presumed concomitant inhalational exposure to the primary aerosol. Treatment of cutaneous anthrax generally prevents progression to systemic disease although it does not prevent the formation and evolution of the eschar. Topical therapy is not useful.[4]

In addition to penicillin, the fluoroquinolones and the tetracycline class of antibiotics, other antibiotics effective in vitro include chloramphenicol, clindamycin, extended-spectrum penicillins, macrolides, aminoglycosides, vancomycin, cefazolin, and other first-generation cephalosporins.[91,99] The efficacy of these antibiotics has not yet been tested

Table 4. Recommended Therapy for Inhalational Anthrax Infection in the Mass Casualty Setting or for Postexposure Prophylaxis*

Category	Initial Oral Therapy†	Alternative Therapy if Strain Is Proved Susceptible	Duration After Exposure, d
Adults	Ciprofloxacin, 500 mg orally every 12 h	Doxycycline, 100 mg orally every 12 h‡ Amoxicillin, 500 mg orally every 8 h§	60
Children	Ciprofloxacin, 20-30 mg/kg per d orally taken in 2 daily doses, not to exceed 1 g/d‖	Weight ≥20 kg: amoxicillin, 500 mg orally every 8 h§ Weight <20 kg: amoxicillin, 40 mg/kg taken orally in 3 doses every 8 h§	60
Pregnant women¶	Ciprofloxacin, 500 mg orally every 12 h	Amoxicillin, 500 mg orally every 8 h§	60
Immunosuppressed persons	Same as for nonimmunosuppressed adults and children		

*Some of these recommendations are based on animal studies or in vitro studies and are not approved by the US Food and Drug Administration.
†In vitro studies suggest ofloxacin (400 mg orally every 12 hours, or levofloxacin, 500 mg orally every 24 hours) could be substituted for ciprofloxacin.
‡In vitro studies suggest that 500 mg of tetracycline orally every 6 hours could be substituted for doxycycline. In addition, 400 mg of gatifloxicin or monifloxacin, both fluoroquinolones with mechanisms of action consistent with ciprofloxacin, taken orally daily could be substituted.
§According to the Centers for Disease Control and Prevention recommendations, amoxicillin is suitable for postexposure prophylaxis only after 10 to 14 days of fluoroquinolones or doxycycline treatment and then only if there are contraindications to these 2 classes of medications (eg, pregnancy, lactating mother, age <18 years, or intolerance of other antibiotics).
‖Doxycycline could also be used if antibiotic susceptibility testing, exhaustion of drug supplies, adverse reactions preclude use of ciprofloxacin. For children heavier than 45 kg, adult dosage should be used. For children lighter than 45 kg, 2.5 mg/kg of doxycycline orally every 12 hours should be used.
¶See "Management of Pregnant Population" for details.

in humans or animal studies. The working group recommends the use of these antibiotics only to augment fluoroquinolones or tetracyclines or if the preferred drugs are contraindicated, not available, or inactive in vitro in susceptibility testing. *B anthracis* strains exhibit natural resistance to sulfamethoxazole, trimethoprim, cefuroxime, cefotaxime sodium, aztreonam, and ceftazidime.[91,92,99] Therefore, these antibiotics should not be used.

Pleural effusions were present in all of the first 10 patients with inhalational anthrax in 2001. Seven needed drainage of their pleural effusions, 3 required chest tubes.[69] Future patients with inhalational anthrax should be expected to have pleural effusions that will likely require drainage.

Table 5. Recommended Therapy for Cutaneous Anthrax Infection Associated With a Bioterrorism Attack*

Category	Initial Oral Therapy†	Duration, d‡
Adults	Ciprofloxacin, 500 mg twice daily† or Doxycycline, 100 mg twice daily†	60
Children§	Ciprofloxacin, 10-15 mg/kg every 12 h (not to exceed 1 g/d)† or Doxycycline for those aged§ >8 y and weight >45 kg: 100 mg every 12 h >8 y and weight ≤45 kg: 2.2 mg/kg every 12 h ≤8 y: 2.2 mg/kg every 12 h	60
Pregnant women‖	Ciprofloxacin, 500 mg twice daily or Doxycycline, 100 mg twice daily	60
Immunocompromised persons	Same for nonimmunocompromised adults and children	

*This table is adapted with permission from the *Morbidity and Mortality Weekly Report*.[98] Cutaneous anthrax with signs of systemic involvement, extensive edema, or lesions on the head or neck require intravenous therapy, and a multidrug approach is recommended (Table 3).
†Ciprofloxacin or doxycycline should be considered first-line therapy. Amoxicillin can be substituted if a patient cannot take a fluoroquinolone or tetracycline class drug. Adults are recommended to take 500 mg of amoxicillin orally 3 times a day. For children, 80 mg/kg of amoxicillin to be divided into 3 doses in 8-hour increments is an option for completion of therapy after clinical improvement. Oral amoxicillin dose is based on the need to achieve appropriate minimum inhibitory concentration levels.
‡Previous guidelines have suggested treating cutaneous anthrax for 7 to 10 days, but 60 days is recommended for bioterrorism attacks, given the likelihood of exposure to aerosolized *Bacillus anthracis*.
§The American Academy of Pediatrics recommends treatment of young children with tetracyclines for serious infections (eg, Rocky Mountain spotted fever).
‖Although tetracyclines or ciprofloxacin is not recommended during pregnancy, their use may be indicated for life-threatening illness. Adverse effects on developing teeth and bones of a fetus are dose related; therefore, doxycycline might be used for a short time (7-14 days) before 6 months of gestation.

Postexposure Prophylaxis

Guidelines for which populations would require postexposure prophylaxis to prevent inhalational anthrax following the release of a *B anthracis* aerosol as a biological weapon will need to be developed by public health officials depending on epidemiological circumstances. These decisions would require estimates of the timing, location, and conditions of the exposure.[100] Ongoing case monitoring would be needed to define the high-risk groups, to direct follow-up, and to guide the addition or deletion of groups requiring postexposure prophylaxis.

There are no FDA-approved postexposure antibiotic regimens following exposure to a *B anthracis* aerosol. Therefore, for postexposure prophylaxis, we recommend the same antibiotic regimen as that recommended for treatment of mass casualties; prophylaxis should be continued for at least 60 days postexposure (Table 4). Preliminary analysis of US postal workers who were advised to take 60 days of antibiotic prophylaxis for exposure to *B anthracis* spores following the anthrax attacks of 2001 showed that 2% sought medical attention because of concern of possible severe allergic reactions related to the medications, but no persons required hospitalization because of an adverse drug reaction.[101] Many persons did not begin or complete their recommended antibiotic course for a variety of reasons, including gastrointestinal tract intolerance, underscoring the need for careful medical follow-up during the period of prophylaxis.[101] In addition, given the uncertainties regarding how many weeks or months spores may remain latent in the period following discontinu-

ation of postexposure prophylaxis, persons should be instructed to report immediately flulike symptoms or febrile illness to their physicians who should then evaluate the need to initiate treatment for possible inhalational anthrax. As noted above, postexposure vaccination is recommended as an adjunct to postexposure antibiotic prophylaxis if vaccine is available.

Management of Special Groups

Consensus recommendations for special groups as set forth herein reflect the clinical and evidence-based judgments of the working group and at this time do not necessarily correspond with FDA-approved use, indications, or labeling.

Children. It has been recommended that ciprofloxacin and other fluoroquinolones should not be used in children younger than 16 to 18 years because of a link to permanent arthropathy in adolescent animals and transient arthropathy in a small number of children.[94] However, balancing these risks against the risks of anthrax infections caused by an engineered antibiotic-resistant strain, the working group recommends that ciprofloxacin be used as a component of combination therapy for children with inhalational anthrax. For postexposure prophylaxis or following a mass casualty attack, monotherapy with fluoroquinolones is recommended by the working group[97] (Table 4).

The American Academy of Pediatrics has recommended that doxycycline not be used in children younger than 9 years because the drug has resulted in retarded skeletal growth in infants and discolored teeth in infants and children.[94] However, the serious risk of infection following an anthrax attack supports the consensus recommendation that doxycycline, instead of ciprofloxacin, be used in children if antibiotic susceptibility testing, exhaustion of drug supplies, or adverse reactions preclude use of ciprofloxacin.

According to CDC recommendations, amoxicillin was suitable for treatment or postexposure prophylaxis of possible anthrax infection following the anthrax attacks of 2001 only after 14 to 21 days of fluoroquinolone or doxycycline administration because of the concern about the presence of a β-lactamase.[102] In a contained casualty setting, the working group recommends that children with inhalational anthrax receive intravenous antibiotics (Table 3). In a mass casualty setting and as postexposure prophylaxis, the working group recommends that children receive oral antibiotics (Table 4).

The US anthrax vaccine is licensed for use only in persons aged 18 to 65 years because studies to date have been conducted exclusively in this group.[77] No data exist for children, but based on experience with other inactivated vaccines, it is likely that the vaccine would be safe and effective.

Pregnant Women. Fluoroquinolones are not generally recommended during pregnancy because of their known association with arthropathy in adolescent animals and small numbers of children. Animal studies have discovered no evidence of teratogenicity related to ciprofloxacin, but no controlled studies of ciprofloxacin in pregnant women have been conducted. Balancing these possible risks against the concerns of anthrax due to engineered antibiotic-resistant strains, the working group recommends that pregnant women receive ciprofloxacin as part of combination therapy for treatment of inhalational anthrax (Table 3). We also recommend that pregnant women receive fluoroquinolones in the usual adult dosages for postexposure prophylaxis or monotherapy treatment in the mass casualty setting (Table 4). The tetracycline class of antibiotics has been associated with both toxic effects in the liver in pregnant women and fetal toxic effects, including retarded skeletal growth.[94]

Balancing the risks of anthrax infection with those associated with doxycycline use in pregnancy, the working group recommends that doxycycline can be used as an alternative to ciprofloxacin as part of combination therapy in pregnant women for treatment of inhalational anthrax. For postexposure prophylaxis or in mass casualty settings, doxycycline can also be used as an alternate to ciprofloxacin in pregnant women. If doxycycline is used in pregnant women, periodic liver function testing should be performed. No adequate controlled trials of penicillin or amoxicillin administration during pregnancy exist. However, the CDC recommends penicillin for the treatment of syphilis during pregnancy and amoxicillin as a treatment alternative for chlamydial infections during pregnancy.[94] According to CDC recommendations, amoxicillin is suitable postexposure prophylaxis or treatment of inhalational anthrax in pregnancy only after 14 to 21 days of fluoroquinolone or doxycycline administration.[102]

Ciprofloxacin (and other fluoroquinolones), penicillin, and doxycycline (and other tetracyclines) are each excreted in breast milk. Therefore, a breastfeeding woman should be treated or given prophylaxis with the same antibiotic as her infant based on what is most safe and effective for the infant.

Immunosuppressed Persons. The antibiotic treatment or postexposure prophylaxis for anthrax among those who are immunosuppressed has not been studied in human or animal models of anthrax infection. Therefore, the working group consensus recommends administering antibiotics in the same regimens recommended for immunocompetent adults and children.

INFECTION CONTROL

There are no data to suggest that patient-to-patient transmission of anthrax occurs and no person-to-person transmission occurred following the anthrax attacks of 2001.[18,67] Standard barrier isolation precautions are recommended for hospitalized patients with all forms of anthrax infection, but the use of high-efficiency particulate air filter masks or other measures for airborne protection are not indicated.[103] There is no need to immunize or provide prophylaxis to patient contacts (eg, household contacts, friends, coworkers) unless a determination is made that they, like the patient, were exposed to the aerosol or surface contamination at the time of the attack.

In addition to immediate notification of the hospital epidemiologist and state health department, the local hospital microbiology laboratories should be notified at the first indication of anthrax so that safe specimen processing under biosafety level 2 conditions can be undertaken as is customary in most hospital laboratories.[56] A number of disinfectants used for standard hospital infection control, such as hypochlorite, are effective in cleaning environmental surfaces contaminated with infected bodily fluids.[22,103]

Proper burial or cremation of humans and animals who have died because of anthrax infection is important in preventing further transmission of the disease. Serious consideration should be given to cremation. Embalming of bodies could be associated with special risks.[103] If autopsies are performed, all related instruments and materials should be autoclaved or incinerated.[103] The CDC can provide advice on postmortem procedures in anthrax cases.

DECONTAMINATION

Recommendations for decontamination in the event of an intentional aerosolization of *B anthracis* spores are based on evidence concerning aerosolization techniques, predicted spore survival, environmental exposures at Sverdlovsk and among goat hair mill workers, and environmental data collected following the anthrax attacks of 2001. The greatest risk to humans exposed to an aerosol of *B anthracis* spores occurs when spores first are made airborne, the period called *primary aerosolization*. The aerobiological factors that affect how long spores remain airborne include the size of the dispersed particles and their hydrostatic properties.[100] Technologically sophisticated dispersal methods, such as aerosol release from military aircraft of large quantities of *B anthracis* spores manipulated for use in a weapon, are potentially capable of exposing high numbers of victims over large areas. Recent research by Canadian investigators has demonstrated that even "low-tech" delivery systems, such as the opening of envelopes containing powdered spores in indoor environments, can rapidly deliver high concentrations of spores to persons in the vicinity.[104] In some circumstances, indoor airflows, activity patterns, and heating, ventilation, and air conditioning systems may transport spores to others parts of the building.

Following the period of primary aerosolization, *B anthracis* spores may settle on surfaces, possibly in high concentrations. The risk that *B anthracis* spores might pose by a process of secondary aerosolization (resuspension of spores into the air) is uncertain and is likely dependent on many variables, including the quantity of spores on a surface; the physical characteristics of the powder used in the attack; the type of surface; the nature of the human or mechanical activity that occurs in the affected area and host factors.

A variety of rapid assay kits are available to detect *B anthracis* spores on environmental surfaces. None of these kits has been independently evaluated or endorsed by the CDC, FDA, or Environmental Protection Agency, and their functional characteristics are not known.[105] Many false-positive results occurred following the anthrax attacks of 2001. Thus, any result using currently available rapid assay kits does not necessarily signify the presence of *B anthracis*; it is simply an indication that further testing is required by a certified microbiology laboratory. Similarly, the sensitivity and false-negative rate of disease kits are unknown.

At Sverdlovsk, no new cases of inhalational anthrax developed beyond 43 days after the presumed date of release. None were documented during the months and years afterward, despite only limited decontamination and vaccination of 47 000 of the city's 1 million inhabitants.[59] Some have questioned whether any of the cases with onset of disease beyond 7 days after release might have represented illness following *secondary aerosolization* from the ground or other surfaces. It is impossible to state with certainty that secondary aerosolizations did not occur in Sverdlovsk, but it appears unlikely. The epidemic curve reported is typical for a common-source epidemic,[3,60] and it is possible to account for virtually all confirmed cases having occurred within the area of the plume on the day of the accident. Moreover, if secondary aerosolization had been important, new cases would have likely continued well beyond the observed 43 days.

Although persons working with animal hair or hides are known to be at increased risk of developing inhalational or cutaneous anthrax, surprisingly few occupational exposures in the United States have resulted in disease. During the first half of the 20th century, a significant number of goat hair mill workers were heavily exposed to aerosolized spores. Mandatory vaccination became a requirement for working in goat hair mills only in the 1960s. Prior to that, many unvaccinated person-years of high-risk exposure had occurred, but only 13 cases of inhalational anthrax were reported.[27,54] One study of environmental exposure, conducted at a Pennsylvania goat hair mill, showed that workers inhaled up to 510 *B anthracis* particles of at least 5 μm in diameter per person per 8-hour shift.[54] These concentrations of spores were constantly present in the environment during the time of this study, but no cases of inhalational anthrax occurred.

Field studies using *B anthracis*–like surrogates have been carried out by US Army scientists seeking to determine the risk of secondary aerosolization. One study concluded that there was no significant threat to personnel in areas contaminated by 1 million spores per square meter either from traffic on asphalt-paved roads or from a runway used by helicopters or jet aircraft.[106] A separate study showed that in areas of ground contaminated with 20 million *Bacillus subtilis* spores per square meter, a soldier exercising actively for a 3-hour period would inhale between 1000 and 15 000 spores.[107]

Much has been written about the technical difficulty of decontaminating an environment contaminated with *B anthracis* spores. A classic case is the experience at Gruinard Island, Scotland. During World War II, British mili-

tary undertook explosives testing with *B anthracis* spores. Spores persisted and remained viable for 36 years following the conclusion of testing. Decontamination of the island occurred in stages, beginning in 1979 and ending in 1987 when the island was finally declared fully decontaminated. The total cost is unpublished, but materials required included 280 tons of formaldehyde and 2000 tons of seawater.[108]

Following the anthrax attacks of 2001, substantial efforts were undertaken to decontaminate environmental surfaces exposed to *B anthracis* spores. Sections of the Hart Senate office building in Washington, DC, contaminated from opening a letter laden with *B anthracis*, were reopened only after months of decontamination procedures at an estimated cost of $23 million.[109] Decontamination efforts at many other buildings affected by the anthrax attacks of 2001 have not yet been completed.

Prior to the anthrax attacks of 2001, there had been no recognition or scientific study showing that *B anthracis* spores of "weapons grade" quality would be capable of leaking out the edges of envelopes or through the pores of envelopes, with resulting risk to the health of those handling or processing those letters. When it became clear that the Florida case of anthrax was likely caused by a letter contaminated with *B anthracis*, assessment of postal workers who might have handled or processed that letter showed no illness.[69] When the anthrax cases were discovered, each was linked to a letter that had been opened. At first, there was no evidence of illness among persons handling or processing unopened mail. This fact influenced the judgment that persons handling or processing unopened *B anthracis* letters were not at risk. These judgments changed when illness was discovered in persons who had handled or processed unopened letters in Washington, DC. Much remains unknown about the risks to persons handling or processing unopened letters containing *B anthracis* spores. It is not well understood how the mechanical systems of mail processing in a specific building would affect the risk of disease acquisition in a worker handling a contaminated letter in that facility. It is still uncertain what the minimum dose of spores would be to cause infection in humans although it may theoretically be as few as 1 to 3 spores.[47] The mechanisms of disease acquisition in the 2 fatal inhalational anthrax cases in New York City and in Connecticut remain unknown although it is speculated that disease in these 2 cases followed the inhalation of small numbers of spores present in some manner in "cross-contaminated" mail.

The discovery of *B anthracis* spores in a contaminated letter in the office of Sen Daschle in the Hart office building led the Environmental Protection Agency to conduct tests in this office to assess the risk of secondary aerosolization of spores. Prior to the initiation of decontamination efforts in the Hart building, 17 blood agar gel plates were placed around the office and normal activity in the office was simulated. Sixteen of the 17 plates yielded *B anthracis*. Although this experiment did not allow conclusions about the specific risk of persons developing anthrax infection in this context, it did demonstrate that routine activity in an environment contaminated with *B anthracis* spores could cause significant spore resuspension.[110]

Given the above considerations, if an environmental surface is proved to be contaminated with *B anthracis* spores in the immediate area of a spill or close proximity to the point of release of *B anthracis* biological weapons, the working group believes that decontamination of that area would likely decrease the risk of acquiring anthrax by secondary aerosolization. However, as has been demonstrated in environmental decontamination efforts following the anthrax attacks of 2001, decontamination of buildings or parts of buildings following an anthrax attack is technically difficult. For these reasons, the working group would advise that decisions about methods for decontamination following an anthrax attack follow full expert analysis of the contaminated environment and the anthrax weapon used in the attack and be made in consultation with experts on environmental remediation. If vaccines were available, postexposure vaccination might be a useful intervention for those working in highly contaminated areas, because it could further lower the risk of anthrax infection.

In the setting of an announced alleged *B anthracis* release, such as the series of anthrax hoaxes occurring in many areas of the United States in 1998[111] and following the anthrax attacks of 2001, any person coming in direct physical contact with a substance alleged to be containing *B anthracis* should thoroughly wash the exposed skin and articles of clothing with soap and water.[112] In addition, any person in direct physical contact with the alleged substance should receive postexposure antibiotic prophylaxis until the substance is proved not to be *B anthracis*. The anthrax attacks of 2001 and new research[104] have shown that opening letters containing substantial quantities of *B anthracis* spores in certain conditions can confer risk of disease to persons at some distance from the location of where the letter was opened. For this reason, when a letter is suspected of containing (or proved to contain) *B anthracis*, immediate consultation with local and state public health authorities and the CDC for advised medical management is warranted.

Additional Research

Development of a recombinant anthrax vaccine that would be more easily manufactured and would require fewer doses should remain a top priority. Rapid diagnostic assays that could reliably identify early anthrax infection and quickly distinguish from other flulike or febrile illnesses would become critical in the event of a large-scale attack. Simple animal models for use in comparing antibiotic prophylactic and treatment strategies are also needed. Operational research to better characterize risks posed by environmental contamination of spores,

particularly inside buildings, and research on approaches to minimize risk in indoor environments by means of air filters or methods for environmental cleaning following a release are also needed. A better understanding of the genetics and pathogenesis of anthrax, as well as mechanisms of virulence and immunity, will be of importance in the prospective evaluation of new therapeutic and diagnostic strategies. Novel therapeutic approaches with promise, such as the administration of competitors against the protective antigen complex,[113] should also be tested in animals and developed where evidence supports this. Recent developments such as the publishing of the *B anthracis* genome and the discovery of the crystalline structure of the lethal and edema factor could hold great clinical hope for both the prevention and treatment of anthrax infection.[114]

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Disclaimers: In many cases, the indication and dosages and other information are not consistent with current approved labeling by the US Food and Drug Administration (FDA). The recommendations on the use of drugs and vaccine for uses not approved by the FDA do not represent the official views of the FDA or of any of the federal agencies whose scientists participated in these discussions. Unlabeled uses of the products recommended are noted in the sections of this article in which these products are discussed. Where unlabeled uses are indicated, information used as the basis for the recommendation is discussed. The views, opinions, assertions, and findings contained herein are those of the authors and should not be construed as official US Department of Health and Human Services, US Department of Defense, or US Department of Army positions, policies, or decisions unless so designated by other documentation.
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Botulinum Toxin as a Biological Weapon
Medical and Public Health Management

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Objective The Working Group on Civilian Biodefense has developed consensus-based recommendations for measures to be taken by medical and public health professionals if botulinum toxin is used as a biological weapon against a civilian population.

Participants The working group included 23 representatives from academic, government, and private institutions with expertise in public health, emergency management, and clinical medicine.

Evidence The primary authors (S.S.A. and R.S.) searched OLDMEDLINE and MEDLINE (1960–March 1999) and their professional collections for literature concerning use of botulinum toxin as a bioweapon. The literature was reviewed, and opinions were sought from the working group and other experts on diagnosis and management of botulism. Additional MEDLINE searches were conducted through April 2000 during the review and revisions of the consensus statement.

Consensus Process The first draft of the working group's consensus statement was a synthesis of information obtained in the formal evidence-gathering process. The working group convened to review the first draft in May 1999. Working group members reviewed subsequent drafts and suggested additional revisions. The final statement incorporates all relevant evidence obtained in the literature search in conjunction with final consensus recommendations supported by all working group members.

Conclusions An aerosolized or foodborne botulinum toxin weapon would cause acute symmetric, descending flaccid paralysis with prominent bulbar palsies such as diplopia, dysarthria, dysphonia, and dysphagia that would typically present 12 to 72 hours after exposure. Effective response to a deliberate release of botulinum toxin will depend on timely clinical diagnosis, case reporting, and epidemiological investigation. Persons potentially exposed to botulinum toxin should be closely observed, and those with signs of botulism require prompt treatment with antitoxin and supportive care that may include assisted ventilation for weeks or months. Treatment with antitoxin should not be delayed for microbiological testing.

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THIS IS THE FOURTH ARTICLE IN A series entitled *Medical and Public Health Management Following the Use of a Biological Weapon: Consensus Statements of The Working Group on Civilian Biodefense*.[1-3] This article is the only one in the series to feature a biological toxin rather than a replicating agent. Botulinum toxin poses a major bioweapon threat because of its extreme potency and lethality; its ease of production, transport, and misuse; and the need for prolonged intensive care among affected persons.[4,5] An outbreak of botulism constitutes a medical emergency that requires prompt provision of botulinum antitoxin and, often, mechanical ventilation, and it constitutes a public health emergency that requires immediate intervention to prevent additional cases. Timely recognition of a botulism outbreak begins with an astute clinician who quickly notifies public health officials.

Botulinum toxin is the most poisonous substance known.[6,7] A single gram of crystalline toxin, evenly dispersed and inhaled, would kill more than 1 million people, although technical factors would make such dissemination difficult. The basis of the phenomenal potency of botulinum toxin is enzymatic; the toxin is a zinc proteinase that cleaves 1 or more of the fusion proteins by which neuronal vesicles release acetylcholine into the neuromuscular junction.[8]

It is regrettable that botulinum toxin still needs to be considered as a bioweapon at the historic moment when it has become the first biological toxin to become licensed for treatment of human disease. In the United States, botulinum toxin is currently licensed for treatment of cervical torticollis, strabismus, and blepharospasm associ-

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ated with dystonia. It is also used "off label" for a variety of more prevalent conditions that include migraine headache, chronic low back pain, stroke, traumatic brain injury, cerebral palsy, achalasia, and various dystonias.[9-13]

CONSENSUS METHODS

The working group included 23 representatives from academic, government, and private institutions with expertise in public health, emergency management, and clinical medicine. The 2 primary authors (S.S.A. and R.S.) conducted a literature search on use of botulinum toxin as a bioweapon. The OLDMEDLINE and MEDLINE databases were queried for all articles published between January 1960 and March 1999 that contained words referring to biological warfare (*bioterrorism*, *biowarfare*, *terrorism*, *war*, *warfare*, and *weapon*) in combination with terms related to *Clostridium botulinum* (*bacillus*, *botulin*, *botulinal*, *botulinum*, *botulinus*, *botulism*, *clostridia*, *clostridial*, and *Clostridium*). The articles identified in the databases were fully reviewed. In addition, published and unpublished articles, books, monographs, and special reports in the primary authors' collections were reviewed. Additional MEDLINE searches were conducted through April 2000 during the review and revisions of the consensus statement.

The first draft of the consensus statement was a synthesis of information obtained in the formal evidence-gathering process. Members of the working group provided written and oral comments about the first draft at their meeting in May 1999. Working group members then reviewed subsequent drafts and suggested additional revisions. The final statement incorporates all relevant evidence obtained in the literature search in conjunction with final consensus recommendations supported by all working group members.

The assessment and recommendations provided herein represent the best professional judgment of the working group based on currently available data and expertise. These conclusions and recommendations should be regularly reassessed as new information becomes available.

HISTORY OF CURRENT THREAT

Terrorists have already attempted to use botulinum toxin as a bioweapon. Aerosols were dispersed at multiple sites in downtown Tokyo, Japan, and at US military installations in Japan on at least 3 occasions between 1990 and 1995 by the Japanese cult Aum Shinrikyō. These attacks failed, apparently because of faulty microbiological technique, deficient aerosol-generating equipment, or internal sabotage. The perpetrators obtained their *C botulinum* from soil that they had collected in northern Japan.[14,15]

Development and use of botulinum toxin as a possible bioweapon began at least 60 years ago.[16,17] The head of the Japanese biological warfare group (Unit 731) admitted to feeding cultures of *C botulinum* to prisoners with lethal effect during that country's occupation of Manchuria, which began in the 1930s.[18] The US biological weapons program first produced botulinum toxin during World War II. Because of concerns that Germany had weaponized botulinum toxin, more than 1 million doses of botulinum toxoid vaccine were made for Allied troops preparing to invade Normandy on D-Day.[19,20] The US biological weapons program was ended in 1969-1970 by executive orders of Richard M. Nixon, then president. Research pertaining to biowarfare use of botulinum toxin took place in other countries as well.[21]

Although the 1972 Biological and Toxin Weapons Convention prohibited offensive research and production of biological weapons, signatories Iraq and the Soviet Union subsequently produced botulinum toxin for use as a weapon.[22,23] Botulinum toxin was 1 of several agents tested at the Soviet site Aralsk-7 on Vozrozhdeniye Island in the Aral Sea.[23,24] A former senior scientist of the Russian civilian bioweapons program reported that the Soviets had attempted splicing the botulinum toxin gene from *C botulinum* into other bacteria.[25] With the economic difficulties in Russia after the demise of the Soviet Union, some of the thousands of scientists formerly employed by its bioweapons program have been recruited by nations attempting to develop biological weapons.[25,26] Four of the countries listed by the US government as "state sponsors of terrorism" (Iran, Iraq, North Korea, and Syria)[27] have developed, or are believed to be developing, botulinum toxin as a weapon.[28,29]

After the 1991 Persian Gulf War, Iraq admitted to the United Nations inspection team to having produced 19 000 L of concentrated botulinum toxin, of which approximately 10 000 L were loaded into military weapons.[22,30] These 19 000 L of concentrated toxin are not fully accounted for and constitute approximately 3 times the amount needed to kill the entire current human population by inhalation. In 1990, Iraq deployed specially designed missiles with a 600-km range; 13 of these were filled with botulinum toxin, 10 with aflatoxin, and 2 with anthrax spores. Iraq also deployed special 400-lb (180-kg) bombs for immediate use; 100 bombs contained botulinum toxin, 50 contained anthrax spores, and 7 contained aflatoxin.[22,30] It is noteworthy that Iraq chose to weaponize more botulinum toxin than any other of its known biological agents.

Some contemporary analyses discount the potential of botulinum toxin as a bioweapon because of constraints in concentrating and stabilizing the toxin for aerosol dissemination. However, these analyses pertain to military uses of botulinum toxin to immobilize an opponent (William C. Patrick, unpublished data, 1998). In contrast, deliberate release of botulinum toxin in a civilian population would be able to cause substantial disruption and distress. For example, it is estimated that a point-source aerosol release of botulinum toxin could incapacitate or kill 10% of persons within 0.5 km downwind (William C. Patrick, unpublished data, 1998). In addition, terrorist use of botulinum toxin might be manifested as deliberate contamination of food. Misuse of toxin in this manner could produce either a large

botulism outbreak from a single meal or episodic, widely separated outbreaks.[31] In the United States, the Centers for Disease Control and Prevention (CDC) maintains a well-established surveillance system for human botulism based on clinician reporting that would promptly detect such events.[32]

MICROBIOLOGY AND VIRULENCE FACTORS

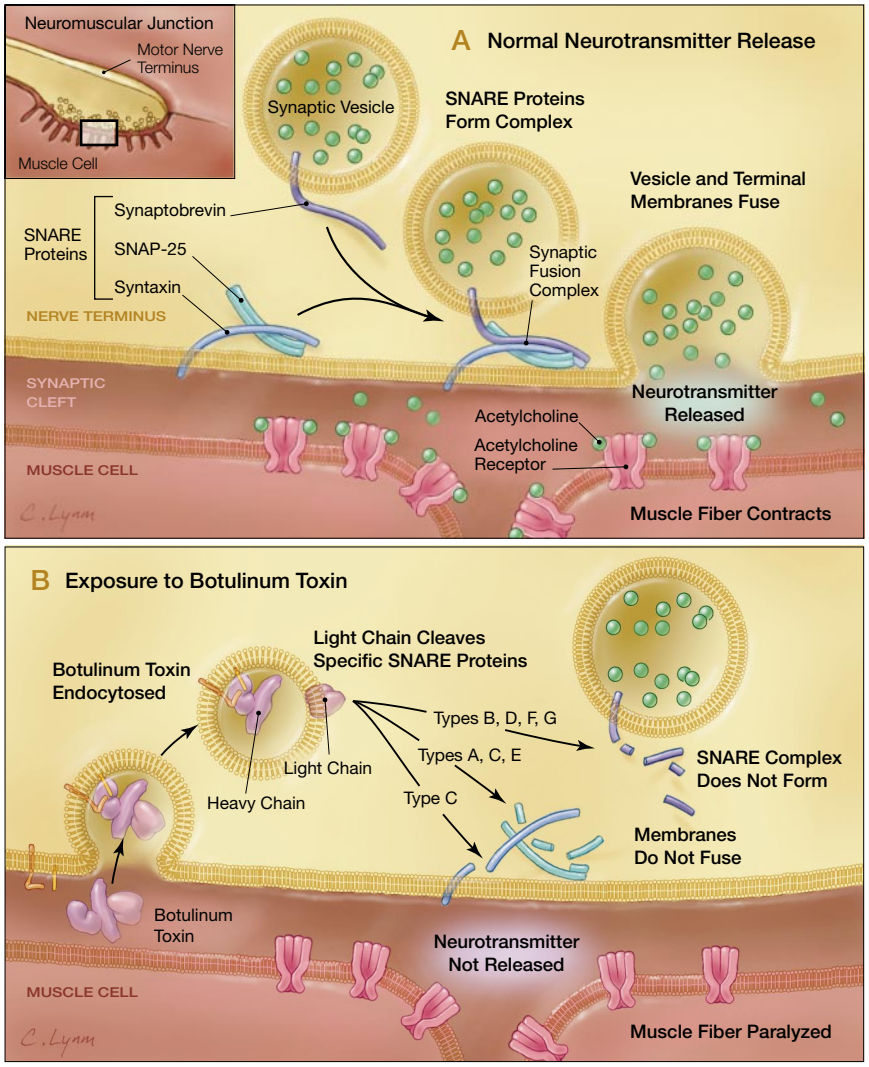
Clostridium botulinum is a spore-forming, obligate anaerobe whose natural habitat is soil, from which it can be isolated without undue difficulty. The species *C botulinum* consists of 4 genetically diverse groups that would not otherwise be designated as a single species except for their common characteristic of producing botulinum toxin.[33,34] Botulinum toxin exists in 7 distinct antigenic types that have been assigned the letters A through G. The toxin types are defined by their absence of cross-neutralization (eg, anti-A antitoxin does not neutralize toxin types B-G). The toxin types also serve as convenient epidemiological markers. In addition to *C botulinum*, unique strains of *Clostridium baratii* and *Clostridium butyricum* have the capacity to produce botulinum toxin.[35-37] Botulinum toxin is a simple dichain polypeptide that consists of a 100-kd "heavy" chain joined by a single disulfide bond to a 50-kd "light" chain; its 3-dimensional structure was recently resolved to 3.3 A.[38] The toxin's light chain is a Zn^{++}-containing endopeptidase that blocks acetylcholine-containing vesicles from fusing with the terminal membrane of the motor neuron, resulting in flaccid muscle paralysis (FIGURE 1).[8]

The lethal dose of botulinum toxin for humans is not known but can be estimated from primate studies. By extrapolation, the lethal amounts of crystalline type A toxin for a 70-kg human would be approximately 0.09-0.15 µg intravenously or intramuscularly, 0.70-0.90 µg inhalationally, and 70 µg orally.[10,39-41] Therapeutic botulinum toxin represents an impractical bioterrorist weapon because a vial of the type A preparation currently licensed in the United States contains only about 0.3% of the estimated human lethal inhalational dose and 0.005% of the estimated lethal oral dose.

PATHOGENESIS AND CLINICAL MANIFESTATIONS

Three forms of naturally occurring human botulism exist: foodborne, wound, and intestinal (infant and adult). Fewer than 200 cases of all forms of botulism are reported annually in the United States.[42] All forms of botulism result from absorption of botulinum toxin into the circulation from either a mucosal surface (gut, lung) or a wound. Botulinum toxin does not penetrate intact skin. Wound botulism and intestinal

Figure 1. Mechanism of Action of Botulinum Toxin

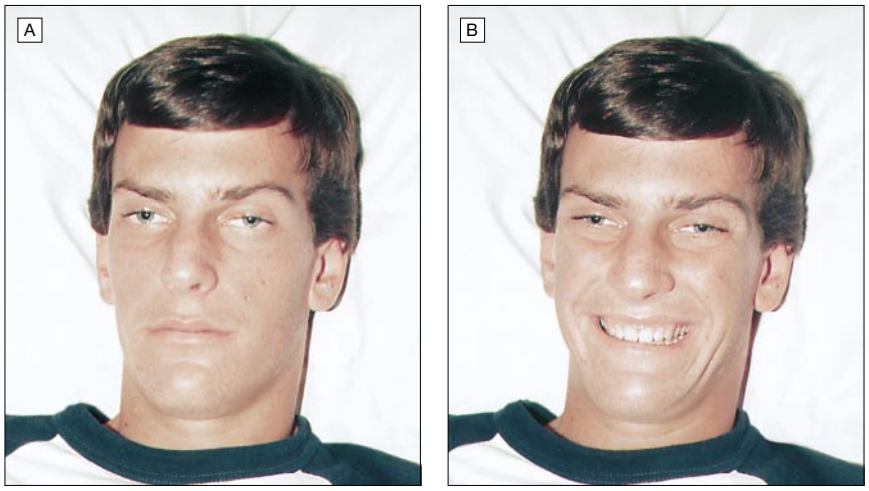


A, Release of acetylcholine at the neuromuscular junction is mediated by the assembly of a synaptic fusion complex that allows the membrane of the synaptic vesicle containing acetylcholine to fuse with the neuronal cell membrane. The synaptic fusion complex is a set of SNARE proteins, which include synaptobrevin, SNAP-25, and syntaxin. After membrane fusion, acetylcholine is released into the synaptic cleft and then bound by receptors on the muscle cell.

B, Botulinum toxin binds to the neuronal cell membrane at the nerve terminus and enters the neuron by endocytosis. The light chain of botulinum toxin cleaves specific sites on the SNARE proteins, preventing complete assembly of the synaptic fusion complex and thereby blocking acetylcholine release. Botulinum toxins types B, D, F, and G cleave synaptobrevin; types A, C, and E cleave SNAP-25; and type C cleaves syntaxin. Without acetylcholine release, the muscle is unable to contract.

SNARE indicates soluble NSF-attachment protein receptor; NSF, N-ethylmaleimide-sensitive fusion protein; and SNAP-25, synaptosomal-associated protein of 25 kd.

Figure 2. Seventeen-Year-Old Patient With Mild Botulism



A, Patient at rest. Note bilateral mild ptosis, dilated pupils, disconjugate gaze, and symmetric facial muscles. B, Patient was requested to perform his maximum smile. Note absent periorbital smile creases, ptosis, disconjugate gaze, dilated pupils, and minimally asymmetric smile. As an indication of the extreme potency of botulinum toxin, the patient had 40×10^{-12}g/mL of type A botulinum toxin in his serum (ie, 1.25 mouse units/mL) when these photographs were taken.

Table 1. Symptoms and Signs of Foodborne Botulism, Types A and B*

	Cases, %
Symptoms	
Fatigue	77
Dizziness	51
Double vision	91
Blurred vision	65
Dysphagia	96
Dry mouth	93
Dysarthria	84
Sore throat	54
Dyspnea	60
Constipation	73
Nausea	64
Vomiting	59
Abdominal cramps	42
Diarrhea	19
Arm weakness	73
Leg weakness	69
Paresthesia	14
Signs	
Alert mental status	90
Ptosis	73
Gaze paralysis	65
Pupils dilated or fixed	44
Nystagmus	22
Facial palsy	63
Diminished gag reflex	65
Tongue weakness	58
Arm weakness	75
Leg weakness	69
Hyporeflexia or areflexia	40
Ataxia	17

*Data are from outbreaks of botulism reported in the United States in 1973-1974. The number of patients with available data varied from 35 to 55. Adapted from Hughes et al[44] with permission.

botulism are infectious diseases that result from production of botulinum toxin by *C botulinum* either in devitalized (ie, anaerobic) tissue[43] or in the intestinal lumen,[37] respectively. Neither would result from bioterrorist use of botulinum toxin.

A fourth, man-made form that results from aerosolized botulinum toxin is inhalational botulism. This mode of transmission has been demonstrated experimentally in primates,[39] has been attempted by bioterrorists,[14,15] and has been the intended outcome of at least 1 country's specially designed missiles and artillery shells.[22,30] Inhalational botulism has occurred accidentally in humans. A brief report from West Germany in 1962 described 3 veterinary personnel who were exposed to reaerosolized botulinum toxin while disposing of rabbits and guinea pigs whose fur was coated with aerosolized type A botulinum toxin. Type A botulinum toxin was detected in serum samples from all 3 affected individuals.[21]

Once botulinum toxin is absorbed, the bloodstream carries it to peripheral cholinergic synapses, principally, the neuromuscular junction, where it binds irreversibly. The toxin is then internalized and enzymatically blocks acetylcholine release (Figure 1). Accordingly, all forms of human botulism display virtually identical neurologic signs. However, the neurologic signs in naturally occurring foodborne botulism may be preceded by abdominal cramps, nausea, vomiting, or diarrhea.[44] These gastrointestinal symptoms are thought to be caused by other bacterial metabolites also present in the food[33] and may not occur if purified botulinum toxin is intentionally placed in foods or aerosols.

Botulism is an acute, afebrile, symmetric, descending flaccid paralysis that always begins in bulbar musculature. It is not possible to have botulism without having multiple cranial nerve palsies. Disease manifestations are similar regardless of botulinum toxin type. However, the extent and pace of paralysis may vary considerably among patients. Some patients may be mildly affected (FIGURE 2), while others may be so paralyzed that they appear comatose and require months of ventilatory support. The rapidity of onset and the severity of paralysis depend on the amount of toxin absorbed into the circulation. Recovery results from new motor axon twigs that sprout to reinnervate paralyzed muscle fibers, a process that, in adults, may take weeks or months to complete.[45,46]

Patients with botulism typically present with difficulty seeing, speaking, and/or swallowing (TABLE 1 and TABLE 2). Prominent neurologic findings in all forms of botulism include ptosis, diplopia, blurred vision, often enlarged or sluggishly reactive pupils, dysarthria, dysphonia, and dysphagia.[5,44,47,48] The mouth may appear dry and the pharynx injected because of peripheral parasympathetic cholinergic blockade. Sensory changes are not observed except for infrequent circumoral and peripheral paresthesias from hyperventilation as a patient becomes frightened by onset of paralysis.

As paralysis extends beyond bulbar musculature, loss of head control, hy-

potonia, and generalized weakness become prominent. Dysphagia and loss of the protective gag reflex may require intubation and, usually, mechanical ventilation. Deep tendon reflexes may be present initially but diminish or disappear in the ensuing days, and constipation may occur. In untreated persons, death results from airway obstruction (pharyngeal and upper airway muscle paralysis) and inadequate tidal volume (diaphragmatic and accessory respiratory muscle paralysis).

Because botulism is an intoxication, patients remain afebrile unless they also have acquired a secondary infection (eg, aspiration pneumonia). The toxin does not penetrate brain parenchyma, so patients are not confused or obtunded. However, they often appear lethargic and have communication difficulties because of bulbar palsies (Figure 2). Botulism may be recognized by its classic triad: (1) symmetric, descending flaccid paralysis with prominent bulbar palsies in (2) an afebrile patient with (3) a clear sensorium. The prominent bulbar palsies can be summarized in part as "4 Ds": diplopia, dysarthria, dysphonia, and dysphagia.

Table 2. Symptoms and Signs of Inhalational Botulism in Order of Onset

Humans (n = 3)[21]	Monkeys (n = 9)[39]*
Third day after exposure	12-18 hours after exposure
Mucus in throat	Mild muscular weakness
Difficulty swallowing solid food	Intermittent ptosis
Dizziness	Disconjugate gaze
Fourth day after exposure	Followed by
Difficulty moving eyes	Severe weakness of postural neck muscles
Mild pupillary dilation and nystagmus	Occasional mouth breathing
Indistinct speech	Serous nasal discharge
Unsteady gait	Salivation, dysphagia
Extreme weakness	Mouth breathing
	Rales
	Anorexia
	Severe generalized weakness
	Lateral recumbency
	Second to fourth day after exposure
	Death in some animals

*After exposure to 4 to 7 monkey median lethal doses of botulinum toxin. The time to onset and pace of paralysis were dose-dependent. Adapted from Middlebrook and Franz[48] with permission.

EPIDEMIOLOGY

Early recognition of outbreaks of botulism, whether natural or intentional, depends on heightened clinical suspicion. Aerosol dissemination may not be difficult to recognize because a large number of cases will share a common temporal and geographical exposure and will lack a common dietary exposure. However, identification of the common exposure site initially may be difficult because of the mobility of persons exposed during the incubation period. Botulism and botulinum toxin are not contagious and cannot be transmitted from person to person. In contrast, a microbe intentionally modified to produce botulinum toxin might be contagious.

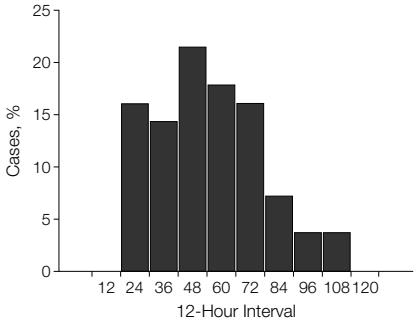
No instances of waterborne botulism have ever been reported.[42,49,50] Although the potency of botulinum toxin has led to speculation that it might be used to contaminate a municipal water supply, this scenario is unlikely for at least 2 reasons.[51] First, botulinum toxin is rapidly inactivated by standard potable water treatments (eg, chlorination, aeration).[52] Second, because of the slow turnover time of large-capacity reservoirs, a comparably large (and technically difficult to produce and deliver) inoculum of botulinum toxin would be needed.[53] In contrast with treated water, botulinum toxin may be stable for several days in untreated water or beverages.[52,54] Hence, such items should be investigated in a botulism outbreak if no other vehicle for toxin can be identified.

If food were deliberately used as a vehicle for the toxin, the outbreak would need to be distinguished from naturally occurring foodborne botulism. During the past 20 years, the epidemiology of foodborne botulism has expanded beyond its traditional association with home-preserved foods and now includes nonpreserved foods and public eating places,[47] features that could make terrorist use of botulinum toxin more difficult to detect. Characteristics of outbreaks of botulism include:

Incubation Period

The rapidity of onset and severity of botulism depend on the rate and amount of toxin absorption. Symptoms of foodborne botulism may begin as early as 2 hours or as long as 8 days after ingestion of toxin.[55,56] Typically, cases present 12 to 72 hours after the implicated meal. In 1 large foodborne outbreak, new cases presented during the ensuing 3 days at a fairly even rate before decreasing (FIGURE 3).[57] The time to onset of inhalational botulism cannot be stated with certainty because so few cases are known. Monkeys showed signs of botulism 12 to 80 hours after aerosol exposure to 4 to 7 multiples of the monkey median lethal dose.[39] The 3 known human cases of inhalational botulism had

Figure 3. Fifty-Nine Cases of Botulism, by Interval Between Eating at a Restaurant and Onset of First Neurologic Symptom—Michigan, 1977



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Box 1. Features of an Outbreak That Would Suggest a Deliberate Release of Botulinum Toxin

Outbreak of a large number of cases of acute flaccid paralysis with prominent bulbar palsies

Outbreak with an unusual botulinum toxin type (ie, type C, D, F, or G, or type E toxin not acquired from an aquatic food)

Outbreak with a common geographic factor among cases (eg, airport, work location) but without a common dietary exposure (ie, features suggestive of an aerosol attack)

Multiple simultaneous outbreaks with no common source

Note: A careful travel and activity history, as well as dietary history, should be taken in any suspected botulism outbreak. Patients should also be asked if they know of other persons with similar symptoms.

onset of symptoms approximately 72 hours after exposure to an unknown but probably small amount of reaerosolized toxin.[21]

Age and Sex

Persons of all ages are potentially susceptible to botulism. There are no sex differences in susceptibility.

Agent and Vehicles

Botulinum toxin in solution is colorless, odorless, and, as far as is known, tasteless. The toxin is readily inactivated by heat (≥85°C for 5 minutes).[33,34,52] Thus, foodborne botulism is always transmitted by foods that are not heated, or not heated thoroughly, before eating. Almost every type of food has been associated with outbreaks of botulism, but the most commonly implicated foods in the United States are vegetables, particularly "low-acid" (ie, higher pH) vegetables such as beans, peppers, carrots, and corn.[42,50,58]

A novel epidemiological development is the occurrence of foodborne botulism after eating various nonpreserved foods in restaurants or delicatessens. Foil-wrapped baked potatoes are now known to be capable of causing restaurant-associated foodborne botulism[59] when held at room temperature after baking and then served plain,[60] as potato salad,[61,62] or as a Mediterranean-style dip.[59] Other outbreaks that originated in restaurants resulted from contaminated condiments such as sautéed onions,[63] garlic in oil,[64] and commercial cheese sauce.[65] Additional examples of notable commercial foods that have caused botulism outbreaks include inadequately eviscerated fish,[66] yogurt,[67] cream cheese,[68] and jarred peanuts.[69]

Incidence and Outbreak Size

Naturally occurring foodborne botulism is a rare disease. Approximately 9 outbreaks of foodborne botulism and a median of 24 cases occur annually in the United States.[42,47] The mean outbreak size has remained constant over the years at approximately 2.5 cases per outbreak. The largest outbreak of foodborne botulism in the United States in the last 100 years occurred in Michigan in 1977; 59 cases resulted from eating home-preserved jalapeño peppers at a restaurant.[57] However, only 45 of the 59 patients had clinically evident weakness and hypotonia.

Toxin Types

Of the 135 foodborne outbreaks in the 16 years from 1980 to 1996 in the United States, the toxin types represented were: type A, 54.1%; type B, 14.8%; type E, 26.7%; type F, 1.5%; and unknown, 3.0%.[42] Type F foodborne outbreaks are rare in the United States; a 1962 outbreak resulted from homemade venison jerky,[70] while other type F cases actually may have had intestinal botulism.[71] Toxin types C and D cause botulism in wildlife and domestic animals but have not caused human foodborne disease. However, humans are thought to be susceptible to these toxin types because they have caused botulism in primates when ingested.[72-74] Toxin type G is produced by a bacteria species discovered in South American soil in 1969 that has never caused recognized foodborne botulism.[75] Aerosol challenge studies in monkeys have established the susceptibility of primates to inhaled botulinum toxin types C, D, and G.[48]

Distribution

Although outbreaks of foodborne botulism have occurred in almost all states, more than half (53.8%) of the US outbreaks have occurred in just 5 western states (California, Washington, Oregon, Colorado, and Alaska). East of the Mississippi River, 60% of the foodborne outbreaks have resulted from type B toxin, while west of the Mississippi River, 85% have resulted from type A toxin. In the 46 years between 1950 and 1996, 20 states, mainly in the eastern United States, did not report any type A botulism outbreaks, while 24 states, mostly in the western United States, did not report any type B outbreaks.[42] In Canada and Alaska, most foodborne outbreaks resulted from type E toxin associated with native Inuit and Eskimo foods.[50,76]

Bioterrorism Considerations

Any outbreak of botulism should bring to mind the possibility of bioterrorism, but certain features would be particularly suggestive (BOX 1). The availability and speed of air transportation mandate that a careful travel and activity history, as well as a careful dietary history, be taken. Patients should also be asked whether they know of other persons with similar symptoms. Absence of a common dietary exposure among temporally clustered patients should suggest the possibility of inhalational botulism.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Clinical diagnosis of botulism is confirmed by specialized laboratory test-

ing that often requires days to complete. Routine laboratory test results are usually unremarkable. Therefore, clinical diagnosis is the foundation for early recognition of and response to a bioterrorist attack with botulinum toxin.

Any case of suspected botulism represents a potential public health emergency because of the possibility that a contaminated food remains available to others or that botulinum toxin has been deliberately released. In these settings, prompt intervention by civil authorities is needed to prevent additional cases. Consequently, clinicians caring for patients with suspected botulism should notify their local public health department and hospital epidemiologist immediately to coordinate shipment of therapeutic antitoxin, laboratory diagnostic testing, and epidemiological investigation (BOX 2). In most jurisdictions of the United States, botulism suspected on clinical grounds alone by law must be reported immediately by telephone to local public health authorities. The attending clinician needs to be both prompt and persistent in accomplishing this notification.

Box 2. Clinicians Caring for Patients With Suspected Botulism Should Immediately Contact Their:

(1) Hospital epidemiologist or infection control practitioner

and

(2) Local and state health departments

Consult your local telephone operator; the telephone directory under "government listings," or the Internet at: http://www.cdc.gov/other.htm#states or http://www.astho.org/state.html

If the local and state health departments are unavailable, contact the Centers for Disease Control and Prevention: (404) 639-2206; (404) 639-2888 [after hours].

Differential Diagnosis

Botulism is frequently misdiagnosed, most often as a polyradiculoneuropathy (Guillain-Barré or Miller-Fisher syndrome), myasthenia gravis, or a disease of the central nervous system (TABLE 3). In the United States, botulism is more likely than Guillain-Barré syndrome, intoxication, or poliomyelitis to cause a cluster of cases of acute flaccid paralysis. Botulism differs from other flaccid paralyses in its prominent cranial nerve palsies disproportionate to milder weakness and hypotonia below the neck, in its symmetry, and in its absence of sensory nerve damage.

Table 3. Selected Mimics and Misdiagnoses of Botulism*

Conditions	Features That Distinguish Condition From Botulism
Common Misdiagnoses	
Guillain-Barré syndrome† and its variants, especially Miller-Fisher syndrome	History of antecedent infection; paresthesias; often ascending paralysis; early areflexia; eventual CSF protein increase; EMG findings
Myasthenia gravis†	Recurrent paralysis; EMG findings; sustained response to anticholinesterase therapy
Stroke†	Paralysis often asymmetric; abnormal CNS image
Intoxication with depressants (eg, acute ethanol intoxication), organophosphates, carbon monoxide, or nerve gas	History of exposure; excessive drug levels detected in body fluids
Lambert-Eaton syndrome	Increased strength with sustained contraction; evidence of lung carcinoma; EMG findings similar to botulism
Tick paralysis	Paresthesias; ascending paralysis; tick attached to skin
Other Misdiagnoses	
Poliomyelitis	Antecedent febrile illness; asymmetric paralysis; CSF pleocytosis
CNS infections, especially of the brainstem	Mental status changes; CSF and EEG abnormalities
CNS tumor	Paralysis often asymmetric; abnormal CNS image
Streptococcal pharyngitis (pharyngeal erythema can occur in botulism)	Absence of bulbar palsies; positive rapid antigen test result or throat culture
Psychiatric illness†	Normal EMG in conversion paralysis
Viral syndrome†	Absence of bulbar palsies and flaccid paralysis
Inflammatory myopathy†	Elevated creatine kinase levels
Diabetic complications†	Sensory neuropathy; few cranial nerve palsies
Hyperemesis gravidarum†	Absence of bulbar palsies and acute flaccid paralysis
Hypothyroidism†	Abnormal thyroid function test results
Laryngeal trauma†	Absence of flaccid paralysis; dysphonia without bulbar palsies
Overexertion†	Absence of bulbar palsies and acute flaccid paralysis

*CSF indicates cerebrospinal fluid; EMG, electromyogram; CNS, central nervous system; and EEG, electroencephalogram.
†Misdiagnoses made in a large outbreak of botulism.[64]

A large, unintentional outbreak of foodborne botulism caused by a restaurant condiment in Canada provides a cautionary lesson about the potential difficulties in recognizing a covert, intentional contamination of food.[64] During a 6-week period in which the condiment was served, 28 persons in 2 countries became ill, but all were misdiagnosed (Table 3). The 28 were identified retrospectively only after correct diagnoses in a mother and her 2 daughters who had returned to their home more than 2000 miles away from the restaurant. Four (14%) of the cases had been misdiagnosed as having psychiatric disease, including "factitious" symptoms. It is possible that hysterical paralysis might occur as a conversion reaction in the anxiety that would

follow a deliberate release of botulinum toxin.

Diagnostic Testing

At present, laboratory diagnostic testing for botulism in the United States is available only at the CDC and approximately 20 state and municipal public health laboratories.[42] The laboratory should be consulted prospectively about specimen collection and processing. Samples used in diagnosis of botulism include serum (≥30 mL of blood in "tiger"-top or red-top tubes from adults, less from children), stool, gastric aspirate, and, if available, vomitus and suspect foods. Serum samples must be obtained before therapy with antitoxin, which nullifies the diagnostic mouse bioassay. An enema may be required to obtain an adequate fecal sample if the patient is constipated. Sterile water should be used for this procedure because saline enema solution can confound the mouse bioassay. Gastric aspirates and, perhaps, stool may be useful for detecting inhaled aerosolized botulinum toxin released in a bioterrorist attack.[77] A list of the patient's medications should accompany the diagnostic samples because anticholinesterases, such as pyridostigmine bromide, and other medicines that are toxic to mice can be dialyzed from samples before testing. All samples should be kept refrigerated after collection.

The standard laboratory diagnostic test for clinical specimens and foods is the mouse bioassay,[42] in which type-specific antitoxin protects mice against any botulinum toxin present in the sample. The mouse bioassay can detect as little as 0.03 ng of botulinum toxin[10] and usually yields results in 1 to 2 days (range, 6-96 hours). Fecal and gastric specimens also are cultured anaerobically, with results typically available in 7 to 10 days (range, 5-21 days). Toxin production by culture isolates is confirmed by the mouse bioassay.

An electromyogram with repetitive nerve stimulation at 20 to 50 Hz can sometimes distinguish between causes of acute flaccid paralysis.[78,79] The characteristic electromyographic findings of botulism include normal nerve conduction velocity, normal sensory nerve function, a pattern of brief, small-amplitude motor potentials, and, most distinctively, an incremental response (facilitation) to repetitive stimulation often seen only at 50 Hz. Immediate access to electrophysiological studies may be difficult to obtain in an outbreak of botulism.

Additional diagnostic procedures may be useful in rapidly excluding botulism as the cause of paralysis (Table 3). Cerebrospinal fluid (CSF) is unchanged in botulism but is abnormal in many central nervous system diseases. Although the CSF protein level eventually is elevated in Guillain-Barré syndrome, it may be normal early in illness. Imaging of the brain, spine, and chest may reveal hemorrhage, inflammation, or neoplasm. A test dose of edrophonium chloride briefly reverses paralytic symptoms in many patients with myasthenia gravis and, reportedly, in some with botulism.[64] A close inspection of the skin, especially the scalp, may reveal an attached tick that is causing paralysis.[80] Other tests that require days for results include stool culture for *Campylobacter jejuni* as a precipitant of Guillain-Barré syndrome and assays for the autoantibodies that cause myasthenia gravis, Lambert-Eaton syndrome, and Guillain-Barré syndrome.

Foods suspected of being contaminated should be refrigerated until retrieval by public health personnel. The US Food and Drug Administration and the US Department of Agriculture can assist other public health laboratories with testing of suspect foods by using methods similar to those applied to clinical samples.

THERAPY

The mortality and sequelae associated with botulism have diminished with contemporary therapy. In the United States, the percentage of persons who died of foodborne botulism decreased from 25% during 1950-1959 to 6% during 1990-1996, with a similar reduction for each botulinum toxin type.[42] Despite this increase in survival, the paralysis of botulism can persist for weeks to months with concurrent requirements for fluid and nutritional support, assisted ventilation, and treatment of complications.

Therapy for botulism consists of supportive care and passive immunization with equine antitoxin. Optimal use of botulinum antitoxin requires early suspicion of botulism. Timely administration of passive neutralizing antibody will minimize subsequent nerve damage and severity of disease but will not reverse existent paralysis.[81,82] Antitoxin should be given to patients with neurologic signs of botulism as soon as possible after clinical diagnosis.[47] Treatment should not be delayed for microbiological testing. Antitoxin may be withheld at the time of diagnosis if it is certain that the patient is improving from maximal paralysis.

In the United States, botulinum antitoxin is available from the CDC via state and local health departments (Box 2). The licensed trivalent antitoxin contains neutralizing antibodies against botulinum toxin types A, B, and E, the most common causes of human botulism. If another toxin type was intentionally disseminated, patients could potentially be treated with an investigational heptavalent (ABCDEFG) antitoxin held by the US Army.[83] However, the time required for correct toxin typing and subsequent administration of heptavalent antitoxin would decrease the utility of this product in an outbreak.

The dose and safety precautions for equine botulinum antitoxin have changed over time. Clinicians should review the package insert with public health authorities before using antitoxin. At present, the dose of licensed botulinum antitoxin is a single 10-mL vial per patient, diluted 1:10 in 0.9% saline solution, administered by slow intravenous infusion. One vial provides between 5500 and 8500 IU of each type-specific antitoxin. The amount of neutralizing antibody in both the licensed and the investigational equine antitoxins far exceeds the highest serum toxin levels found in foodborne botu-

lism patients, and additional doses are usually not required. If a patient has been exposed to an unnaturally large amount of botulinum toxin as a biological weapon, the adequacy of neutralization by antitoxin can be confirmed by retesting serum for toxin after treatment.

There are few published data on the safety of botulinum antitoxins. From 1967 to 1977, when the recommended dose was larger than today, approximately 9% of recipients of equine botulinum antitoxin in the United States displayed urticaria, serum sickness, or other reactions suggestive of hypersensitivity.[84] Anaphylaxis occurred within 10 minutes of receiving antitoxin in 2% of recipients. When the US Army's investigational heptavalent antitoxin was given to 50 individuals in a large Egyptian outbreak of type E foodborne botulism in 1991, 1 recipient (2%) displayed serum sickness, and 9 (18%) had mild reactions.[83] To screen for hypersensitivity, patients are given small challenge doses of equine antitoxin before receiving a full dose. Patients responding to challenge with a substantial wheal and flare may be desensitized over 3 to 4 hours before additional antitoxin is given. During the infusion of antitoxin, diphenhydramine and epinephrine should be on hand for rapid administration in case of adverse reaction. Although both equine antitoxins have been partially despeciated by enzymatic cleavage of the allogenic F_c region, each contains a small residual of intact antibody that may sensitize recipients to additional doses.

Botulism patients require supportive care that often includes feeding by enteral tube or parenteral nutrition, intensive care, mechanical ventilation, and treatment of secondary infections. Patients with suspected botulism should be closely monitored for impending respiratory failure. In nonventilated infants with botulism, a reverse Trendelenburg positioning with cervical vertebral support has been helpful, but applicability of this positioning to adults with botulism remains untested. This tilted, flat-body positioning with neck support may improve ventilation by reducing entry of oral secretions into the airway and by suspending more of the weight of the abdominal viscera from the diaphragm, thereby improving respiratory excursion (FIGURE 4). In contrast, placing a botulism patient in a supine or semirecumbent position (trunk flexed 45° at the waist) may impede respiratory excursion and airway clearance, especially if the patient is obese. The desired angle of the reverse Trendelenburg position is 20° to 25°.

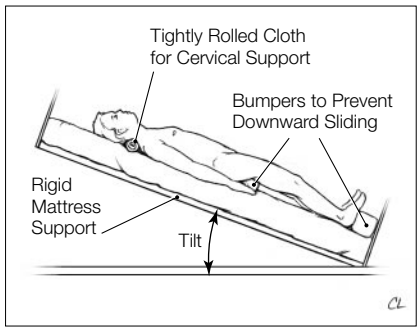
Botulism patients should be assessed for adequacy of gag and cough reflexes, control of oropharyngeal secretions, oxygen saturation, vital capacity, and inspiratory force. Airway obstruction or aspiration usually precedes hypoventilation in botulism. When respiratory function deteriorates, controlled, anticipatory intubation is indicated. The proportion of patients with botulism who require mechanical ventilation has varied from 20% in a foodborne outbreak[64] to more than 60% in infant botulism.[85] In a large outbreak of botulism, the need for mechanical ventilators, critical care beds, and skilled personnel might quickly exceed local capacity and persist for weeks or months. Development of a reserve stockpile of mechanical ventilators in the United States is under way[86] and will require a complement of staff trained in their use.

Antibiotics have no known direct effect on botulinum toxin. However, secondary infections acquired during botulism often require antibiotic therapy. Aminoglycoside antibiotics and clindamycin are contraindicated because of their ability to exacerbate neuromuscular blockade.[87,88] Standard treatments for detoxification, such as activated charcoal,[89] may be given before antitoxin becomes available, but there are no data regarding their effectiveness in human botulism.

SPECIAL POPULATIONS

Based on limited information, there is no indication that treatment of children, pregnant women, and immunocompromised persons with botulism should differ from standard therapy.

Figure 4. Preferred Positioning of Nonventilated Botulism Patients



Note flat, rigid mattress tilted at 20°, tightly rolled cloth to support cervical vertebrae, and bumpers to prevent downward sliding. Use of this position may postpone or avoid the need for mechanical ventilation in mildly affected patients because of improved respiratory mechanics and airway protection.

Despite the risks of immediate hypersensitivity and sensitization to equine proteins, both children[43,90] and pregnant women[91,92] have received equine antitoxin without apparent short-term adverse effects. The risks to fetuses of exposure to equine antitoxin are unknown. Treatment with human-derived neutralizing antibody would decrease the risk of allergic reactions posed by equine botulinum antitoxin, but use of the investigational product, Botulism Immune Globulin Intravenous (Human) (California Department of Health Services, Berkeley), is limited to suspected cases of infant botulism.[82,93]

PROPHYLAXIS

Botulism can be prevented by the presence of neutralizing antibody in the bloodstream. Passive immunity can be provided by equine botulinum antitoxin or by specific human hyperimmune globulin, while endogenous immunity can be induced by immunization with botulinum toxoid.

Use of antitoxin for postexposure prophylaxis is limited by its scarcity and its reactogenicity. Because of the risks of equine antitoxin therapy, it is less certain how best to care for persons who may have been exposed to botulinum toxin but who are not yet ill. In a small

study of primates exposed to aerosolized toxin in which supportive care was not provided, all 7 monkeys given antitoxin after exposure but before the appearance of neurologic signs survived, while 2 of 4 monkeys treated with antitoxin only after the appearance of neurologic signs died.[39] Moreover, all monkeys infused with neutralizing antibody before exposure to toxin displayed no signs of botulism. In a balance between avoiding the potential adverse effects of equine antitoxin and needing to rapidly neutralize toxin, it is current practice in foodborne botulism outbreaks to closely monitor persons who may have been exposed to botulinum toxin and to treat them promptly with antitoxin at the first signs of illness.[47] To facilitate distribution of scarce antitoxin following the intentional use of botulinum toxin, asymptomatic persons who are believed to have been exposed should remain under close medical observation and, if feasible, near critical care services.

In the United States, an investigational pentavalent (ABCDE) botulinum toxoid is distributed by the CDC for laboratory workers at high risk of exposure to botulinum toxin and by the military for protection of troops against attack.[94] A recombinant vaccine is also in development.[95] The pentavalent toxoid has been used for more than 30 years to immunize more than 3000 laboratory workers in many countries. Immunization of the population with botulinum toxoid could in theory eliminate the hazard posed by botulinum toxins A through E. However, mass immunization is neither feasible nor desirable for reasons that include scarcity of the toxoid, rarity of natural disease, and elimination of the potential therapeutic benefits of medicinal botulinum toxin. Accordingly, preexposure immunization currently is neither recommended for nor available to the general population. Botulinum toxoid induces immunity over several months and, so, is ineffective as postexposure prophylaxis.

DECONTAMINATION

Despite its extreme potency, botulinum toxin is easily destroyed. Heating to an internal temperature of 85°C for at least 5 minutes will detoxify contaminated food or drink.[52] All foods suspected of contamination should be promptly removed from potential consumers and submitted to public health authorities for testing.

Persistence of aerosolized botulinum toxin at a site of deliberate release is determined by atmospheric conditions and the particle size of the aerosol. Extremes of temperature and humidity will degrade the toxin, while fine aerosols will eventually dissipate into the atmosphere. Depending on the weather, aerosolized toxin has been estimated to decay at between less than 1% to 4% per minute.[96] At a decay rate of 1% per minute, substantial inactivation (≥13 logs) of toxin occurs by 2 days after aerosolization.

Recognition of a covert release of finely aerosolized botulinum toxin would probably occur too late to prevent additional exposures. When exposure is anticipated, some protection may be conferred by covering the mouth and nose with clothing such as an undershirt, shirt, scarf, or handkerchief.[97] In contrast with mucosal surfaces, intact skin is impermeable to botulinum toxin.

After exposure to botulinum toxin, clothing and skin should be washed with soap and water.[98] Contaminated objects or surfaces should be cleaned with 0.1% hypochlorite bleach solution if they cannot be avoided for the hours to days required for natural degradation.[33,52,98]

INFECTION CONTROL

Medical personnel caring for patients with suspected botulism should use standard precautions. Patients with suspected botulism do not need to be isolated, but those with flaccid paralysis from suspected meningitis require droplet precautions.

RESEARCH NEEDS

Additional research in diagnosis and treatment of botulism is required to minimize its threat as a weapon. Rapid diagnostic and toxin typing techniques currently under development would be useful for recognizing and responding to a bioterrorist attack. Although polymerase chain reaction assays can detect the botulinum toxin gene,[99] they are unable, as yet, to determine whether the toxin gene is expressed and whether the expressed protein is indeed toxic. Assays that exploit the enzymatic activity of botulinum toxin have the potential to supplant the mouse bioassay as the standard for diagnosis.[100] Detection of botulinum toxin in aerosols by enzyme-linked immunosorbent assay[101] is a component of the US military's Biological Integrated Detection System for rapid recognition of biological agents in the battlefield.[17]

The distribution of botulinum antitoxin to local hospitals from regional depots takes several hours. In contrast, standard detoxification techniques can be applied immediately. Studies are needed to assess whether activated charcoal and osmotic catharsis can prevent gastrointestinal tract absorption or reduce circulating levels of botulinum toxin. Enteral detoxification may be less useful in inhalational botulism than in foodborne disease.

The competing needs for immunity to weaponized botulinum toxin and for susceptibility to medicinal botulinum toxin could be reconciled by supplying human antibody that neutralizes toxin. With a half-life of approximately 1 month,[102] human antibody would provide immunity for long periods and avoid the reactogenicity of equine products. Existing in vitro technologies could produce the stockpiles of fully human antibody necessary both to deter terrorist attacks and to avoid the rationing of antitoxin that currently would be required in a large outbreak of botulism.[103-106] A single small injection of oligoclonal human antibodies could, in theory, provide protection against toxins A through G for many months. Until such a product becomes available, the possibilities for reducing the population's vulnerability to the intentional misuse of botulinum toxin remain limited.

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Disclaimers: In some instances, the indications, dosages, and other information in this article are not consistent with current approved labeling by the US Food and Drug Administration (FDA). The recommendations on use of drugs and vaccine for uses not approved by the FDA do not represent the official views of the FDA nor of any of the federal agencies whose scientists participated in these discussions. Unlabeled uses of the products recommended are noted in the sections of this article in which these products are discussed. Where unlabeled uses are indicated, information used as the basis for the recommendation is discussed.

The views, opinions, assertions, and findings contained herein are those of the authors and should not be construed as official US Department of Defense or US Department of Army positions, policies, or decisions unless so designated by other documentation.

Additional Articles: This article is the fourth in a series entitled *Medical and Public Health Management Following the Use of a Biological Weapon: Consensus Statements of The Working Group on Civilian Biodefense*. See references 1 through 3.

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current national point prevalence data are available. In addition, there are no quantitative data suggesting isotretinoin misuse, and the informed consent specifically indicates that the patient has been diagnosed with the FDA-approved indication. It is important to note that Roche Laboratories promotes the use of isotretinoin exclusively for patients with this approved indication.

Finally, it is important to state that the clinical criteria for the use of this drug in an individual patient must be left to the judgment of the physician, who is the only appropriate person to define the treatment plan for that patient.

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RESEARCH LETTER

Persistent Pain in Nursing Home Residents

To the Editor: More than 1.5 million people in the United States reside in nursing homes and an estimated 43% of adults 65 years and older will enter a nursing home prior to death.[1] Previous research using an early version of the Minimum Data Set (MDS), a nationally mandated nursing home resident assessment instrument, noted that daily pain was prevalent among nursing home residents diagnosed with cancer who had been discharged from a hospital, as well as among the residents of nursing homes in general.[2] Prior research was restricted by a limited MDS pain frequency measure of "none" or "daily," but since 1998, information on both frequency (none, daily, or less than daily) and severity of pain (mild, moderate, or excruciating at times) has been collected. We report the rates of persistent severe pain among US nursing home residents by analyzing a national repository of MDS data, which represents all nursing home residents in all 50 states.

Methods. We determined the rate of persistent severe pain among all 2.2 million residents of US nursing homes within 60 days of April 1, 1999. The term "persistent pain" indicates residents with pain at an assessment around that time who were also reported to be in daily moderate or excruciating pain at a second assessment, 60 to 180 days later. Using state as the unit of analysis, we adjusted observed rates of persistent severe pain for the nursing home discharge rate and the prevalence of severe pain among all 1999 admissions.

Results. Nationwide, 14.7% of residents in a nursing home for 2 assessments were in persistent pain and 41.2% of residents in pain at first assessment were in severe pain 60 to 180 days later. This rate varied from 37.7% (Mississippi) to 49.5% (Utah). Forty-one states had rates of persistent pain between 39.5% and 46.1%. Individual state reports are available online at http://www.chcr.brown.edu/dying/factsondying.htm.

Comment. We believe that these results underestimate the true pain burden experienced by nursing home residents because the data were reported by nursing home staff rather than by patients. States in which pain is not adequately assessed may report lower rates of persistent pain. Although facilities in states with higher rates of reported pain may be doing a better job of recognizing pain, nearly half of these residents were apparently not afforded adequate palliation. The high rate of persistent pain is consistent with previous research noting that pain is often not appropriately treated in nursing home residents.[2,3] Untreated pain results in impaired mobility, depression, and diminishes quality of life.[3-5] These population results indicate that pain control represents an often neglected need of this vulnerable population.

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1. Kemper P, Murtaugh CM. Lifetime use of nursing home care. *N Engl J Med*. 1991;324:595-600.
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CORRECTION

Incorrect Wording and Web Site Address: In the Consensus Statement entitled "Botulinum Toxin as a Biological Weapon: Medical and Public Health Management" published in the February 28, 2001, issue of THE JOURNAL (2001;285:1059-1070), 3 errors appeared. In the third introductory paragraph on page 1059, the word "biological" should be "microbial." In the paragraph labeled "Toxin Types" on page 1064, the word "bacteria" should be "bacterial." Finally, on page 1069, the Web site address for reference 27 should be http://www.state.gov/www/global/terrorism/1999report/1999index.html.

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Plague as a Biological Weapon
Medical and Public Health Management

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Objective 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.

Participants The working group included 25 representatives from major academic medical centers and research, government, military, public health, and emergency management institutions and agencies.

Evidence MEDLINE databases were searched from January 1966 to June 1998 for the Medical Subject Headings *plague*, *Yersinia pestis*, *biological weapon*, *biological terrorism*, *biological warfare*, and *biowarfare*. Review of the bibliographies of the references identified by this search led to subsequent identification of relevant references published prior to 1966. In addition, participants identified other unpublished references and sources. Additional MEDLINE searches were conducted through January 2000.

Consensus Process The first draft of the consensus statement was a synthesis of information obtained in the formal evidence-gathering process. The working group was convened to review drafts of the document in October 1998 and May 1999. The final statement incorporates all relevant evidence obtained by the literature search in conjunction with final consensus recommendations supported by all working group members.

Conclusions An aerosolized plague weapon could cause fever, cough, chest pain, and hemoptysis with signs consistent with severe pneumonia 1 to 6 days after exposure. Rapid evolution of disease would occur in the 2 to 4 days after symptom onset and would lead to septic shock with high mortality without early treatment. Early treatment and prophylaxis with streptomycin or gentamicin or the tetracycline or fluoroquinolone classes of antimicrobials would be advised.

JAMA. 2000;283:2281-2290 www.jama.com

THIS IS THE THIRD ARTICLE IN A series entitled *Medical and Public Health Management Following the Use of a Biological Weapon: Consensus Statements of the Working Group on Civilian Biodefense.*[1,2] The working group has identified a limited number of agents that, if used as weapons, could cause disease and death in sufficient numbers to cripple a city or region. These agents also comprise the top of the list of "Critical Biological Agents" recently developed by the Centers for Disease Control and Prevention (CDC).[3] *Yersinia pestis*, the causative agent of plague, is one of the most serious of these. Given the availability of *Y pestis* around the world, capacity for its mass production and aerosol dissemination, difficulty in preventing such activities, high fatality rate of pneumonic plague, and potential for secondary spread of cases during an epidemic, the potential use of plague as a biological weapon is of great concern.

CONSENSUS METHODS

The working group comprised 25 representatives from major academic medical centers and research, government, military, public health, and emergency management institutions and agencies.

MEDLINE databases were searched from January 1966 to June 1998 using the Medical Subject Headings (MeSH) *plague*, *Yersinia pestis*, *biological weapon*, *biological terrorism*, *biological warfare*, and *biowarfare*. Review of the bibliographies of the references identified by

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this search led to subsequent identification of relevant references published prior to 1966. In addition, participants identified other unpublished references and sources in their fields of expertise. Additional MEDLINE searches were conducted through January 2000 during the review and revisions of the statement.

The first draft of the consensus statement was a synthesis of information obtained in the initial formal evidence-gathering process. Members of the working group were asked to make formal written comments on this first draft of the document in September 1998. The document was revised incorporating changes suggested by members of the working group, which was convened to review the second draft of the document on October 30, 1998. Following this meeting and a second meeting of the working group on May 24, 1999, a third draft of the document was completed, reviewed, and revised. Working group members had a final opportunity to review the document and suggest revisions. The final document incorporates all relevant evidence obtained by the literature search in conjunction with consensus recommendations supported by all working group members.

The assessment and recommendations provided herein represent the best professional judgment of the working group based on data and expertise currently available. The conclusions and recommendations need to be regularly reassessed as new information becomes available.

HISTORY AND POTENTIAL AS A BIOTERRORIST AGENT

In AD 541, the first recorded plague pandemic began in Egypt and swept across Europe with attributable population losses of between 50% and 60% in North Africa, Europe, and central and southern Asia.[4] The second plague pandemic, also known as the *black death* or *great pestilence*, began in 1346 and eventually killed 20 to 30 million people in Europe, one third of the European population.[5] Plague spread slowly and inexorably from village to village by infected rats and humans or more quickly from country to country by ships. The pandemic lasted more than 130 years and had major political, cultural, and religious ramifications. The third pandemic began in China in 1855, spread to all inhabited continents, and ultimately killed more than 12 million people in India and China alone.[4] Small outbreaks of plague continue to occur throughout the world.[4,5]

Advances in living conditions, public health, and antibiotic therapy make future pandemics improbable. However, plague outbreaks following use of a biological weapon are a plausible threat. In World War II, a secret branch of the Japanese army, Unit 731, is reported to have dropped plague-infected fleas over populated areas of China, thereby causing outbreaks of plague.[6] In the ensuing years, the biological weapons programs of the United States and the Soviet Union developed techniques to aerosolize plague directly, eliminating dependence on the unpredictable flea vector. In 1970, the World Health Organization (WHO) reported that, in a worst-case scenario, if 50 kg of *Y pestis* were released as an aerosol over a city of 5 million, pneumonic plague could occur in as many as 150000 persons, 36000 of whom would be expected to die.[7] The plague bacilli would remain viable as an aerosol for 1 hour for a distance of up to 10 km. Significant numbers of city inhabitants might attempt to flee, further spreading the disease.[7]

While US scientists had not succeeded in making quantities of plague organisms sufficient to use as an effective weapon by the time the US offensive program was terminated in 1970, Soviet scientists were able to manufacture large quantities of the agent suitable for placing into weapons.[8] More than 10 institutes and thousands of scientists were reported to have worked with plague in the former Soviet Union.[8] In contrast, few scientists in the United States study this disease.[9]

There is little published information indicating actions of autonomous groups or individuals seeking to develop plague as a weapon. However, in 1995 in Ohio, a microbiologist with suspect motives was arrested after fraudulently acquiring *Y pestis* by mail.[10] New antiterrorism legislation was introduced in reaction.

EPIDEMIOLOGY

Naturally Occurring Plague

Human plague most commonly occurs when plague-infected fleas bite humans who then develop bubonic plague. As a prelude to human epidemics, rats frequently die in large numbers, precipitating the movement of the flea population from its natural rat reservoir to humans. Although most persons infected by this route develop bubonic plague, a small minority will develop sepsis with no bubo, a form of plague termed *primary septicemic plague*. Neither bubonic nor septicemic plague spreads directly from person to person. A small percentage of patients with bubonic or septicemic plague develop secondary pneumonic plague and can then spread the disease by respiratory droplet. Persons contracting the disease by this route develop primary pneumonic plague.[11]

Plague remains an enzootic infection of rats, ground squirrels, prairie dogs, and other rodents on every populated continent except Australia.[4] Worldwide, on average in the last 50 years, 1700 cases have been reported annually.[4] In the United States, 390 cases of plague were reported from 1947 to 1996, 84% of which were bubonic, 13% septicemic, and 2% pneumonic. Concomitant case fatality rates were 14%, 22%, and 57%, respectively.[12] Most US cases were in New Mexico, Arizona, Colorado, and California. Of the 15 cases following exposure to domestic cats with plague, 4 were primary pneumonic plague.[13] In the United States, the last case of human-to-human transmission of plague occurred in Los Angeles in 1924.[14,15]

Although pneumonic plague has rarely been the dominant manifestation of the disease, large outbreaks of pneumonic plague have occurred.[16] In an outbreak in Manchuria in 1910-1911, as many as 60000 persons developed pneumonic plague; a second large Manchurian pneumonic plague outbreak occurred in 1920-1921.[16,17] As

would be anticipated in the preantibiotic era, nearly 100% of these cases were reported to be fatal.[16,17] Reports from the Manchurian outbreaks suggested that indoor contacts of affected patients were at higher risk than outdoor contacts and that cold temperature, increased humidity, and crowding contributed to increased spread.[14,15] In northern India, there was an epidemic of pneumonic plague with 1400 deaths reported at about the same time.[15] While epidemics of pneumonic plague of this scale have not occurred since, smaller epidemics of pneumonic plague have occurred recently. In 1997 in Madagascar, 1 patient with bubonic plague and secondary pneumonic infection transmitted pneumonic plague to 18 persons, 8 of whom died.[18]

Plague Following Use of a Biological Weapon

The epidemiology of plague following its use as a biological weapon would differ substantially from that of naturally occurring infection. Intentional dissemination of plague would most probably occur via an aerosol of *Y pestis*, a mechanism that has been shown to produce disease in nonhuman primates.[19] A pneumonic plague outbreak would result with symptoms initially resembling those of other severe respiratory illnesses. The size of the outbreak would depend on factors including the quantity of biological agent used, characteristics of the strain, environmental conditions, and methods of aerosolization. Symptoms would begin to occur 1 to 6 days following exposure, and people would die quickly following onset of symptoms.[16] Indications that plague had been artificially disseminated would be the occurrence of cases in locations not known to have enzootic infection, in persons without known risk factors, and in the absence of prior rodent deaths.

MICROBIOLOGY AND VIRULENCE FACTORS

Y pestis is a nonmotile, gram-negative bacillus, sometimes coccobacillus, that shows bipolar (also termed *safety pin*) staining with Wright, Giemsa, or Wayson stain (FIGURE 1).[20] *Y pestis* is a lactose nonfermenter, urease and indole negative, and a member of the Enterobacteriaceae family.[21] It grows optimally at 28°C on blood agar or MacConkey agar, typically requiring 48 hours for observable growth, but colonies are initially much smaller than other Enterobacteriaceae and may be overlooked. *Y pestis* has a number of virulence factors that enable it to survive in humans by facilitating use of host nutrients, causing damage to host cells, and subverting phagocytosis and other host defense mechanisms.[4,11,21,22]

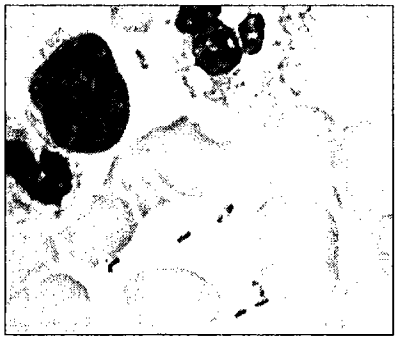
PATHOGENESIS AND CLINICAL MANIFESTATIONS

Naturally Occurring Plague

In most cases of naturally occurring plague, the bite by a plague-infected flea leads to the inoculation of up to thousands of organisms into a patient's skin. The bacteria migrate through cutaneous lymphatics to regional lymph nodes where they are phagocytosed but resist destruction. They rapidly multiply, causing destruction and necrosis of lymph node architecture with subsequent bacteremia, septicemia, and endotoxemia that can lead quickly to shock, disseminated intravascular coagulation, and coma.[21]

Patients typically develop symptoms of bubonic plague 2 to 8 days after being bitten by an infected flea. There is sudden onset of fever, chills, and weakness and the development of an acutely swollen tender lymph node, or bubo, up to 1 day later.[23] The bubo most typically develops in the groin, axilla, or cervical region (FIGURE 2, A) and is often so painful that it prevents patients from moving the affected area of the body. Buboes are 1 to 10 cm in diameter, and the overlying skin is erythematous.[21] They are extremely tender, nonfluctuant, and warm and are often associated with considerable surrounding edema, but seldom lymphangitis. Rarely, buboes become fluctuant and suppurate. In addition, pustules or skin ulcerations may occur at the site of the flea bite in a minority of patients. A small minority of patients infected by fleas develop *Y pestis* septicemia without a discernable bubo, the form of disease termed *primary septicemic plague*.[23] Septicemia can also arise secondary to bubonic plague.[21] Septicemic plague may lead to disseminated intravascular coagulation, necrosis of small vessels, and purpuric skin lesions (Figure 2, B). Gangrene of acral regions such as the digits and nose may also occur in advanced disease, a process believed responsible for the name *black death* in the second plague pandemic (Figure 2, C).[21] However, the finding of gangrene would not be expected to be helpful in diagnosing the disease in the early stages of illness when early antibiotic treatment could be lifesaving.

Figure 1. Peripheral Blood Smear From Patient With Septicemic Plague

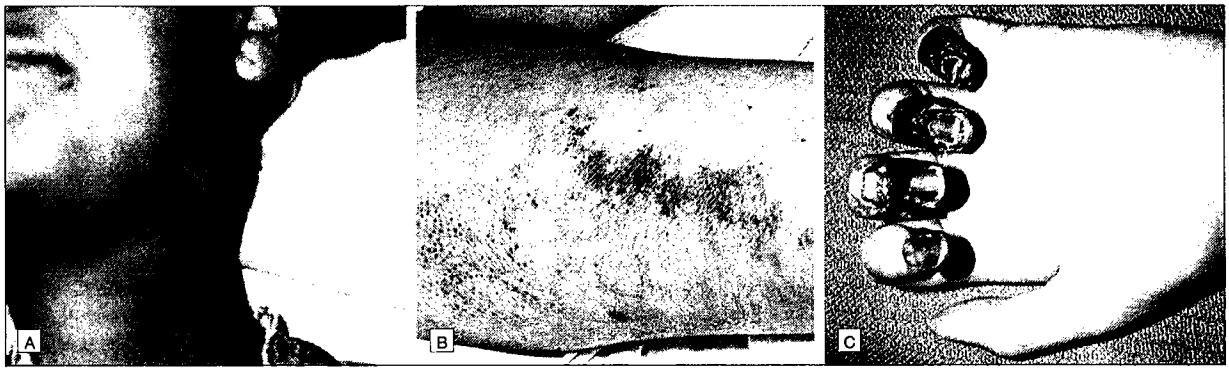


Smear shows characteristic bipolar staining of *Yersinia pestis* bacilli (Wright-Giemsa stain; magnification, ×1000). Figure from Centers for Disease Control and Prevention, Division of Vector-Borne Infectious Diseases, Fort Collins, Colo.

Secondary pneumonic plague develops in a minority of patients with bubonic or primary septicemic plague—approximately 12% of total cases in the United States over the last 50 years.[4] This process, termed *secondary pneumonic plague*, develops via hematogenous spread of plague bacilli to the lungs. Patients commonly have symptoms of severe bronchopneumonia, chest pain, dyspnea, cough, and hemoptysis.[16,21]

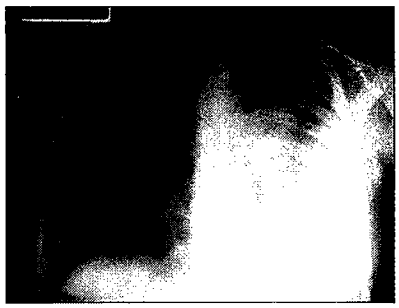
Primary pneumonic plague resulting from the inhalation of plague bacilli occurs rarely in the United States.[12] Reports of 2 recent cases of primary pneumonic plague, contracted after handling cats with pneumonic plague, reveal that both patients had pneumonic symptoms as well as prominent gastro-

Figure 2. Patients With Naturally Occurring Plague



A, Cervical bubo in patient with bubonic plague; B, petechial and ecchymotic bleeding into the skin in patient with septicemic plague; and C, gangrene of the digits during the recovery phase of illness of patient shown in B. In plague following the use of a biological weapon, presence of cervical bubo is rare; purpuric skin lesions and necrotic digits occur only in advanced disease and would not be helpful in diagnosing the disease in the early stages of illness when antibiotic treatment can be life-saving. Figures from Centers for Disease Control and Prevention, Division of Vector-Borne Infectious Diseases, Fort Collins, Colo.

Figure 3. Chest Radiograph of Patient With Primary Pneumonic Plague



Radiograph shows extensive lobar consolidation in left lower and left middle lung fields. Figure from Centers for Disease Control and Prevention, Division of Vector-Borne Infectious Diseases, Fort Collins, Colo.

intestinal symptoms including nausea, vomiting, abdominal pain, and diarrhea. Diagnosis and treatment were delayed more than 24 hours after symptom onset in both patients, both of whom died.[24,25]

Less common plague syndromes include plague meningitis and plague pharyngitis. Plague meningitis follows the hematogenous seeding of bacilli into the meninges and is associated with fever and meningismus. Plague pharyngitis follows inhalation or ingestion of plague bacilli and is associated with cervical lymphadenopathy.[21]

Plague Following Use of a Biological Weapon

The pathogenesis and clinical manifestations of plague following a biological attack would be notably different than naturally occurring plague. Inhaled aerosolized *Y pestis* bacilli would cause primary pneumonic plague. The time from exposure to aerosolized plague bacilli until development of first symptoms in humans and nonhuman primates has been found to be 1 to 6 days and most often, 2 to 4 days.[12,16,19,26] The first sign of illness would be expected to be fever with cough and dyspnea, sometimes with the production of bloody, watery, or less commonly, purulent sputum.[16,19,27] Prominent gastrointestinal symptoms, including nausea, vomiting, abdominal pain, and diarrhea, might be present.[24,25]

The ensuing clinical findings of primary pneumonic plague are similar to those of any severe rapidly progressive pneumonia and are quite similar to those of secondary pneumonic plague. Clinicopathological features may help distinguish primary from secondary pneumonic plague.[11] In contrast to secondary pneumonic plague, features of primary pneumonic plague would include absence of buboes (except, rarely, cervical buboes) and, on pathologic examination, pulmonary disease with areas of profound lobular exudation and bacillary aggregation.[11] Chest radiographic findings are variable but bilateral infiltrates or consolidation are common (FIGURE 3).[22]

Laboratory studies may reveal leukocytosis with toxic granulations, coagulation abnormalities, aminotransferase elevations, azotemia, and other evidence of multiorgan failure. All are nonspecific findings associated with sepsis and systemic inflammatory response syndrome.[11,21]

The time from respiratory exposure to death in humans is reported to have been between 2 to 6 days in epidemics during the preantibiotic era, with a mean of 2 to 4 days in most epidemics.[16]

DIAGNOSIS

Given the rarity of plague infection and the possibility that early cases are a harbinger of a larger epidemic, the first clinical or laboratory suspicion of plague must lead to immediate notification of the hospital epidemiologist or infection control practitioner, health department, and the local or state health laboratory. Definitive tests can thereby be arranged rapidly through a state reference laboratory or, as necessary, the Diagnostic and Reference Laboratory of the CDC and early interventions instituted.

The early diagnosis of plague requires a high index of suspicion in naturally occurring cases and even more so following the use of a biological weapon. There are no effective environmental warning systems to detect an aerosol of plague bacilli.[28]

The first indication of a clandestine terrorist attack with plague would most likely be a sudden outbreak of illness presenting as severe pneumonia and

sepsis. If there are only small numbers of cases, the possibility of them being plague may be at first overlooked given the clinical similarity to other bacterial or viral pneumonias and that few Western physicians have ever seen a case of pneumonic plague. However, the sudden appearance of a large number of previously healthy patients with fever, cough, shortness of breath, chest pain, and a fulminant course leading to death should immediately suggest the possibility of pneumonic plague or inhalational anthrax.[1] The presence of hemoptysis in this setting would strongly suggest plague (TABLE 1).[22]

Table 1. Diagnosis of Pneumonic Plague Infection Following Use of a Biological Weapon

Epidemiology and symptoms	Sudden appearance of many persons with fever, cough, shortness of breath, hemoptysis, and chest pain
	Gastrointestinal symptoms common (eg, nausea, vomiting, abdominal pain, and diarrhea)
	Patients have fulminant course and high mortality
Clinical signs	Tachypnea, dyspnea, and cyanosis
	Pneumonic consolidation on chest examination
	Sepsis, shock, and organ failure
	Infrequent presence of cervical bubo
	(Purpuric skin lesions and necrotic digits only in advanced disease)
Laboratory studies	Sputum, blood, or lymph node aspirate
	Gram-negative bacilli with bipolar (safety pin) staining on Wright, Giemsa, or Wayson stain
	Rapid diagnostic tests available only at some health departments, the Centers for Disease Control and Prevention, and military laboratories
	Pulmonary infiltrates or consolidation on chest radiograph
Pathology	Lobular exudation, bacillary aggregation, and areas of necrosis in pulmonary parenchyma

There are no widely available rapid diagnostic tests for plague.[28] Tests that would be used to confirm a suspected diagnosis—antigen detection, IgM enzyme immunoassay, immunostaining, and polymerase chain reaction—are available only at some state health departments, the CDC, and military laboratories.[21] The routinely used passive hemagglutination antibody detection assay is typically only of retrospective value since several days to weeks usually pass after disease onset before antibodies develop.

Microbiologic studies are important in the diagnosis of pneumonic plague. A Gram stain of sputum or blood may reveal gram-negative bacilli or coccobacilli.[4,21,29] A Wright, Giemsa, or Wayson stain will often show bipolar staining (Figure 1), and direct fluorescent antibody testing, if available, may be positive. In the unlikely event that a cervical bubo is present in pneumonic plague, an aspirate (obtained with a 20-gauge needle and a 10-mL syringe containing 1-2 mL of sterile saline for infusing the node) may be cultured and similarly stained (Table 1).[22]

Cultures of sputum, blood, or lymph node aspirate should demonstrate growth approximately 24 to 48 hours after inoculation. Most microbiology laboratories use either automated or semiautomated bacterial identification systems. Some of these systems may misidentify *Y pestis*.[12,30] In laboratories without automated bacterial identification, as many as 6 days may be required for identification, and there is some chance that the diagnosis may be missed entirely. Approaches for biochemical characterization of *Y pestis* are described in detail elsewhere.[20]

If a laboratory using automated or nonautomated techniques is notified that plague is suspected, it should split the culture: 1 culture incubated at 28°C for rapid growth and the second culture incubated at 37°C for identification of the diagnostic capsular (F_1) antigen. Using these methods, up to 72 hours may be required following specimen procurement to make the identification (May Chu, PhD, CDC, Fort Collins, Colo, written communication, April 9, 1999). Antibiotic susceptibility testing should be performed at a reference laboratory because of the lack of standardized susceptibility testing procedures for *Y pestis*. A process establishing criteria and training measures for laboratory diagnosis of this disease is being undertaken jointly by the Association of Public Health Laboratories and the CDC.

VACCINATION

The US-licensed formaldehyde-killed whole bacilli vaccine was discontinued by its manufacturers in 1999 and is no longer available. Plans for future licensure and production are unclear. This killed vaccine demonstrated efficacy in preventing or ameliorating bubonic disease, but it does not prevent or ameliorate the development of primary pneumonic plague.[19,31] It was used in special circumstances for individuals deemed to be at high risk of developing plague, such as military personnel working in plague endemic areas, microbiologists working with *Y pestis* in the laboratory, or researchers working with plague-infected rats or fleas. Research is ongoing in the pursuit of a vaccine that protects against primary pneumonic plague.[22,32]

THERAPY

Recommendations for the use of antibiotics following a plague biological weapon exposure are conditioned by the lack of published trials in treating plague in humans, limited number of studies in animals, and possible requirement to treat large numbers of persons. A number of possible therapeutic regimens for treating plague have yet to be adequately studied or submitted for approval to the Food and Drug Administration (FDA). For these reasons, the working group offers consensus recommendations based on the best available evidence. The recommendations do not necessarily represent uses currently approved by the FDA or an official position on the part of any of the federal agencies whose scientists participated in these discussions. Recommendations will need to be revised as further relevant information becomes available.

In the United States during the last 50 years, 4 of the 7 reported primary pneumonic plague patients died.[12] Fatality rates depend on various factors including time to initiation of antibiotics, access to advanced supportive care, and the dose of inhaled bacilli. The fatality rate of patients with pneumonic plague when treatment is delayed more than 24 hours after symptom onset is extremely high.[14,24,25,33]

Historically, the preferred treatment for plague infection has been streptomycin, an FDA-approved treatment for plague.[21,34,35] Administered early during the disease, streptomycin has reduced overall plague mortality to the 5% to 14% range.[12,21,34] However, streptomycin is infrequently used in the United States and only modest supplies are available.[35] Gentamicin is not FDA approved for the treatment of plague but has been used successfully[36-39] and is recommended as an acceptable alternative by experts.[23,40] In 1 case series, 8 patients with plague were treated with gentamicin with morbidity or mortality equivalent to that of patients treated with streptomycin (Lucy Boulanger, MD, Indian Health Services, Crown Point, NM, written communication, July 20, 1999). In vitro studies and an in vivo study in mice show equal or improved activity of gentamicin against many strains of *Y pestis* when compared with streptomycin.[41,42] In addition, gentamicin is widely available, inexpensive, and can be given once daily.[35]

Tetracycline and doxycycline also have been used in the treatment and prophylaxis of plague; both are FDA approved for these purposes. In vitro studies have shown that *Y pestis* susceptibility to tetracycline[43] and doxycycline[41,44] is equivalent to that of the aminoglycosides. In another investigation, 13% of *Y pestis* strains in Madagascar were found to have some in vitro resistance to tetracycline.[45] Experimental murine models of *Y pestis* infection have yielded data that are difficult to extrapolate to humans. Some mouse studies have shown doxycycline to be a highly efficacious treatment of infection[44,46] or prophylaxis[47] against naturally occurring plague strains. Experimental murine infection with F_1-deficient variants of *Y pestis* have shown decreased efficacy of doxycycline,[47,48] but only 1 human case of F_1-deficient plague infection has been reported.[49] Russell and colleagues[50] reported poor efficacy of doxycycline against plague-infected mice, but the dosing schedules used in this experiment would have failed to maintain drug levels above the minimum inhibitory concentration due to the short half-life of doxycycline in mice. In another study, doxycycline failed to prevent death in mice intraperitoneally infected with 29 to 290 000 times the median lethal inocula of *Y pestis*.[51]

There are no controlled clinical trials comparing either tetracycline or doxycycline to aminoglycoside in the treatment of plague, but anecdotal case series and a number of medical authorities support use of this class of antimicrobials for prophylaxis and for therapy in the event that streptomycin or gentamicin cannot be administered.[23,27,38-40,52-54] Based on evidence from in vitro studies, animal studies, and uncontrolled human data, the working group recommends that the tetracycline class of antibiotics be used to treat pneumonic plague if aminoglycoside therapy cannot be administered. This might be the case in a mass casualty scenario when parenteral therapy was either unavailable or impractical. Doxycycline would be considered pharmacologically superior to other antibiotics in the tetracycline class for this indication, because it is well absorbed without food interactions, is well distributed with good tissue penetration, and has a long half-life.[35]

The fluoroquinolone family of antimicrobials has demonstrated efficacy in animal studies. Ciprofloxacin has been demonstrated to be at least as efficacious as aminoglycosides and tetracyclines in studies of mice with experimentally induced pneumonic plague.[44,50,51] In vitro studies also suggest equivalent or greater activity of ciprofloxacin, levofloxacin, and ofloxacin against *Y pestis* when compared with aminoglycosides or tetracyclines.[41,55] However, there have been no trials of fluoroquinolones in human plague, and they are not FDA approved for this indication.

Chloramphenicol has been used to treat plague infection and has been recommended for treatment of plague meningitis because of its ability to cross the blood-brain barrier.[21,34] However, human clinical trials demonstrating the superiority of chloramphenicol in the therapy of classic plague infection or plague meningitis have not been performed. It has been associated with dose dependent hematologic abnormalities and with rare idiosyncratic fatal aplastic anemia.[35]

A number of different sulfonamides have been used successfully in the treatment of human plague infection: sulfathiazole,[56] sulfadiazine, sulfamerazine, and trimethoprim-sulfamethoxazole.[57,58] The 1970 WHO analysis reported that sulfadiazine reduced mortality for bubonic plague but was ineffective against pneumonic plague and was less effective than tetracycline overall.[59] In a study comparing trimethoprim-sulfamethoxazole with streptomycin, patients treated with trimethoprim-sulfamethoxazole had a longer median duration of fever and a higher incidence of complications.[58] Authorities have generally considered trimethoprim-sulfamethoxazole a second-tier choice.[21,23,34] Some have recommended sulfonamides only in the setting of pediatric prophylaxis.[22] No sulfonamides have been FDA approved for the treatment of plague.

Antimicrobials that have been shown to have poor or only modest efficacy in animal studies have included rifampin, aztreonam, ceftazidime, cefotetan, and cefazolin; these antibiotics should not be used.[42]

Antibiotic resistance patterns must also be considered in making treatment recommendations. Naturally occurring antibiotic resistance to the tetracycline class of drugs has occurred rarely.[4] Recently, a plasmid-mediated multidrug-resistant strain was isolated in Madagascar.[60] A report published by Russian scientists cited quinolone-resistant *Y pestis*.[61] There have been assertions that Russian scientists have en-

gineered multidrug-resistant strains of *Y pestis*,[8] although there is as yet no scientific publication confirming this.

Recommendations for Antibiotic Therapy

The working group treatment recommendations are based on literature reports on treatment of human disease, reports of studies in animal models, reports on in vitro susceptibility testing, and antibiotic safety. Should antibiotic susceptibility testing reveal resistance, proper antibiotic substitution would need to be made.

In a contained casualty setting, a situation in which a modest number of patients require treatment, the working group recommends parenteral antibiotic therapy (TABLE 2). Preferred parenteral forms of the antimicrobials streptomycin or gentamicin are recommended. However, in a mass casualty setting, intravenous or intramuscular therapy may not be possible for reasons of patient care logistics and/or exhaustion of equipment and antibiotic supplies, and parenteral therapy will need to be supplanted by oral therapy. In a mass casualty setting, the working group recommends oral therapy, preferably with doxycycline (or tetracycline) or ciprofloxacin (Table 2).

Patients with pneumonic plague will require substantial advanced medical supportive care in addition to antimicrobial therapy. Complications of gram-negative sepsis would be expected, including adult respiratory distress syndrome, disseminated intravascular coagulation, shock, and multiorgan failure.[23]

Once it was known or strongly suspected that pneumonic plague cases were occurring, anyone with fever or cough in the presumed area of exposure should be immediately treated with antimicrobials for presumptive pneumonic plague. Delaying therapy until confirmatory testing is performed would greatly decrease survival.[59] Clinical deterioration of patients despite early initiation of empiric therapy could signal antimicrobial resistance and should be promptly evaluated.

Table 2. Working Group Recommendations for Treatment of Patients With Pneumonic Plague in the Contained and Mass Casualty Settings and for Postexposure Prophylaxis*

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 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‡
	Chloramphenicol, 25 mg/kg IV 4 times daily§
Children‖	Preferred choices Streptomycin, 15 mg/kg IM twice daily (maximum daily dose, 2 g)
	Gentamicin, 2.5 mg/kg IM or IV 3 times daily†
	Alternative choices Doxycycline, If ≥45 kg, give adult dosage
	If <45 kg, give 2.2 mg/kg IV twice daily (maximum, 200 mg/d)
	Ciprofloxacin, 15 mg/kg IV twice daily‡
	Chloramphenicol, 25 mg/kg IV 4 times daily§
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 choice Doxycycline,†† If ≥45 kg, give adult dosage
	If <45 kg, then give 2.2 mg/kg orally twice daily
	Ciprofloxacin, 20 mg/kg orally twice daily
	Alternative choices 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 choices Chloramphenicol, 25 mg/kg orally 4 times daily§**

*These are consensus recommendations of the Working Group on Civilian Biodefense and are not necessarily approved by the Food and Drug Administration. See "Therapy" section for explanations. One antimicrobial agent should be selected. Therapy should be continued for 10 days. Oral therapy should be substituted when patient's condition improves. IM indicates intramuscularly; IV, intravenously.

†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 dosage should not exceed 1 g/d in children.

§Concentration should be maintained between 5 and 20 μg/mL. Concentrations greater than 25 μg/mL can cause reversible bone marrow suppression.[35,82]

‖Refer to "Management of Special Groups" for details. In children, ciprofloxacin dose should not exceed 1 g/d, chloramphenicol should not exceed 4 g/d. Children younger than 2 years should not receive chloramphenicol.

¶Refer to "Management of Special Groups" for details and for discussion of breastfeeding women. In neonates, gentamicin loading dose of 4 mg/kg should be given initially.[63]

#Duration of treatment of plague in mass casualty setting is 10 days. Duration of postexposure prophylaxis to prevent plague infection is 7 days.

**Children younger than 2 years should not receive chloramphenicol. Oral formulation available only outside the United States.

††Tetracycline could be substituted for doxycycline.

Management of Special Groups

Consensus recommendations for special groups as set forth in the following reflect the clinical and evidence-based judgments of the working group and do not necessarily correspond to FDA approved use, indications, or labeling.

Children. The treatment of choice for plague in children has been streptomycin or gentamicin.[21,40] If aminoglycosides are not available or cannot be used, recommendations for alternative antimicrobial treatment with efficacy against plague are conditioned by balancing risks associated with treatment against those posed by pneumonic plague. Children aged 8 years and older can be treated with tetracycline antibiotics safely.[35,40] However, in children younger than 8 years, tetracycline antibiotics may cause discolored teeth, and rare instances of retarded skeletal growth have been reported in infants.[35] Chloramphenicol is considered safe in children except for children younger than 2 years who are at risk of "gray baby syndrome."[35,40] Some concern exists that fluoroquinolone use in children may cause arthropathy,[35] although fluoroquinolones have been used to treat serious infections in children.[64] No comparative studies assessing efficacy or safety of alternative treatment strategies for plague in children has or can be performed.

Given these considerations, the working group recommends that children in the contained casualty setting receive streptomycin or gentamicin. In a mass casualty setting or for postexposure prophylaxis, we recommend that doxycycline be used. Alternatives are listed for both settings (Table 2). The working group assessment is that the potential benefits of these antimicrobials in the treating of pneumonic plague infection substantially outweigh the risks.

Pregnant Women. It has been recommended that aminoglycosides be avoided in pregnancy unless severe illness warrants,[35,65] but there is no more efficacious treatment for pneumonic plague. Therefore, the working group recommends that pregnant women in the contained casualty setting receive gentamicin (Table 2). Since streptomycin has been associated with rare reports of irreversible deafness in children following fetal exposure, this medication should be avoided if possible.[35] The tetracycline class of antibiotics has been associated with fetal toxicity including retarded skeletal growth,[35] although a large case-control study of doxycycline use in pregnancy showed no significant increase in teratogenic risk to the fetus.[66] Liver toxicity has been reported in pregnant women following large doses of intravenous tetracycline (no longer sold in the United States), but it has also been reported following oral administration of tetracycline to nonpregnant individuals.[35] Balancing the risks of pneumonic plague infection with those associated with doxycycline use in pregnancy, the working group recommends that doxycycline be used to treat pregnant women with pneumonic plague if gentamicin is not available.

Of the oral antibiotics historically used to treat plague, only trimethoprim-sulfamethoxazole has a category C pregnancy classification[65]; however, many experts do not recommend trimethoprim-sulfamethoxazole for treatment of pneumonic plague. Therefore, the working group recommends that pregnant women receive oral doxycycline for mass casualty treatment or postexposure prophylaxis. If the patient is unable to take doxycycline or the medication is unavailable, ciprofloxacin or other fluoroquinolones would be recommended in the mass casualty setting (Table 2).

The working group recommendation for treatment of breastfeeding women is to provide the mother and infant with the same antibiotic based on what is most safe and effective for the infant: gentamicin in the contained casualty setting and doxycycline in the mass casualty setting. Fluoroquinolones would be the recommended alternative (Table 2).

Immunosuppressed Persons. The antibiotic treatment or postexposure prophylaxis for pneumonic plague among those who are immunosuppressed has not been studied in human or animal models of pneumonic plague infection. Therefore, the consensus recommendation is to administer antibiotics according to the guidelines developed for immunocompetent adults and children.

POSTEXPOSURE PROPHYLAXIS RECOMMENDATIONS

The working group recommends that in a community experiencing a pneumonic plague epidemic, all persons developing a temperature of 38.5°C or higher or new cough should promptly begin parenteral antibiotic treatment. If the resources required to administer parenteral antibiotics are unavailable, oral antibiotics should be used according to the mass casualty recommendations (Table 2). For infants in this setting, tachypnea would also be an additional indication for immediate treatment.[29] Special measures would need to be initiated for treatment or prophylaxis of those who are either unaware of the outbreak or require special assistance, such as the homeless or mentally handicapped persons. Continuing surveillance of patients would be needed to identify individuals and communities at risk requiring postexposure prophylaxis.

Asymptomatic persons having household, hospital, or other close contact with persons with untreated pneumonic plague should receive postexposure antibiotic prophylaxis for 7 days[29] and watch for fever and cough. Close contact is defined as contact with a patient at less than 2 meters.[16,31] Tetracycline, doxycycline, sulfonamides, and chloramphenicol have each been used or recommended as postexposure prophylaxis in this setting.[16,22,29,31,59] Fluoroquinolones could also be used based on studies in mice.[51]

The working group recommends the use of doxycycline as the first choice antibiotic for postexposure prophylaxis; other recommended antibiotics are noted (Table 2). Contacts who develop fever or cough while receiving prophylaxis should seek prompt medical attention and begin antibiotic treatment as described in Table 2.

INFECTION CONTROL

Previous public health guidelines have advised strict isolation for all close contacts of patients with pneumonic plague who refuse prophylaxis.[29] In the modern setting, however, pneumonic plague has not spread widely or rapidly in a community,[4,14,24] and therefore isolation of close contacts refusing antibiotic prophylaxis is not recommended by the working group. Instead, persons refusing prophylaxis should be carefully watched for the development of fever or cough during the first 7 days after exposure and treated immediately should either occur.

Modern experience with person-to-person spread of pneumonic plague is limited; few data are available to make specific recommendations regarding appropriate infection control measures. The available evidence indicates that person-to-person transmission of pneumonic plague occurs via respiratory droplets; transmission by droplet nuclei has not been demonstrated.[14-17] In large pneumonic plague epidemics earlier this century, pneumonic plague transmission was prevented in close contacts by wearing masks.[14,16,17] Commensurate with this, existing national infection control guidelines recommend the use of disposable surgical masks to prevent the transmission of pneumonic plague.[29,67]

Given the available evidence, the working group recommends that, in addition to beginning antibiotic prophylaxis, persons living or working in close contact with patients with confirmed or suspect pneumonic plague that have had less than 48 hours of antimicrobial treatment should follow respiratory droplet precautions and wear a surgical mask. Further, the working group recommends avoidance of unnecessary close contact with patients with pneumonic plague until at least 48 hours of antibiotic therapy and clinical improvement has taken place. Other standard respiratory droplet precautions (gown, gloves, and eye protection) should be used as well.[29,31]

The patient should remain isolated during the first 48 hours of antibiotic therapy and until clinical improvement occurs.[29,31,59] If large numbers of patients make individual isolation impossible, patients with pneumonic plague may be cohorted while undergoing antibiotic therapy. Patients being transported should also wear surgical masks. Hospital rooms of patients with pneumonic plague should receive terminal cleaning in a manner consistent with standard precautions, and clothing or linens contaminated with body fluids of patients infected with plague should be disinfected as per hospital protocol.[29]

Microbiology laboratory personnel should be alerted when *Y pestis* is suspected. Four laboratory-acquired cases of plague have been reported in the United States.[68] Simple clinical materials and cultures should be processed in biosafety level 2 conditions.[31,69] Only during activities involving high potential for aerosol or droplet production (eg, centrifuging, grinding, vigorous shaking, and animal studies) are biosafety level 3 conditions necessary.[69]

Bodies of patients who have died following infection with plague should be handled with routine strict precautions.[29] Contact with the remains should be limited to trained personnel, and the safety precautions for transporting corpses for burial should be the same as those when transporting ill patients.[70] Aerosol-generating procedures, such as bone-sawing associated with surgery or postmortem examinations, would be associated with special risks of transmission and are not recommended. If such aerosol-generating procedures are necessary, then high-efficiency particulate air filtered masks and negative-pressure rooms should be used as would be customary in cases in which contagious biological aerosols, such as *Mycobacterium tuberculosis*, are deemed a possible risk.[71]

ENVIRONMENTAL DECONTAMINATION

There is no evidence to suggest that residual plague bacilli pose an environmental threat to the population following the dissolution of the primary aerosol. There is no spore form in the *Y pestis* life cycle, so it is far more susceptible to environmental conditions than sporulating bacteria such as *Bacillus anthracis*. Moreover, *Y pestis* is very sensitive to the action of sunlight and heating and does not survive long outside the host.[72] Although some reports suggest that the bacterium may survive in the soil for some time,[72] there is no evidence to suggest environmental risk to humans in this setting and thus no need for environmental decontamination of an area exposed to an aerosol of plague. In the WHO analysis, in a worst case scenario, a plague aerosol was estimated to be effective and infectious for as long as 1 hour.[7] In the setting of a clandestine release of plague bacilli, the aerosol would have dissipated long before the first case of pneumonic plague occurred.

ADDITIONAL RESEARCH

Improving the medical and public health response to an outbreak of plague following the use of a biological weapon will require additional knowledge of the organism, its genetics, and pathogenesis. In addition, improved rapid diagnostic and standard laboratory microbiology techniques are necessary. An improved understanding of prophylactic and therapeutic antibiotic regimens would be of benefit in defining optimal antibiotic strategy.

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CONSENSUS STATEMENT

Smallpox as a Biological Weapon
Medical and Public Health Management

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Objective To develop consensus-based recommendations for measures to be taken by medical and public health professionals following the use of smallpox as a biological weapon against a civilian population.

Participants The working group included 21 representatives from staff of major medical centers and research, government, military, public health, and emergency management institutions and agencies.

Evidence The first author (D.A.H.) conducted a literature search in conjunction with the preparation of another publication on smallpox as well as this article. The literature identified was reviewed and opinions were sought from experts in the diagnosis and management of smallpox, including members of the working group.

Consensus Process The first draft of the consensus statement was a synthesis of information obtained in the evidence-gathering process. Members of the working group provided formal written comments that were incorporated into the second draft of the statement. The working group reviewed the second draft on October 30, 1998. No significant disagreements existed and comments were incorporated into a third draft. The fourth and final statement incorporates all relevant evidence obtained by the literature search in conjunction with final consensus recommendations supported by all working group members.

Conclusions Specific recommendations are made regarding smallpox vaccination, therapy, postexposure isolation and infection control, hospital epidemiology and infection control, home care, decontamination of the environment, and additional research needs. In the event of an actual release of smallpox and subsequent epidemic, early detection, isolation of infected individuals, surveillance of contacts, and a focused selective vaccination program will be the essential items of an effective control program.

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THIS IS THE SECOND ARTICLE IN a series entitled *Medical and Public Health Management Following the Use of a Biological Weapon: Consensus Statements of the Working Group on Civilian Biodefense.*[1] The working group has identified a limited number of widely known organisms that could cause disease and deaths in sufficient numbers to cripple a city or region. Smallpox is one of the most serious of these diseases.

If used as a biological weapon, smallpox represents a serious threat to civilian populations because of its case-fatality rate of 30% or more among unvaccinated persons and the absence of specific therapy. Although smallpox has long been feared as the most devastating of all infectious diseases,[2] its potential for devastation today is far greater than at any previous time. Routine vaccination throughout the United States ceased more than 25 years ago. In a now highly susceptible, mobile population, smallpox would be able to spread widely and rapidly throughout this country and the world.

CONSENSUS METHODS

Members of the working group were selected by the chairman in consultation with principal agency heads in the Department of Health and Human Services (DHHS) and the US Army Medical Research Institute of Infectious Diseases (USAMRIID).

The first author (D.A.H.) conducted a literature search in conjunction with the preparation of another

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publication on smallpox[2] as well as this article. The literature was reviewed and opinions were sought from experts in the diagnosis and management of smallpox, including members of the working group.

The first draft of the working group's consensus statement was the result of synthesis of information obtained in the evidence-gathering process. Members of the working group were asked to make written comments on the first draft of the document in September 1998. Suggested revisions were incorporated into the second draft of the statement. The working group was convened to review the second draft of the statement on October 30, 1998. Consensus recommendations were made and no significant disagreements existed at the conclusion of this meeting. The third draft incorporated changes suggested at the conference and working group members had an additional opportunity to suggest final revisions. The final statement incorporates all relevant evidence obtained by the literature search in conjunction with final consensus recommendations supported by all working group members.

This article is intended to provide the scientific foundation and initial framework for the detailed planning that would follow a bioterrorist attack with smallpox. This planning must encompass coordinated systems approaches to bioterrorism, including public policies and consequence management by local and regional public and private institutions. The assessment and recommendations provided herein represent the best professional judgment of the working group at this time based on data and expertise currently available. The conclusions and recommendations need to be regularly reassessed as new information becomes available.

HISTORY AND POTENTIAL AS A BIOWEAPON

Smallpox probably was first used as a biological weapon during the French and Indian Wars (1754-1767) by British forces in North America.[3] Soldiers distributed blankets that had been used by smallpox patients with the intent of initiating outbreaks among American Indians. Epidemics occurred, killing more than 50% of many affected tribes. With Edward Jenner's demonstration in 1796 that an infection caused by cowpox protected against smallpox and the rapid diffusion worldwide of the practice of cowpox inoculation (ie, vaccination),[4] the potential threat of smallpox as a bioweapon was greatly diminished.

A global campaign, begun in 1967 under the aegis of the World Health Organization (WHO), succeeded in eradicating smallpox in 1977.[1] In 1980, the World Health Assembly recommended that all countries cease vaccination.[5] A WHO expert committee recommended that all laboratories destroy their stocks of variola virus or transfer them to 1 of 2 WHO reference laboratories—the Institute of Virus Preparations in Moscow, Russia, or the Centers for Disease Control and Prevention (CDC) in Atlanta, Ga. All countries reported compliance. The WHO committee later recommended that all virus stocks be destroyed in June 1999, and the 1996 World Health Assembly concurred.[6] In 1998, possible research uses for variola virus were reviewed by a committee of the Institute of Medicine (IOM).[7] The IOM committee concluded, as did the preceding WHO committee, that there were research questions that might be addressed if the virus were to be retained. However, the IOM committee did not explore the costs or relative priority to be assigned to such an effort, and that committee was not asked to weigh the possible benefits resulting from such research activities contrasted with the possible benefits resulting from an international decision to destroy all virus stocks. These considerations will be weighed and decided by the 1999 World Health Assembly.

Recent allegations from Ken Alibek, a former deputy director of the Soviet Union's civilian bioweapons program, have heightened concern that smallpox might be used as a bioweapon. Alibek[8] reported that beginning in 1980, the Soviet government embarked on a successful program to produce the smallpox virus in large quantities and adapt it for use in bombs and intercontinental ballistic missiles; the program had an industrial capacity capable of producing many tons of smallpox virus annually. Furthermore, Alibek reports that Russia even now has a research program that seeks to produce more virulent and contagious recombinant strains. Because financial support for laboratories in Russia has sharply declined in recent years, there are increasing concerns that existing expertise and equipment might fall into non-Russian hands.

The deliberate reintroduction of smallpox as an epidemic disease would be an international crime of unprecedented proportions, but it is now regarded as a possibility. An aerosol release of variola virus would disseminate widely, given the considerable stability of the orthopoxviruses in aerosol form[9] and the likelihood that the infectious dose is very small.[10] Moreover, during the 1960s and 1970s in Europe, when smallpox was imported during the December to April period of high transmission, as many as 10 to 20 second-generation cases were often infected from a single case. Widespread concern and, sometimes, panic occurred, even with outbreaks of fewer than 100 cases, resulting in extensive emergency control measures.[2]

EPIDEMIOLOGY

Smallpox was once worldwide in scope, and before vaccination was practiced, almost everyone eventually contracted the disease. There were 2 principal forms of the disease, variola major and a much milder form, variola minor (or alastrim). Before eradication took place, these forms could be differentiated clinically only when occurring in outbreaks; virological differentiation is now possible.[11,12] Through the end of the 19th century, variola major predominated throughout the world. However, at the turn of the century, variola minor was first detected in South Africa and later in Florida, from whence it spread

across the United States and into Latin America and Europe.[13] Typical variola major epidemics such as those that occurred in Asia resulted in case-fatality rates of 30% or higher among the unvaccinated, whereas variola minor case-fatality rates were customarily 1% or less.[2]

Smallpox spreads from person to person,[10,14] primarily by droplet nuclei or aerosols expelled from the oropharynx of infected persons and by direct contact. Contaminated clothing or bed linens can also spread the virus.[15] There are no known animal or insect reservoirs or vectors.

Historically, the rapidity of smallpox transmission throughout the population was generally slower than for such diseases as measles or chickenpox. Patients spread smallpox primarily to household members and friends; large outbreaks in schools, for example, were uncommon. This finding was accounted for in part by the fact that transmission of smallpox virus did not occur until onset of rash. By then, many patients had been confined to bed because of the high fever and malaise of the prodromal illness. Secondary cases were thus usually restricted to those who came into contact with patients, usually in the household or hospital.

The seasonal occurrence of smallpox was similar to that of chickenpox and measles—its incidence was highest during winter and early spring.[16] This pattern was consonant with the observation that the duration of survival of orthopoxviruses in the aerosolized form was inversely proportional to both temperature and humidity.[9] Likewise, when imported cases occurred in Europe, large outbreaks sometimes developed during the winter months, rarely during the summer.[17]

The patient was most infectious from onset of rash through the first 7 to 10 days of rash (FIGURE 1).[17,18] As scabs formed, infectivity waned rapidly. Although the scabs contained large amounts of viable virus, epidemiological and laboratory studies indicate that they were not especially infectious, presumably because the virions were bound tightly in the fibrin matrix.[19]

The age distribution of cases depended primarily on the degree of smallpox susceptibility in the population. In most areas, cases predominated among children because adults were protected by immunity induced by vaccination or previous smallpox infection. In rural areas that had seen little vaccination or smallpox, the age distribution of cases was similar to the age distribution of the population. The age distribution pattern of cases in the United States presumably would be such if smallpox were to occur now because vaccination immunity in the population has waned so substantially.

MICROBIOLOGY

Smallpox, a DNA virus, is a member of the genus orthopoxvirus.[20] The orthopoxviruses are among the largest and most complex of all viruses. The virion is characteristically a brick-shaped structure with a diameter of about 200 nm. Three other members of this genus (monkeypox, vaccinia, and cowpox) can also infect humans, causing cutaneous lesions, but only smallpox is readily transmitted from person to person.[2] Monkeypox, a zoonotic disease, presently is found only in tropical rain forest areas of central and western Africa and is not readily transmitted among humans.[21] Vaccinia and cowpox seldom spread from person to person.

PATHOGENESIS AND CLINICAL PRESENTATION

Natural infection occurs following implantation of the virus on the oropharyngeal or respiratory mucosa.[2] The infectious dose is unknown but is believed to be only a few virions.[10] After the migration of virus to and multiplication in regional lymph nodes, an asymptomatic viremia develops on about the third or fourth day, followed by multiplication of virus in the spleen, bone marrow, and lymph nodes. A secondary viremia begins on about the eighth day and is followed by fever and toxemia. The virus, contained in leukocytes, then localizes in small blood vessels of the dermis and beneath the oral and pharyngeal mucosa and subsequently infects adjacent cells.

At the end of the 12- to 14-day incubation period (range, 7-17 days), the patient typically experiences high fever, malaise, and prostration with headache and backache.[2] Severe abdominal pain and delirium are sometimes present. A maculopapular rash then appears on the mucosa of the mouth and pharynx, face, and forearms, and spreads to the trunk and legs (FIGURE 2).[2] Within 1 to 2 days, the rash becomes vesicular and, later, pustu-

Figure 1. Typical Temperature Chart of Patient With Smallpox Infection

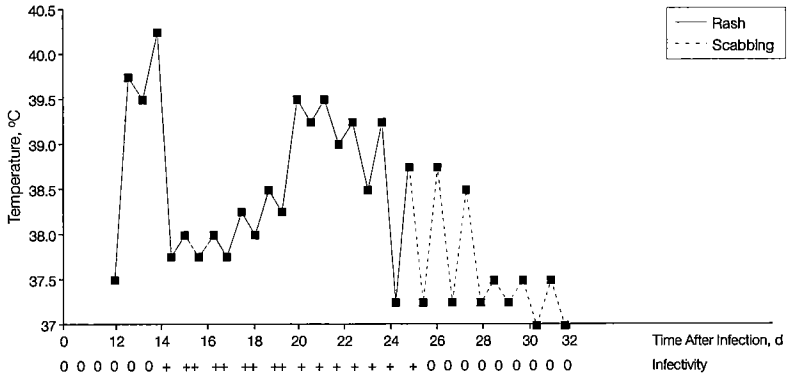


Chart shows approximate time of appearance, evolution of the rash, and magnitude of infectivity relative to the number of days after acquisition of infection.[3,26,29]

lar. The pustules are characteristically round, tense, and deeply embedded in the dermis; crusts begin to form on about the eighth or ninth day of rash. As the patient recovers, the scabs separate and characteristic pitted scarring gradually develops. The scars are most evident on the face and result from the destruction of sebaceous glands followed by shrinking of granulation tissue and fibrosis.[2]

The lesions that first appear in the mouth and pharynx ulcerate quickly because of the absence of a stratum corneum, releasing large amounts of virus into the saliva.[22] Virus titers in saliva are highest during the first week of illness, corresponding with the period during which patients are most infectious. Although the virus in some instances can be detected in swabs taken from the oropharynx as many as 5 to 6 days before the rash develops,[22] transmission does not occur during this period.

Except for the lesions in the skin and mucous membranes and reticulum cell hyperplasia, other organs are seldom involved. Secondary bacterial infection is not common, and death, which usually occurs during the second week of illness, most likely results from the toxemia associated with circulating immune complexes and soluble variola antigens.[2] Encephalitis sometimes ensues that is indistinguishable from the acute perivascular demyelination observed as a complication of infection due to vaccinia, measles, or varicella.[23]

Neutralizing antibodies can be detected by the sixth day of rash and remain at high titers for many years.[24] Hemagglutinin-inhibiting antibodies can be detected on about the sixth day of rash, or about 21 days after infection, and complement-fixing antibodies appear approximately 2 days later. Within 5 years, hemagglutinin-inhibiting antibodies decline to low levels and complement-fixing antibodies rarely persist for longer than 6 months.[2]

Although at least 90% of smallpox cases are clinically characteristic and readily diagnosed in endemic areas, 2 other forms of smallpox are difficult to recognize—hemorrhagic and malignant. Hemorrhagic cases are uniformly fatal and occur among all ages and in both sexes, but pregnant women appear to be unusually susceptible. Illness usually begins with a somewhat shorter incubation period and is characterized by a severely prostrating prodromal illness with high fever and head, back, and abdominal pain. Soon thereafter, a dusky erythema develops, followed by petechiae and frank hemorrhages into the skin and mucous membranes. Death usually occurs by the fifth or sixth day after onset of rash.[23]

In the frequently fatal malignant form, the abrupt onset and prostrating constitutional symptoms are similar. The confluent lesions develop slowly, never progressing to the pustular stage but remaining soft, flattened, and velvety to the touch. The skin has the appearance of a fine-grained, reddish-colored crepe rubber, sometimes with hemorrhages. If the patient survives, the lesions gradually disappear without forming scabs or, in severe cases, large amounts of epidermis might peel away.[23]

The illness associated with variola minor is generally less severe, with fewer constitutional symptoms and a more sparse rash.[25] A milder form of disease is also seen among those who have residual immunity from previous vaccination. In partially immune persons, the rash tends to be atypical and more scant and the evolution of the lesions more rapid.[15]

There is little information about how individuals with different types of immune deficiency responded to natural smallpox infection. Smallpox was eradicated before human immunodeficiency virus (HIV) was identified and

Figure 2. Typical Case of Smallpox Infection in a Child

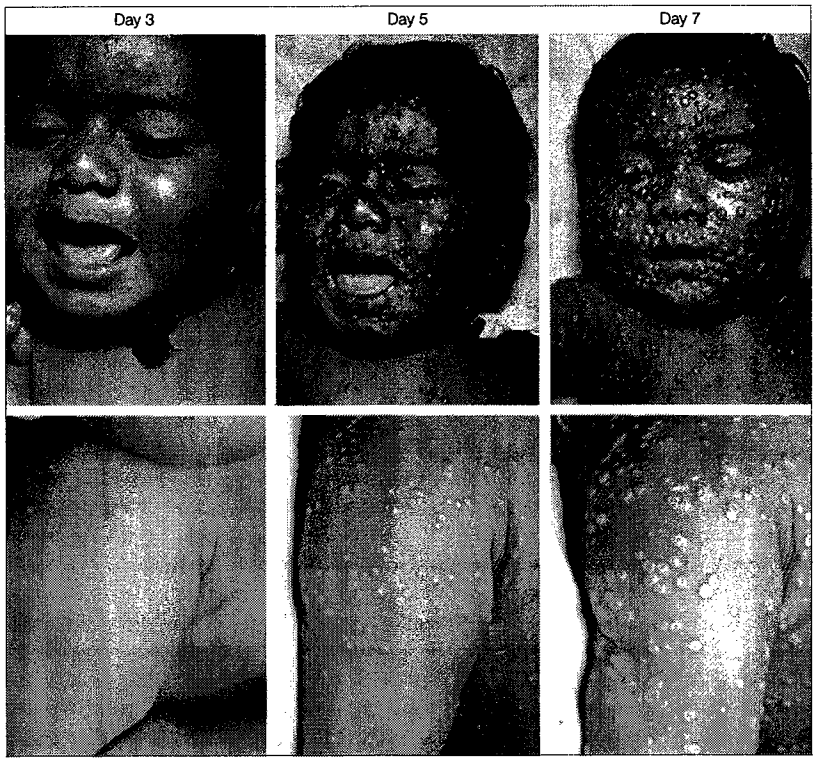


Figure shows the appearance of the rash at days 3, 5, and 7 of evolution. Note that lesions are more dense on the face and extremities than on the trunk; that they appear on the palms of the hand; and that they are similar in appearance to each other. If this were a case of chickenpox, one would expect to see, in any area, macules, papules, pustules, and lesions with scabs. Reproduced with permission from the World Health Organization.[2]

before suitable techniques became available for measuring cell-mediated immunity. However, it is probable that the underlying cause of some cases of malignant and hemorrhagic smallpox resulted from defective immune responses. Vaccination of immune-deficient persons sometimes resulted in a continually spreading primary lesion, persistent viremia, and secondary viral infection of many organs. One such case is documented to have occurred in a vaccinated soldier who had HIV infection.[26]

DIAGNOSIS

The discovery of a single suspected case of smallpox must be treated as an international health emergency and be brought immediately to the attention of national officials through local and state health authorities.

The majority of smallpox cases present with a characteristic rash that is centrifugal in distribution, ie, most dense on the face and extremities. The lesions appear during a 1- to 2-day period and evolve at the same rate. On any given part of the body, they are generally at the same stage of development. In varicella (chickenpox), the disease most frequently confused with smallpox, new lesions appear in crops every few days and lesions at very different stages of maturation (ie, vesicles, pustules, and scabs) are found in adjacent areas of skin. Varicella lesions are much more superficial and are almost never found on the palms and soles. The distribution of varicella lesions is centripetal, with a greater concentration of lesions on the trunk than on the face and extremities.

The signs and symptoms of both hemorrhagic and malignant smallpox were such that smallpox was seldom suspected until more typical cases were seen and it was recognized that a smallpox outbreak was in progress. Hemorrhagic cases were most often initially identified as meningococcemia or severe acute leukemia. Malignant cases likewise posed diagnostic problems, most often being mistaken for hemorrhagic chickenpox or prompting surgery because of severe abdominal pain.

Laboratory confirmation of the diagnosis in a smallpox outbreak is important. Specimens should be collected by someone who has recently been vaccinated (or is vaccinated that day) and who wears gloves and a mask. To obtain vesicular or pustular fluid, it is often necessary to open lesions with the blunt edge of a scalpel. The fluid can then be harvested on a cotton swab. Scabs can be picked off with forceps. Specimens should be deposited in a vacutainer tube that should be sealed with adhesive tape at the juncture of stopper and tube. This tube, in turn, should be enclosed in a second durable, watertight container. State or local health department laboratories should immediately be contacted regarding the shipping of specimens. Laboratory examination requires high-containment (BL-4) facilities and should be undertaken only in designated laboratories with the appropriate training and equipment. Once it is established that the epidemic is caused by smallpox virus, clinically typical cases would not require further laboratory confirmation.

Smallpox infection can be rapidly confirmed in the laboratory by electron microscopic examination of vesicular or pustular fluid or scabs. Although all orthopoxviruses exhibit identically appearing brick-shaped virions, history taking and clinical picture readily identify cowpox and vaccinia. Although smallpox and monkeypox virions may be indistinguishable, naturally occurring monkeypox is found only in tropical rain forest areas of Africa. Definitive laboratory identification and characterization of the virus involves growth of the virus in cell culture or on chorioallantoic egg membrane and characterization of strains by use of various biologic assays, including polymerase chain reaction techniques and restriction fragment-length polymorphisms.[27-29] The latter studies can be completed within a few hours.

PREEXPOSURE PREVENTIVE VACCINATION

Before 1972, smallpox vaccination was recommended for all US children at age 1 year. Most states required that each child be vaccinated before school entry. The only other requirement for vaccination was for military recruits and tourists visiting foreign countries. Most countries required that the individual be successfully vaccinated within a 3-year period prior to entering the country. Routine vaccination in the United States stopped in 1972 and since then, few persons younger than 27 years have been vaccinated. The US Census Bureau reported that in 1998, approximately 114 million persons, or 42% of the US population, were aged 29 years or younger.[30]

In addition, the immune status of those who were vaccinated more than 27 years ago is not clear. The duration of immunity, based on the experience of naturally exposed susceptible persons, has never been satisfactorily measured. Neutralizing antibodies are reported to reflect levels of protection, although this has not been validated in the field. These antibodies have been shown to decline substantially during a 5- to 10-year period.[24] Thus, even those who received the recommended single-dose vaccination as children do not have lifelong immunity. However, among a group who had been vaccinated at birth and at ages 8 and 18 years as part of a study, neutralizing antibody levels remained stable during a 30-year period.[31] Because comparatively few persons today have been successfully vaccinated on more than 1 occasion, it must be assumed that the population at large is highly susceptible to infection.

In the United States, a limited reserve supply of vaccine that was produced by Wyeth Laboratories, Lancaster, Pa, in the 1970s is in storage. This supply is believed to be sufficient to vaccinate between 6 and 7 million persons. This vaccine, now under the control of the CDC, consists of vaccine virus (New York Board of Health strain) grown on scarified calves. After purification, it was freeze-dried in rubber-stoppered vials that contain sufficient vaccine for at least 50 doses when a bifurcated needle is used. It is stored at −20°C (James LeDuc, PhD, oral communication, 1998). Although quantities of vaccine have also been retained

by a number of other countries, none have reserves large enough to meet more than their own potential emergency needs. WHO has 500 000 doses.[32]

There are no manufacturers now equipped to produce smallpox vaccine in large quantities. The development and licensure of a tissue cell culture vaccine and the establishment of a new vaccine production facility is estimated to require at least 36 months (Thomas Monath, MD, unpublished data, 1999).

Because of the small amounts of vaccine available, a preventive vaccination program to protect individuals such as emergency and health care personnel is not an option at this time. When additional supplies of vaccine are procured, a decision to undertake preventive vaccination of some portion of the population will have to weigh the relative risk of vaccination complications against the threat of contracting smallpox.

A further deterrent to extensive vaccination is the fact that presently available supplies of vaccinia immune globulin (VIG), also maintained by the CDC, are very limited in quantity. The working group recommends VIG for the treatment of severe cutaneous reactions occurring as a complication of vaccination.[33,34] Vaccinia immune globulin has also been given along with vaccination to protect those who needed vaccination but who were at risk of experiencing vaccine-related complications.[33] It has been estimated that if 1 million persons were vaccinated, as many as 250 persons would experience adverse reactions of a type that would require administration of VIG (James LeDuc, PhD, oral communication, 1998). How much VIG would be needed to administer with vaccine to those at risk is unknown.

POSTEXPOSURE THERAPY

At this time, the best that can be offered to the patient infected with smallpox is supportive therapy plus antibiotics as indicated for treatment of occasional secondary bacterial infections. No antiviral substances have yet proved effective for the treatment of smallpox, and the working group is not aware of any reports that suggest any antiviral product is therapeutic. Encouraging initial reports in the 1960s describing the therapeutic benefits of the thiosemicarbazones, cytosine arabinoside, and adenine arabinoside proved questionable on further study.[21,35,36]

Recent studies on tissue culture, mice, and a small number of monkeys have suggested the possibility that cidofovir, a nucleoside analog DNA polymerase inhibitor, might prove useful in preventing smallpox infection if administered within 1 or 2 days after exposure (John Huggins, PhD, oral communication, 1998). At this time, there is no evidence that cidofovir is more effective than vaccination in this early period. Moreover, the potential utility of this drug is limited, given the fact that it must be administered intravenously and its use is often accompanied by serious renal toxicity.[37]

POSTEXPOSURE INFECTION CONTROL

A smallpox outbreak poses difficult public health problems because of the ability of the virus to continue to spread throughout the population unless checked by vaccination and/or isolation of patients and their close contacts.

A clandestine aerosol release of smallpox, even if it infected only 50 to 100 persons to produce the first generation of cases, would rapidly spread in a now highly susceptible population, expanding by a factor of 10 to 20 times or more with each generation of cases.[2,10,38] Between the time of an aerosol release of smallpox virus and diagnosis of the first cases, an interval as long as 2 weeks or more is apt to occur because of the average incubation period of 12 to 14 days and the lapse of several additional days before a rash was sufficiently distinct to suggest the diagnosis of smallpox. By that time, there would be no risk of further environmental exposure from the original aerosol release because the virus is fully inactivated within 2 days.

As soon as the diagnosis of smallpox is made, all individuals in whom smallpox is suspected should be isolated immediately and all household and other face-to-face contacts should be vaccinated and placed under surveillance. Because the widespread dissemination of smallpox virus by aerosol poses a serious threat in hospitals, patients should be isolated in the home or other nonhospital facility whenever possible. Home care for most patients is a reasonable approach, given the fact that little can be done for a patient other than to offer supportive therapy.

In the event of an aerosol release of smallpox and a subsequent outbreak, the rationale for vaccinating patients suspected to have smallpox at this time is to ensure that some with a mistaken diagnosis are not placed at risk of acquiring smallpox. Vaccination administered within the first few days after exposure and perhaps as late as 4 days may prevent or significantly ameliorate subsequent illness.[39] An emergency vaccination program is also indicated that would include all health care workers at clinics or hospitals that might receive patients; all other essential disaster response personnel, such as police, firefighters, transit workers, public health staff, and emergency management staff; and mortuary staff who might have to handle bodies. The working group recommends that all such personnel for whom vaccination is not contraindicated should be vaccinated immediately irrespective of prior vaccination status.

Vaccination administered within 4 days of first exposure has been shown to offer some protection against acquiring infection and significant protection against a fatal outcome.[15] Those who have been vaccinated at some time in the past will normally exhibit an accelerated immune response. Thus, it would be prudent, when possible, to assign those who had been previously vaccinated to duties involving close patient contact.

It is important that discretion be used in identifying contacts of patients to ensure, to the extent that is possible, that vaccination and adequate surveillance measures are focused on those at great-

est risk. Specifically, it is recommended that *contacts* be defined as persons who have been in the same household as the infected individual or who have been in face-to-face contact with the patient after the onset of fever. Experience during the smallpox global eradication program showed that patients did not transmit infection until after the prodromal fever had given way to the rash stage of illness.[17,18]

Isolation of all contacts of exposed patients would be logistically difficult and, in practice, should not be necessary. Because contacts, even if infected, are not contagious until onset of rash, a practical strategy calls for all contacts to have temperatures checked at least once each day, preferably in the evening. Any increase in temperature higher than 38°C (101°F) during the 17-day period following last exposure to the case would suggest the possible development of smallpox[2] and be cause for isolating the patient immediately, preferably at home, until it could be determined clinically and/or by laboratory examination whether the contact had smallpox. All close contacts of the patients should be promptly vaccinated.

Although cooperation by most patients and contacts in observing isolation could be ensured through counseling and persuasion, there may be some for whom forcible quarantine will be required. Some states and cities in the United States, but not all, confer broad discretionary powers on health authorities to ensure the safety of the public's health and, at one time, this included powers to quarantine. Under epidemic circumstances, this could be an important power to have. Thus, each state and city should review its statutes as part of its preparedness activities.

During the smallpox epidemics in the 1960s and 1970s in Europe, there was considerable public alarm whenever outbreaks occurred and, often, a demand for mass vaccination throughout a very widespread area, even when the vaccination coverage of the population was high.[2] In the United States, where few people now have protective levels of immunity, such levels of concern must be anticipated. However, the US vaccine supply is limited at present; thus, vaccine would have to be carefully conserved and used in conjunction with measures to implement rapid isolation of smallpox patients.

HOSPITAL EPIDEMIOLOGY AND INFECTION CONTROL

Smallpox transmission within hospitals has long been recognized as a serious problem. For this reason, separate hospitals for smallpox patients were used for more than 200 years. Throughout the 1970s, both England and Germany had fully equipped standby hospitals in case smallpox should be imported.[2] Infections acquired in hospitals may occur as the result of droplets spread from patients to staff and visitors in reasonably close contact or by a fine particle aerosol. In 1 such occurrence in Germany, a smallpox patient with a cough, although isolated in a single room, infected persons on 3 floors of a hospital.[10] Persons with the usually fatal hemorrhagic or malignant forms of the disease pose a special problem because they often remain undiagnosed until they are near death and extremely contagious. A number of outbreaks have occurred in laundry workers who handled linens and blankets used by patients.[15] The working group recommends that in an outbreak setting, all hospital employees as well as patients in the hospital be vaccinated. For individuals who are immunocompromised or for whom vaccination is otherwise contraindicated, VIG should be provided, if available. If it is not available, a judgment will have to be made regarding the relative risks of acquiring the disease in contrast with the risks associated with vaccination.

In the event of a limited outbreak with few cases, patients should be admitted to the hospital and confined to rooms that are under negative pressure and equipped with high-efficiency particulate air filtration. In larger outbreaks, home isolation and care should be the objective for most patients. However, not all will be able to be so accommodated and, to limit nosocomial infections, authorities should consider the possibility of designating a specific hospital or hospitals for smallpox care. All persons isolated as such and those caring for them should be immediately vaccinated. Employees for whom vaccination is contraindicated should be furloughed.

Standard precautions using gloves, gowns, and masks should be observed. All laundry and waste should be placed in biohazard bags and autoclaved before being laundered or incinerated. A special protocol should be developed for decontaminating rooms after they are vacated by patients (see "Decontamination" section).

Laboratory examination requires high-containment (BL-4) facilities and should be undertaken only in designated laboratories with the appropriate trained personnel and equipment. Specific recommendations for safe specimen transport are described in the section on "Differential Diagnosis and Diagnostic Tests."

Protecting against the explosive spread of virus from the hemorrhagic or malignant case is difficult. Such cases occurring during the course of an outbreak may be detected if staff is alert to the possibility that any severe, acute, prostrating illness must be considered smallpox until proven otherwise.

Patients who die of smallpox should be cremated whenever possible and mortuary workers should be vaccinated.

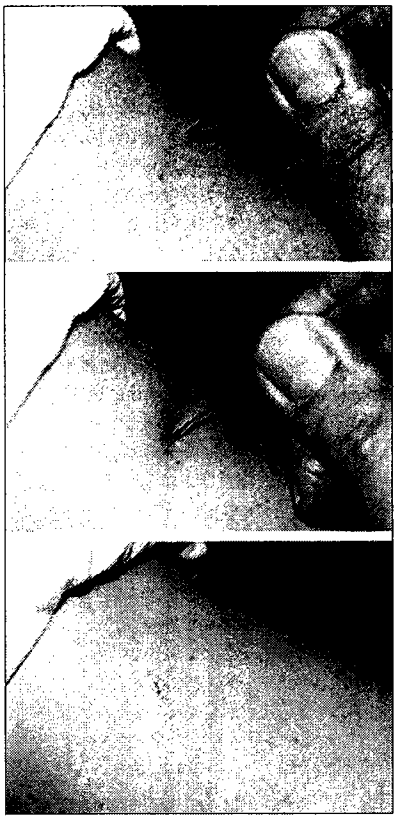
VACCINE ADMINISTRATION AND COMPLICATIONS

Smallpox vaccine is currently approved by the US Food and Drug Administration (FDA) for use only in persons in special-risk categories, including laboratory workers directly involved with smallpox or closely related orthopoxviruses. Under epidemic circumstances, widespread vaccination would be indicated, as recommended by the working group.

Vaccination has been successfully and safely administered to persons of all ages, from birth onward.[40] However, there are certain groups for whom elective vaccination has not been recommended be-

cause of the risk of complications. Under epidemic circumstances, however, such contraindications will have to be weighed against the grave risks posed by smallpox. If available, VIG can be administered concomitantly with vaccination to minimize the risk of complications in these persons.

Figure 3. Vaccination With the Bifurcated Needle



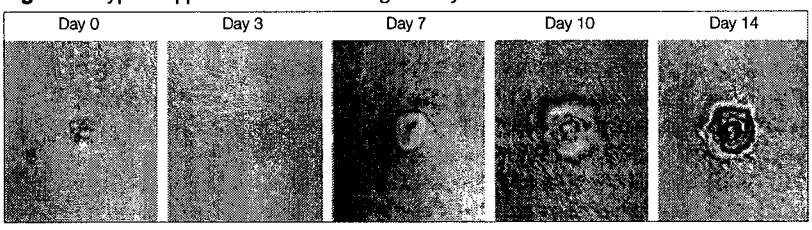
The requisite amount of reconstituted vaccine is held between the prongs of the needle and vaccination is done by multiple punctures; 15 strokes, at right angles to the skin over the deltoid muscle, are rapidly made within an area of about 5 mm in diameter.

Vaccination is normally performed using the bifurcated needle (FIGURE 3). A sterile needle is inserted into an ampoule of reconstituted vaccine and, on withdrawal, a droplet of vaccine sufficient for vaccination is held by capillarity between the 2 tines. The needle is held at right angles to the skin; the wrist of the vaccinator rests against the arm. Fifteen perpendicular strokes of the needle are rapidly made in an area of about 5 mm in diameter.[41,42] The strokes should be sufficiently vigorous so that a trace of blood appears at the vaccination site after 15 to 30 seconds. After vaccination, excess vaccine should be wiped from the site with gauze that should be discarded in a hazardous waste receptacle. The site should be covered with a loose, nonocclusive bandage to deter the individual from touching the site and perhaps transferring virus to other parts of the body.

After about 3 days, a red papule appears at the vaccination site and becomes vesicular on about the fifth day (FIGURE 4). By the seventh day, it becomes the typical Jennerian pustule—whitish, umbilicated, multilocular, containing turbid lymph and surrounded by an erythematous areola that may continue to expand for 3 more days. Regional lymphadenopathy and fever is not uncommon. As many as 70% of children have 1 or more days of temperature higher than 39°C (100°F) between days 4 and 14.[43] The pustule gradually dries, leaving a dark crust, which normally falls off after about 3 weeks.

A successful vaccination for those with partial immunity may manifest a gradient of responses. These range from what appears to be a primary take (as described herein) to an accelerated reaction in which there may be little more than a papule surrounded by erythema that reaches a peak between 3 and 7 days. A response that reaches a peak in erythema within 48 hours represents a hypersensitivity reaction and does not signify that growth of the vaccinia virus has occurred.[2] Persons exhibiting such a reaction should be revaccinated.

Figure 4. Typical Appearance of an Evolving Primary Vaccination Take



Reproduced with permission from the Centers for Disease Control and Prevention.[3]

Complications

The frequency of complications associated with use of the New York Board of Health strain (the strain used throughout the United States and Canada for vaccine) is the lowest for any established vaccinia virus strain, but the risks are not inconsequential.[44,45] Data on complications gathered by the CDC in 1968 are shown in TABLE 1. Complications occurred most frequently among primary vaccinees.

Postvaccinial Encephalitis. Postvaccinial encephalitis occurred at a rate of 1 case per 300 000 vaccinations and was observed only in primary vaccinees; one fourth of these cases were fatal and several had permanent neurological residua. Between 8 and 15 days after vaccination, encephalitic symptoms developed—fever, headache, vomiting, drowsiness, and, sometimes, spastic paralysis, meningitic signs, coma, and convulsions. Cerebrospinal fluid usually showed a pleocytosis. Recovery was either complete or associated with residual paralysis and other central nervous system symptoms and, sometimes, death. There was no treatment.

Progressive Vaccinia (Vaccinia Gangrenosa). Cases of progressive vaccinia occurred both among primary vaccinees and revaccinees. It was a frequently fatal complication among those with immune deficiency disorders. The vaccinial lesion failed to heal and progressed to involve adjacent skin with necrosis of tissue, spreading to other parts of the skin, to bones, and to viscera. Vaccinia immune globulin was used for this problem.[34,46] One case in a soldier with acquired immunodeficiency syndrome was successfully

treated with VIG and ribavirin. These treatment strategies were off-label and would be considered experimental.[26]

Eczema Vaccinatum. A sometimes serious complication, eczema vaccinatum occurred in some vaccinees and contacts with either active or healed eczema. Vaccinial skin lesions extended to cover all or most of the area once or currently afflicted with eczema. Vaccinia immune globulin was therapeutic.[46]

Generalized Vaccinia. A secondary eruption almost always following primary vaccination, generalized vaccinia resulted from blood-borne dissemination of virus. Lesions emerged between 6 and 9 days after vaccination and were either few in number or generalized. This complication was usually self-limited. In severe cases, VIG was indicated.[46]

Inadvertent Inoculation. Transmission to close contacts or autoinoculation to sites such as face, eyelid, mouth, and genitalia sometimes occurred. Most lesions healed without incident, although VIG was useful in some cases of periocular implantation.

Miscellaneous. Many different rashes have been associated with vaccination. Most common are erythema multiforme and variously distributed urticarial, maculopapular, and blotchy erythematous eruptions, which normally clear without therapy.

Groups at Special Risk for Complications

Consensus recommendations for special-risk groups as set forth herein reflect the best clinical and science-based judgment of the working group and do not necessarily correspond to FDA-approved uses.

Five groups of persons are ordinarily considered at special risk of smallpox vaccine complications: (1) persons with eczema or other significant exfoliative skin conditions; (2) patients with leukemia, lymphoma, or generalized malignancy who are receiving therapy with alkylating agents, antimetabolites, radiation, or large doses of corticosteroids; (3) patients with HIV infection; (4) persons with hereditary immune deficiency disorders; and (5) pregnant women. If persons with contraindications have been in close contact with a smallpox patient or the individual is at risk for occupational reasons, VIG, if available, may be given simultaneously with vaccination in a dose of 0.3 mL/kg of body weight to prevent complications. This does not alter vaccine efficacy. If VIG is not available, vaccine administration may still be warranted, given the far higher risk of an adverse outcome from smallpox infection than from vaccination.

VIG Therapy for Complications

Vaccinia immune globulin is valuable in treating patients with progressive vaccinia, eczema vaccinatum, severe generalized vaccinia, and periocular infections resulting from inadvertent inoculation. It is administered intramuscularly in a dose of 0.6 mL/kg of body weight. Because the dose is large (eg, 42 mL for a person weighing 70 kg), the product is given intramuscularly in divided doses over a 24- to 36-hour period and may be repeated, if necessary, after 2 to 3 days if improvement is not occurring.[47] Because the availability of VIG is so limited, its use should be reserved for the most serious cases. Vaccinia immune globulin, as well as vaccinia vaccine, is made available by the CDC through state health departments. Consultative assistance in the diagnosis and management of patients with complications can be obtained through state health departments.

DECONTAMINATION

Vaccinia virus, if released as an aerosol and not exposed to UV light, may persist for as long as 24 hours or somewhat longer under favorable conditions.[9] It is believed that variola virus would exhibit similar properties. However, by the time patients had become ill and it had been determined that an aerosol release of smallpox virus had occurred, there would be no viable smallpox virus in the environment. Vaccinia virus, if released as an aerosol, is almost completely destroyed within 6 hours in an atmosphere of high temperature (31°C-33°C) and humidity (80%) (TABLE 2).[9] In cooler temperatures (10°C-11°C) and lower humidity (20%), nearly two thirds of a vaccinia aerosol survives for as long as 24 hours.[9] It is believed that variola would behave similarly.

The occurrence of smallpox infection among personnel who handled laundry from infected patients is well documented[15] and it is believed that virus in such material remains viable for extended periods. Thus, special precautions need to be taken to ensure that all bedding and clothing of smallpox patients is autoclaved or laundered in hot water to which bleach has been added. Disinfectants that are used for standard hospital infection control, such as

Table 1. Complications of Smallpox Vaccination in the United States for 1968—Centers for Disease Control and Prevention National Survey[45]

Vaccination Status, Age, y	Estimated No. of Vaccinations	No. of Cases						
		Postvaccinial Encephalitis*	Progressive Vaccinia*	Eczema Vaccinatum*	Generalized Vaccinia	Accidental Infection	Other	Total
Primary vaccination†	5 594 000	16 (4)	5 (2)	58	131	142	66	418
Revaccination	8 574 000	0	6 (2)	8	10	7	9	40
Contacts	. . .‡	0	0	60 (1)	2	44	8	114
Total	**14 168 000**	**16 (4)**	**11 (4)**	**126 (1)**	**143**	**193**	**83**	**572**

*Data in parentheses indicate number of deaths attributable to vaccination.
†Data include 31 patients with unknown vaccination status.
‡Ellipses indicate contacts were not vaccinated.

hypochlorite and quaternary ammonia, are effective for cleaning surfaces possibly contaminated with virus.

Virus in scabs is more durable. At a temperature of 35°C and 65% relative humidity, the virus has persisted for 3 weeks.[48] At cooler temperatures (26°C), the virus has survived for 8 weeks at high relative humidity and 12 weeks at a relative humidity less than 10%.[48] Dutch investigators demonstrated that it was possible to isolate variola virus from scabs that had been sitting on a shelf for 13 years.[49] It is unlikely, however, that the smallpox virus, bound in the fibrin matrix of a scab, is infectious in humans. This is borne out by studies conducted during the eradication program and by surveillance for cases in newly smallpox-free areas.[2] It was reasoned that if the virus were able to persist in nature and infect humans, there would be cases occurring for which no source could be identified. Cases of this type were not observed. Rather, when cases were found, there were antecedent human cases with whom they had direct contact.

RESEARCH

Priority should be directed to 3 areas of smallpox research: vaccines, immunotherapy and drugs, and diagnostics.

The working group recommends that an emergency stockpile of at least 40 million doses of vaccine and a standby manufacturing capacity to produce more is a critical need. At a minimum, this quantity of vaccine would be needed in the control of an epidemic during the first 4 to 8 weeks after an attack. Smallpox vaccine, contained in glass-sealed ampoules and stored at −20°C, retains its potency almost indefinitely. However, several steps are necessary before manufacturing can begin. The traditional method for producing vaccine on the scarified flank of a calf is no longer acceptable because the product inevitably contains some microbial contaminants, however stringent the purification measures. Contemporary vaccines require the use of tissue cell cultures. Thus, as a first step, the traditional New York Board of Health strain needs to be grown in a suitable tissue cell culture and comparative studies performed of the reactogenicity and immunogenicity of calf-derived and tissue cell culture vaccines. This should be a comparatively straightforward exercise. The cost of such a stockpile should be comparatively modest because the vaccine would be packaged in 50-dose rather than costly single-dose containers. In the mid-1970s, 40 million doses would have cost less than $5 million (D.A.H., unpublished data, 1975).

The frequency of vaccine complications is sufficiently great to recommend development, if possible, of a more attenuated strain that, hopefully, would retain full efficacy. Development of an entirely new, genetically engineered strain would be both costly and time consuming. Moreover, it would be difficult at this time to justify its use in large numbers of human subjects to evaluate safety. There is, however, a candidate attenuated strain that was developed and field tested in Japan in the mid-1970s (a Lister strain–derived vaccine[50] that has been produced in volume in rabbit kidney cell culture and has been given to more than 100 000 persons in Japan). Research showed no severe complications among the first 30 000 vaccinees.[51] The cutaneous responses to vaccination were much less severe and far fewer vaccinees developed fever. More than 95% developed a Jennerian pustule; immunogenicity, as measured by neutralizing antibody, was slightly lower than for nonattenuated strains.

Vaccinia immune globulin has been used for the treatment of vaccine complications and for administration with vaccine to those for whom vaccine is otherwise contraindicated. Production of VIG should be a high priority for research. An alternative to VIG is also needed because VIG is difficult to produce and cumbersome to administer. Immunotherapy using humanized monoclonal antibodies is an alternative that should be explored. Studies of antiviral agents or drugs, already approved or near approval for marketing for use in other viral diseases, have suggested that 1 or more such products might prove useful.

Finally, a simple, rapid diagnostic test to identify variola virus in the oropharynx during the prodrome or early in the exanthematous phase of illness would be of considerable help in triage of suspected patients during the course of an outbreak.

Table 2. Viability of Vaccinia Virus in Aerosols at Various Intervals After Spraying[9]

Temperature, °C	Relative Humidity, %	Viable Vaccinia, %*			
		1 h	4 h	6 h	23 h
10.5-11.5	20	82	79	81	66
	50	83	92	77	59
	82-84	79	59	60	27
21.0-23.0	18-19	66	46	45	15
	48-51	86	57	50	12
	82-84	66	24	18	Trace
31.5-33.5	17-19	61	51	33	13
	50	51	26	15	Trace
	80-83	36	5.9	1.2	Trace

*Initial titer of $10^{7.7}$ plaque-forming units per milliliter of McIlvaine buffer, containing 1% dialyzed horse serum.

SUMMARY

The specter of resurgent smallpox is ominous, especially given the enormous efforts that have been made to eradicate what has been characterized as the most devastating of all the pestilential diseases. Unfortunately, the threat of an aerosol release of smallpox is real and the potential for a catastrophic scenario is great unless effective control measures can quickly be brought to bear.

Early detection, isolation of infected individuals, surveillance of contacts, and a focused selective vaccina-

tion program are the essential items of a control program. Educating health care professionals about the diagnostic features of smallpox should permit early detection; advance regionwide planning for isolation and care of infected individuals in their homes as appropriate and in hospitals when home care is not an option will be critical to deter spread. Ultimately, success in controlling a burgeoning epidemic will depend on the availability of adequate supplies of vaccine and VIG. An adequate stockpile of those commodities would offer a relatively inexpensive safeguard against tragedy.

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The views, opinions, assertions, and findings contained herein are those of the authors and should not be construed as official US Department of Defense or US Department of Army positions, policies, or decisions unless so designated by other documentation.

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Tularemia as a Biological Weapon
Medical and Public Health Management

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Objective The Working Group on Civilian Biodefense has developed consensus-based recommendations for measures to be taken by medical and public health professionals if tularemia is used as a biological weapon against a civilian population.

Participants The working group included 25 representatives from academic medical centers, civilian and military governmental agencies, and other public health and emergency management institutions and agencies.

Evidence MEDLINE databases were searched from January 1966 to October 2000, using the Medical Subject Headings *Francisella tularensis*, *Pasteurella tularensis*, *biological weapon*, *biological terrorism*, *bioterrorism*, *biological warfare*, and *biowarfare*. Review of these references led to identification of relevant materials published prior to 1966. In addition, participants identified other references and sources.

Consensus Process Three formal drafts of the statement that synthesized information obtained in the formal evidence-gathering process were reviewed by members of the working group. Consensus was achieved on the final draft.

Conclusions A weapon using airborne tularemia would likely result 3 to 5 days later in an outbreak of acute, undifferentiated febrile illness with incipient pneumonia, pleuritis, and hilar lymphadenopathy. Specific epidemiological, clinical, and microbiological findings should lead to early suspicion of intentional tularemia in an alert health system; laboratory confirmation of agent could be delayed. Without treatment, the clinical course could progress to respiratory failure, shock, and death. Prompt treatment with streptomycin, gentamicin, doxycycline, or ciprofloxacin is recommended. Prophylactic use of doxycycline or ciprofloxacin may be useful in the early postexposure period.

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I know of no other infection of animals communicable to man that can be acquired from sources so numerous and so diverse. In short, one can but feel that the status of tularemia, both as a disease in nature and of man, is one of potentiality.

R. R. Parker[1]

TULAREMIA, A BACTERIAL ZOONOsis, is the subject of this fifth article in a series providing recommendations for medical and public health management following use of various agents as biological weapons of terrorism.[2-5] The causative agent of tularemia, *Francisella tularensis*, is one of the most infectious pathogenic bacteria known, requiring inoculation or inhalation of as few as 10 organisms to cause disease.[6,7] Humans become incidentally infected through diverse environmental exposures and can develop severe and sometimes fatal illness but do not transmit infection to others. The Working Group on Civilian Biodefense considers *F tularensis* to be a dangerous potential biological weapon because of its extreme infectivity, ease of dissemination, and substantial capacity to cause illness and death.[8-11]

CONSENSUS METHODS

The working group comprised 25 representatives from academic medical centers, civilian and military governmental agencies, and other public health and emergency management institutions. This group followed a specified process in developing a consensus statement. MEDLINE databases from January 1966 to October 2000 were searched

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using the Medical Subject Headings *Francisella tularensis*, *Pasteurella tularensis*, *biological weapon*, *biological terrorism*, *bioterrorism*, *biological warfare*, and *biowarfare*. Review of the bibliographies of these references led to identification of relevant materials published prior to 1966. In addition, participants identified other published and unpublished references and sources for review.

The first draft of the consensus statement was a synthesis of information obtained in the formal evidence-gathering process. Members of the working group were asked to make written comments on this first draft in May 1999. Subsequent revised drafts were reviewed and edited until full consensus of the working group was achieved.

HISTORY AND POTENTIAL AS A BIOLOGICAL WEAPON

Tularemia was first described as a plague-like disease of rodents in 1911 and, shortly thereafter, was recognized as a potentially severe and fatal illness in humans.[12] Tularemia's epidemic potential became apparent in the 1930s and 1940s, when large waterborne outbreaks occurred in Europe and the Soviet Union[13-15] and epizootic-associated cases occurred in the United States.[16,17] As well, *F tularensis* quickly gained notoriety as a virulent laboratory hazard.[18,19] Public health concerns impelled substantial early investigations into tularemia's ecology, microbiology, pathogenicity, and prevention.[19-22]

Francisella tularensis has long been considered a potential biological weapon. It was one of a number of agents studied at Japanese germ warfare research units operating in Manchuria between 1932 and 1945[23]; it was also examined for military purposes in the West. A former Soviet Union biological weapons scientist, Ken Alibeck, has suggested that tularemia outbreaks affecting tens of thousands of Soviet and German soldiers on the eastern European front during World War II may have been the result of intentional use.[24] Following the war, there were continuing military studies of tularemia. In the 1950s and 1960s, the US military developed weapons that would disseminate *F tularensis* aerosols[10]; concurrently, it conducted research to better understand the pathophysiology of tularemia and to develop vaccines and antibiotic prophylaxis and treatment regimens. In some studies, volunteers were infected with *F tularensis* by direct aerosol delivery systems and by exposures in an aerosol chamber.[10] A live attenuated vaccine was developed that partially protected against respiratory and intracutaneous challenges with the virulent SCHU S-4 strain of *F tularensis*,[6,7] and various regimens of streptomycin, tetracyclines, and chloramphenicol were found to be effective in prophylaxis and treatment.[25-27] By the late 1960s, *F tularensis* was one of several biological weapons stockpiled by the US military.[10] According to Alibeck, a large parallel effort by the Soviet Union continued into the early 1990s and resulted in weapons production of *F tularensis* strains engineered to be resistant to antibiotics and vaccines.[24]

In 1969, a World Health Organization expert committee estimated that an aerosol dispersal of 50 kg of virulent *F tularensis* over a metropolitan area with 5 million inhabitants would result in 250 000 incapacitating casualties, including 19 000 deaths.[28] Illness would be expected to persist for several weeks and disease relapses to occur during the ensuing weeks or months. It was assumed that vaccinated individuals would be only partially protected against an aerosol exposure. Referring to this model, the Centers for Disease Control and Prevention (CDC) recently examined the expected economic impact of bioterrorist attacks and estimated the total base costs to society of an *F tularensis* aerosol attack to be $5.4 billion for every 100 000 persons exposed.[9]

The United States terminated its biological weapons development program by executive order in 1970 and, by 1973, had destroyed its entire biological arsenal.[10] Since then, the US Army Medical Research Institute of Infectious Diseases has been responsible for defensive medical research on *F tularensis* and other potential biological warfare agents to better protect the US military, including protocols on decontamination, prophylaxis, clinical recognition, laboratory diagnosis, and medical management.[29] The CDC operates a national program for bioterrorism preparedness and response that incorporates a broad range of public health partnerships.[30,31]

EPIDEMIOLOGY

Geographic Distribution and Human Exposures

Tularemia occurs throughout much of North America and Eurasia.[15,21,22,32] In the United States, human cases have been reported from every state except Hawaii; however, most cases occur in south-central and western states (especially Missouri, Arkansas, Oklahoma, South Dakota, and Montana).[33-35] In Eurasia, the disease is also widely endemic, although the greatest numbers of human cases are reported from northern and central Europe, especially Scandinavian countries and those of the former Soviet Union.[36,37] Tularemia is almost entirely a rural disease, although urban and suburban exposures occasionally do occur.[38-41]

Throughout its range, *F tularensis* is found in widely diverse animal hosts and habitats and can be recovered from contaminated water, soil, and vegetation.[15,20-22,32] A variety of small mammals, including voles, mice, water rats, squirrels, rabbits, and hares, are natural reservoirs of infection. They acquire infection through bites by ticks, flies, and mosquitoes, and by contact with contaminated environments. Although enzootic cycles of *F tularensis* typically occur without notice, epizootics with sometimes extensive die-offs of animal hosts may herald outbreaks of tularemia in humans.[16,22,42,43] Humans become infected with *F tularensis* by various modes, including bites by infective arthropods,[42,44-47] handling infectious animal tissues or fluids,[17,48,49] direct contact with or ingestion of contaminated water, food, or soil,[13,20,40,50,51] and inhalation of infective aerosols.[43,52-56] Persons of all ages

and both sexes appear to be equally susceptible to tularemia. Certain activities, such as hunting, trapping, butchering, and farming, are most likely to expose adult men. Laboratory workers are especially vulnerable to infection, either by accidentally inoculating themselves or by inhaling aerosolized organisms.[18,22,56-58] Ordinary exposures during examination of an open culture plate can cause infection. Although *F tularensis* is highly infectious and pathogenic, its transmission from person to person has not been documented.

Incidence

The worldwide incidence of tularemia is not known, and the disease is probably greatly underrecognized and underreported. In the United States, reported cases have dropped sharply from several thousand per year prior to 1950 to less than 200 per year in the 1990s.[33-35] Between 1985 and 1992, 1409 cases and 20 deaths were reported in the United States, for a mean of 171 cases per year and a case-fatality rate of 1.4%.[34] Persons in all age groups were affected, but most were children younger than 10 years and adults aged 50 years or older. Of 1298 cases for which information on sex was available, 942 (72.6%) occurred in males, and males outnumbered females in all age groups. Most cases occur in June through September, when arthropod-borne transmission is most common.[17,35,59] Cases in winter usually occur among hunters and trappers who handle infected animal carcasses.[17,35,48] In the United States, cases are mostly sporadic or occur in small clusters[34,35,49]; in Eurasia, waterborne, arthropod-borne, and airborne outbreaks involving hundreds of persons have been reported.[40,43,44,51,53-55]

Natural Occurrences of Inhalational Tularemia

The largest recorded airborne tularemia outbreak occurred in 1966-1967 in an extensive farming area of Sweden.[43] This outbreak involved more than 600 patients infected with strains of the milder European biovar of *F tularensis* (*F tularensis* biovar palaearctica) [type B]), most of whom acquired infection while doing farm work that created contaminated aerosols. Case exposures and disease onsets occurred during a period of months but peaked during the winter, when rodent-infested hay was being sorted and moved from field storage sites to barns. Among 140 serologically confirmed cases thought to have been infected by inhalation, most had typical acute symptoms of fever, fatigue, chills, headache, and malaise; only 14 (10%) of confirmed patients had symptoms of pneumonia, such as dyspnea and chest pains. Patients generally responded well to tetracycline, and no deaths were reported. Inhalational tularemia in the United States has involved only single cases or small clusters of cases, variously resulting from laboratory exposures,[18,56,57] disturbance of contaminated animal carcasses,[38,39,41] and suspected infective environmental aerosols.[41,52] Cases of inhalational tularemia in the United States are thought to be due mostly to the more virulent *F tularensis* biovar tularensis (type A) and usually follow an acute and severe course, with prominent pneumonitis. Some cases, however, have radiographic evidence of pleuropneumonia with minimal or absent respiratory signs on physical examination.[39,41,52]

Although airborne *F tularensis* would be expected to principally cause primary pleuropneumonic infection, some exposures might contaminate the eye, resulting in ocular tularemia; penetrate broken skin, resulting in ulceroglandular or glandular disease; or cause oropharyngeal disease with cervical lymphadenitis. In the aforementioned Swedish outbreak, conjunctivitis was reported in 26% of 140 confirmed cases and an infected ulcer of the skin was reported in nearly 12%; pharyngitis was reported in 31% and oral ulcers in about 9% of the cases; and 32% of these patients had various exanthemas, such as erythema multiforme and erythema nodosum.[43] Tularemia outbreaks arising from similar agricultural exposures have been reported from Finland,[53] mostly presenting with general constitutional symptoms rather than specific manifestations of pneumonia; enlargement of hilar nodes was the principal radiographic finding in these cases.[54]

Inhalational Tularemia Following Use as a Biological Weapon

Although *F tularensis* could be used as a weapon in a number of ways, the working group believes that an aerosol release would have the greatest adverse medical and public health consequences. Release in a densely populated area would be expected to result in an abrupt onset of large numbers of cases of acute, nonspecific febrile illness beginning 3 to 5 days later (incubation range, 1-14 days), with pleuropneumonitis developing in a significant proportion of cases during the ensuing days and weeks. Public health authorities would most likely become aware of an outbreak of unusual respiratory disease in its early stages, but this could be difficult to distinguish from a natural outbreak of community-acquired infection, especially influenza or various atypical pneumonias. The abrupt onset of large numbers of acutely ill persons, the rapid progression in a relatively high proportion of cases from upper respiratory symptoms and bronchitis to life-threatening pleuropneumonitis and systemic infection affecting, among others, young, previously healthy adults and children should, however, quickly alert medical professionals and public health authorities to a critical and unexpected public health event and to bioterrorism as a possible cause (TABLE 1). Until the etiology became clear, clinicians would need to work closely with epidemiologists and diagnostic laboratories to differentiate the illness from various community-acquired pneumonias and to determine if it could have resulted from use of one of several potential bioterrorism weapons agents, such as those causing tularemia, plague, anthrax, or Q fever.[2,4,29]

In general, tularemia would be expected to have a slower progression of illness and a lower case-fatality rate than either inhalational plague or anthrax. Plague would most likely progress very

Table 1. Diagnosis of Inhalational Tularemia Following Use of a Biological Weapon

Clinical Findings
Sudden onset of acute febrile illness, progressing in some patients to pharyngitis, bronchiolitis, pneumonitis, pleuritis, hilar lymphadenitis. Complications of overwhelming untreated infection may lead to sepsis and inflammatory response syndrome.
Epidemiology
Point-source outbreak pattern; likely urban, nonagricultural setting. Unexpected severe respiratory illness in otherwise healthy persons. Risk related to degree of exposure with no differences in susceptibility by age or sex.
Microbiology
Small, gram-negative coccobacilli in direct stain of respiratory secretions. Sputum, tracheobronchial secretions, and blood should be cultured using cysteine-enriched medium. Antimicrobial susceptibility of isolates should be determined. Direct fluorescent antibody stain is first-line, rapid identification procedure at reference laboratories. Polymerase chain reaction and antigen detection procedures may also provide rapid identification. Microagglutination assay can detect serum antibodies beginning 10 days after illness onset. Virulence testing and molecular genetic characterizations are performed at specialized laboratories.
Pathology
Histological findings of acute suppurative necrosis followed by granulomatous reactions. Target organs include lungs, lymph nodes, spleen, liver, and kidney.
Radiology
Peribronchial infiltrates leading to bronchopneumonia in 1 or more lobes, often accompanied by pleural effusion and enlarged hilar nodes. Signs may be absent or minimal, with only 1 or several small, discrete pulmonary infiltrates, or scattered granulomatous lesions of lung parenchyma or pleura.

rapidly to severe pneumonia, with copious watery or purulent sputum production, hemoptysis, respiratory insufficiency, sepsis, and shock.[4] Inhalational anthrax would be differentiated by its characteristic radiological findings of prominent symmetric mediastinal widening and absence of bronchopneumonia.[2] As well, anthrax patients would be expected to develop fulminating, toxic, and fatal illness despite antibiotic treatment.[29] Milder forms of inhalational tularemia could be clinically indistinguishable from Q fever; establishing a diagnosis of either would be problematic without reference laboratory testing. Presumptive laboratory diagnoses of plague or anthrax would be expected to be made relatively quickly, although microbiological confirmation could take days. Isolation and identification of *F tularensis* using routine laboratory procedures could take several weeks.

Once a substantial cluster of cases of inhalational tularemia had been identified, epidemiological findings should suggest a bioterrorist event. The abrupt onset and single peak of cases would implicate a point-source exposure without secondary transmission. Among exposed persons, attack rates would likely be similar across sex and age groups, and risk would be related to degree of exposure to the point source (Table 1). An outbreak of inhalational tularemia in an urban setting should trigger a high level of suspicion of an intentional event, since all reported inhalational tularemia outbreaks have occurred in rural areas.

MICROBIOLOGY AND VIRULENCE FACTORS

Francisella tularensis is a small, nonmotile, aerobic, gram-negative coccobacillus. It has a thin lipopolysaccharide-containing envelope and is a hardy non–spore-forming organism that survives for weeks at low temperatures in water, moist soil, hay, straw, and decaying animal carcasses.[21,22,60,61] *Francisella tularensis* has been divided into 2 major subspecies (biovars) by virulence testing, biochemical reactions, and epidemiological features.[62] *Francisella tularensis* biovar tularensis (type A) may be highly virulent in humans and animals, produces acid from glycerol, demonstrates citrulline ureidase activity, and is the most common biovar isolated in North America.[22,60] *Francisella tularensis* biovar palaearctica (type B) is relatively avirulent, does not produce acid from glycerol, and does not demonstrate citrulline ureidase activity. In Europe and Asia, all human tularemia is thought to be caused by the milder type B strains, although recent studies there have identified naturally occurring *F tularensis* related to *F tularensis* biovar tularensis.[63,64] A few rapidly growing strains of *F tularensis* have been recovered from the blood of immunocompromised patients not showing seroreactivity to *F tularensis*.[65]

Transformed plasmids have been engineered to express chloramphenicol and tetracycline resistance in *F tularensis*.[66] Virulent, streptomycin-resistant *F tularensis* strains have been examined in biowarfare agent studies both in the United States and the Soviet Union.[24,27,56] Although *F tularensis* virulence factors are poorly understood and characterized,[67,68] it is possible that strain virulence could be enhanced through laboratory manipulation.

PATHOGENESIS AND CLINICAL MANIFESTATIONS

Pathogenesis

Francisella tularensis can infect humans through the skin, mucous membranes, gastrointestinal tract, and lungs. It is a facultative intracellular bacterium that multiplies within macrophages.[68,69] The major target organs are the lymph nodes, lungs and pleura, spleen, liver, and kidney.[19,20,49,70-72] Untreated, bacilli inoculated into skin or mucous membranes multiply, spread to the regional lymph nodes and further multiply, and may then disseminate to organs throughout the body. Bacteremia may be common in the early phase of infection. The initial tissue reaction to infection is a focal, intensely suppurative necrosis consisting largely of accumulations of polymorphonuclear leukocytes, followed by invasion of macrophages, epithelioid cells, and lymphocytes. Suppurative lesions become granulomatous, and histopathological examination of the granulomas shows a central necrotic, sometimes caseating zone surrounded by a layer of epithelioid cells, multinucleated giant cells, and fibroblasts in a radial arrange-

ment, typical of other granulomatous conditions, such as tuberculosis and sarcoidosis.[20,70,71]

Monkeys that inhaled the virulent SCHU S-4 strain of *F tularensis* (type A) developed acute bronchiolitis within 24 hours of exposure to 1-µm particles and within 48 hours of exposure to 8-µm particles.[73] By 72 hours following challenge, inflammation was present in peribronchial tissues and alveolar septa. Bronchopneumonia was most pronounced in animals exposed to the smaller particles and was characterized by tracheobronchial lymph node enlargement and reddish, firm, 0.2- to 0.5-cm-diameter discrete inflammatory lesions scattered throughout the lungs. In the absence of treatment, the disease progressed to pneumonic consolidation and organization, granuloma formation, and eventual chronic interstitial fibrosis.

Humans with inhalational exposures also develop hemorrhagic inflammation of the airways early in the course of illness, which may progress to bronchopneumonia.[54] Histopathological examination of affected lungs shows alveolar spaces filled with an exudate of mononuclear cells. Pleuritis with adhesions and effusion and hilar lymphadenopathy are common radiological and pathological findings.[70,72]

Clinical Manifestations

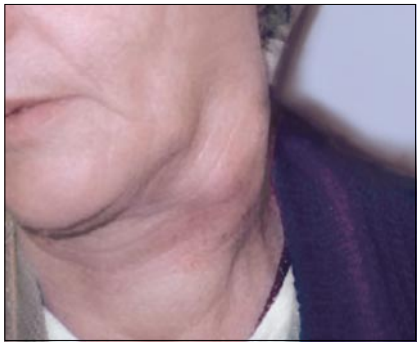
The primary clinical forms of tularemia vary in severity and presentation according to virulence of the infecting organism, dose, and site of inoculum. Primary disease presentations include ulceroglandular, glandular, oculoglandular, oropharyngeal, pneumonic, typhoidal, and septic forms.[19,20,49,70,72,74,75] The term *typhoidal tularemia* has been used to describe illness in tularemia patients with systemic infections manifesting as fever and other constitutional signs without cutaneous or mucosal membrane lesions or regional lymphadenitis. Sometimes, these patients present with prominent gastrointestinal manifestations, such as diarrhea and pain. Confusion is created when *typhoidal tularemia* is used to describe the illness in patients infected by inhalation, especially when there are signs of pleuropneumonic disease; this usage can be misleading and has been discouraged.[54,75]

The onset of tularemia is usually abrupt, with fever (38°C-40°C), headache, chills and rigors, generalized body aches (often prominent in the low back), coryza, and sore throat. A pulse-temperature dissociation has been noted in as many as 42% of patients.[49] A dry or slightly productive cough and substernal pain or tightness frequently occur with or without objective signs of pneumonia, such as purulent sputum, dyspnea, tachypnea, pleuritic pain, or hemoptysis.[7,19,26,70,74] Nausea, vomiting, and diarrhea sometimes occur. Sweats, fever and chills, progressive weakness, malaise, anorexia, and weight loss characterize the continuing illness. Studies of volunteers have shown that *F tularensis* aerosol exposures can incapacitate some persons in the first 1 or 2 days of illness, and significant impairment in performing tasks can continue for days after antibiotic treatment is begun.[76] In untreated tularemia, symptoms often persist for several weeks and, sometimes, for months, usually with progressive debility. Any form of tularemia may be complicated by hematogenous spread, resulting in secondary pleuropneumonia, sepsis, and, rarely, meningitis.[74,77]

Prior to the advent of antibiotics, the overall mortality from infections with the more severe type A strains was in the range of 5% to 15%, and fatality rates as high as 30% to 60% were reported for untreated pneumonic and severe systemic forms of disease.[72,78] Currently, the overall case-fatality rate of reported cases in the United States is less than 2%.[34,49] Type B infections are rarely fatal.

In ulceroglandular tularemia, the form that typically arises from handling a contaminated carcass or following an infective arthropod bite, a local cutaneous papule appears at the inoculation site at about the time of onset of generalized symptoms, becomes pustular, and ulcerates within a few days of its first appearance. The ulcer is tender, generally has an indolent character, and may be covered by an eschar. Typically, one or more regional afferent lymph nodes may become enlarged and tender within several days of the appearance of the papule. Even with antibiotic treatment, the affected nodes may become fluctuant and rupture. In oculoglandular tularemia, which follows direct contamination of the eye, ulceration occurs on the conjunctiva, accompanied by pronounced chemosis, vasculitis, and regional lymphadenitis. Glandular tularemia is characterized by lymphadenopathy without an ulcer.

Figure 1. Cervical Lymphadenitis in a Patient With Pharyngeal Tularemia

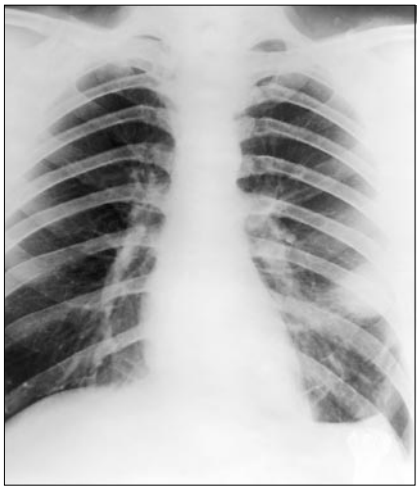


Patient has marked swelling and fluctuant suppuration of several anterior cervical nodes. Infection was acquired by ingestion of contaminated food or water. Source: World Health Organization.

Oropharyngeal tularemia is acquired by drinking contaminated water, ingesting contaminated food, and, sometimes, by inhaling contaminated droplets or aerosols.[14,20,36,43,50,51,79] Affected persons may develop stomatitis but more commonly develop exudative pharyngitis or tonsillitis, sometimes with ulceration. Pronounced cervical or retropharyngeal lymphadenopathy may occur (FIGURE 1).[74,79]

Tularemia pneumonia can be the direct result of inhaling contaminated aerosols or be secondary to hematogenous spread from a distal site. An aerosol release of *F tularensis* would be expected to result in acute illness with signs and symptoms of 1 or more of pharyngitis, bronchiolitis, pleuropneumonitis, and hilar lymphadenitis, accompanied by various manifesta-

Figure 2. Chest Radiograph of a Patient With Pulmonary Tularemia



Infiltrates in left lower lung, tenting of diaphragm, probably caused by pleural effusion, and enlargement of left hilum. Source: Armed Forces Institute of Pathology.

Box. Clinicians Caring for Patients With Suspected Tularemia Should Immediately Contact Their:

(1) Hospital epidemiologist or infection control practitioner and

(2) Local or state health departments

Consult your local telephone operator, the telephone directory under "governmental listings," or the Internet at http://www.cdc.gov/other.htm#states or http://www.astho.org/state.html

If the local and state health departments are unavailable, contact the Centers for Disease Control and Prevention at (970) 221-6400 or http://www.cdc.gov/ncidod/dvbid/dvbid.htm

tions of systemic illness. Inhalational exposures, however, commonly result in an initial clinical picture of systemic illness without prominent signs of respiratory disease.[7,43,53,56] The earliest pulmonary radiographic findings of inhalational tularemia may be peribronchial infiltrates, typically advancing to bronchopneumonia in 1 or more lobes, and often accompanied by pleural effusions and hilar lymphadenopathy (FIGURE 2).[72,75] Signs may, however, be minimal or absent, and some patients will show only 1 or several small, discrete pulmonary infiltrates or scattered granulomatous lesions of lung parenchyma or pleura. Although volunteers challenged with aerosols of virulent *F tularensis* (type A) regularly developed systemic symptoms of acute illness 3 to 5 days following exposure, only 25% to 50% of participants had radiological evidence of pneumonia in the early stages of infection.[7,26] On the other hand, pulmonary infection can sometimes rapidly progress to severe pneumonia, respiratory failure, and death.[72,80] Lung abscesses occur infrequently.[75]

Typhoidal tularemia is used to describe systemic illness in the absence of signs indicating either site of inoculation or anatomic localization of infection. This should be differentiated from inhalational tularemia with pleuropneumonic disease.[54,75]

Tularemia sepsis is potentially severe and fatal. As in typhoidal tularemia, nonspecific findings of fever, abdominal pain, diarrhea, and vomiting may be prominent early in the course of illness. The patient typically appears toxic and may develop confusion and coma. Unless treated promptly, septic shock and other complications of systemic inflammatory response syndrome may ensue, including disseminated intravascular coagulation and bleeding, acute respiratory distress syndrome, and organ failure.[80]

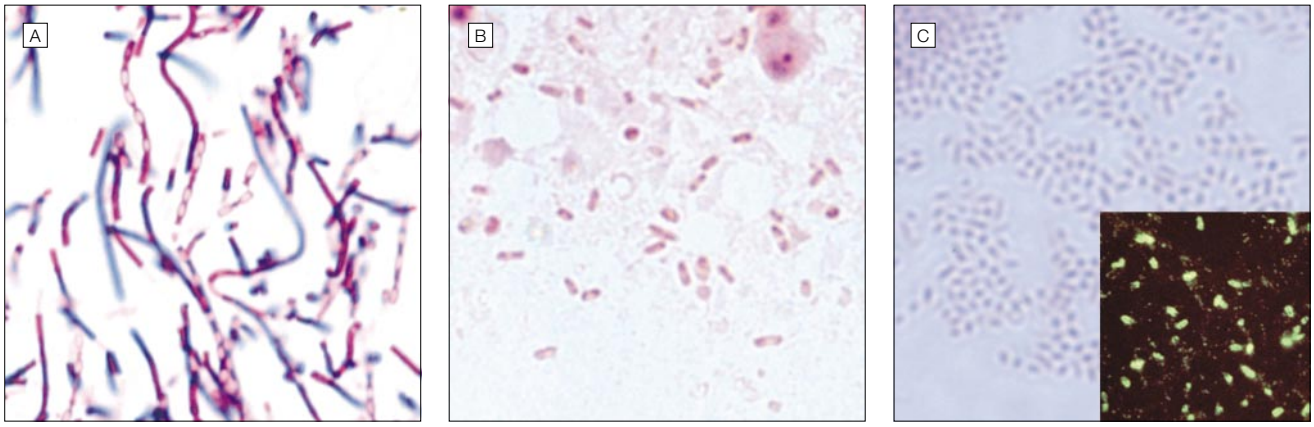
DIAGNOSIS

Tularemia in humans occurs infrequently, resulting in a low index of diagnostic suspicion among clinicians and laboratorians. Since rapid diagnostic testing for tularemia is not widely available, the first indication of intentional tularemia might follow recognition by public health authorities of a clustering of acute, severe respiratory illness with unusual epidemiological features (Table 1). Suspicion of tularemia might be triggered in alert clinicians encountering patients with findings of atypical pneumonia, pleuritis, and hilar lymphadenopathy. Identification of *F tularensis* in clinical specimens may be missed or delayed for days or weeks when procedures for routine microbiological screening of bacterial pathogens are followed, and it is unlikely that a serendipitous laboratory identification would be the sentinel event that alerted authorities to a major bioterrorism action.

Physicians who suspect inhalational tularemia should promptly collect specimens of respiratory secretions and blood and alert the laboratory to the need for special diagnostic and safety procedures. *Francisella tularensis* may be identified by direct examination of secretions, exudates, or biopsy specimens using direct fluorescent antibody or immunohistochemical stains.[81-83] By light microscopy, the organism is characterized by its small size (0.2 μm × 0.2-0.7 μm), pleomorphism, and faint staining. It does not show the bipolar staining characteristics of *Yersinia pestis*,[4] the agent of plague, and is easily distinguished from the large gram-positive rods characteristic of vegetative forms of *Bacillus anthracis* (FIGURE 3).[2] Microscopic demonstration of *F tularensis* using fluorescent-labeled antibodies is a rapid diagnostic procedure performed in designated reference laboratories in the National Public Health Laboratory Network; test results can be made available within several hours of receiving the appropriate specimens if the laboratory is alerted and prepared. Suspicion of inhalational tularemia must be promptly reported to local or state public health authorities so timely epidemiological and environmental investigations can be made (BOX).

Growth of *F tularensis* in culture is the definitive means of confirming the diagnosis of tularemia.[60,81] *Francisella tularensis* can be grown from pharyngeal washings, sputum specimens, and even fasting gastric aspirates in a high proportion of patients with inhalational tularemia.[56] It is only occasionally isolated from the blood. *Fran-*

Figure 3. Gram Stain Smears of the Agents of Anthrax (*Bacillus anthracis*), Plague (*Yersinia pestis*), and Tularemia (*Francisella tularensis*), Demonstrating Comparative Morphology, Size, and Staining Characteristics

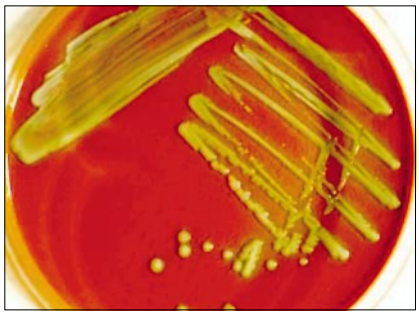


A, *B anthracis* is a large (0.5-1.2 µm × 2.5-10.0 µm), chain-forming, gram-positive rod that sporulates under certain conditions (Gram stain of organism from culture; original magnification ×250); B, *Y pestis* is a gram-negative, plump, non–spore-forming, bipolar-staining bacillus that is approximately 0.5-0.8 µm × 1-3 µm (Gram stain of smear from infected tissue; original magnification ×250); C, *F tularensis* is a small (0.2 µm × 0.2-0.7 µm), pleomorphic, poorly staining, gram-negative coccobacillus (Gram stain of organism from culture; original magnification ×500) (inset, direct immunofluorescence of smear of *F tularensis*; original magnification ×400. Sources: A and B, Sherif Zaki, Centers for Disease Control and Prevention; C, Armed Forces Institute of Pathology.

cisella tularensis grows best in cysteine-enriched broth and thioglycollate broth and on cysteine heart blood agar, buffered charcoal-yeast agar, and chocolate agar. Selective agar (such as chocolate agar selective for *Neisseria gonorrhea* isolation) may be useful when culturing materials from nonsterile sites, such as sputum. Inoculated media should be incubated at 37°C. Although growth may be visible as early as 24 to 48 hours after inoculation, growth may be delayed and cultures should be held for at least 10 days before discarding. Under ideal conditions, bacterial colonies on cysteine-enriched agar are typically 1 mm in diameter after 24 to 48 hours of incubation and 3 to 5 mm in diameter by 96 hours.[60,81] On cysteine heart agar, *F tularensis* colonies are characteristically opalescent and do not discolor the medium (FIGURE 4).

Antigen detection assays, polymerase chain reaction, enzyme-linked immunoassays, immunoblotting, pulsed-field gel electrophoresis, and other specialized techniques may be used to identify *F tularensis* and to characterize strains.[84-87] These procedures are usually performed only in research and reference laboratories, however. In laboratories where advanced methods are established, results of antigen detection and polymerase chain reaction analyses can be obtained within several hours of receipt of isolates. Typically, serum antibody titers do not attain diagnostic levels until 10 or more days after onset of illness, and serology would provide minimal useful information for managing an outbreak. Serological confirmation of cases, however, may be of value for forensic or epidemiological purposes. Most laboratories use tube agglutination or microagglutination tests that detect combined immunoglobulin M and immunoglobulin G.[84,85] A 4-fold change in titer between acute and convalescent serum specimens, a single titer of at least 1:160 for tube agglutination or 1:128 for microagglutination is diagnostic for *F tularensis* infection. Information on reference diagnostic testing and shipping/handling of specimens can be obtained from state public health laboratories and from the Division of Vector-Borne Infectious Diseases, CDC, Fort Collins, Colo (telephone: [970] 221-6400; e-mail: dvbid@cdc.gov).

Figure 4. *Francisella tularensis* Growth at 72 Hours After Inoculation



These *Francisella tularensis* colonies show characteristic opalescence on cysteine heart agar with sheep blood (cultured at 37°C for 72 hours). Source: Centers for Disease Control and Prevention.

VACCINATION

Beginning in the 1930s, the Soviet Union used a live attenuated vaccine to immunize tens of millions of persons living in tularemia-endemic areas.[88] In the United States, a live attenuated vaccine derived from the avirulent live vaccine strain has been used to protect laboratorians routinely working with *F tularensis*; until recently, this vaccine was available as an investigational new drug.[89] It is currently under review by the US Food and Drug Administration (FDA), and its future availability is undetermined.

In a retrospective study of civilians working with *F tularensis* at a US Army research facility, the incidence of accidental acute inhalational tularemia among laboratorians declined from 5.70 cases per 1000 person-years of risk at

Table 2. Working Group Consensus Recommendations for Treatment of Patients With Tularemia in a Contained Casualty Setting*

Contained Casualty Recommended Therapy
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 (should not exceed 2 g/d)
Gentamicin, 2.5 mg/kg IM or IV 3 times daily†
Alternative choices
Doxycycline; if weight ≥45 kg, 100 mg IV twice daily; if weight <45 kg, give 2.2 mg/kg IV twice daily
Chloramphenicol, 15 mg/kg IV 4 times daily†
Ciprofloxacin, 15 mg/kg IV twice daily†‡
Pregnant Women
Preferred choices
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†

*Treatment with streptomycin, gentamicin, or ciprofloxacin should be continued for 10 days; treatment with doxycycline or chloramphenicol should be continued for 14-21 days. Persons beginning treatment with intramuscular (IM) or intravenous (IV) doxycycline, ciprofloxacin, or chloramphenicol can switch to oral antibiotic administration when clinically indicated.
†Not a US Food and Drug Administration–approved use.
‡Ciprofloxacin dosage should not exceed 1 g/d in children.

Table 3. Working Group Consensus Recommendations for Treatment of Patients With Tularemia in a Mass Casualty Setting and for Postexposure Prophylaxis*

Mass Casualty Recommended Therapy
Adults
Preferred choices
Doxycycline, 100 mg orally twice daily
Ciprofloxacin, 500 mg orally twice daily†
Children
Preferred choices
Doxycycline; if ≥45 kg, give 100 mg orally twice daily; if <45 kg, give 2.2 mg/kg orally twice daily
Ciprofloxacin, 15 mg/kg orally twice daily†‡
Pregnant Women
Preferred choices
Ciprofloxacin, 500 mg orally twice daily†
Doxycycline, 100 mg orally twice daily

*One antibiotic, appropriate for patient age, should be chosen from among alternatives. The duration of all recommended therapies in Table 3 is 14 days.
†Not a US Food and Drug Administration–approved use.
‡Ciprofloxacin dosage should not exceed 1 g/d in children.

a time when a killed vaccine was in use to 0.27 cases per 1000 person-years of risk after introduction of the live vaccine.[58] Although the incidence of ulceroglandular disease remained unchanged in the 2 periods, signs and symptoms were considered milder among those who received the live vaccine. In volunteer studies, the live attenuated vaccine did not protect all recipients against aerosol challenges with virulent *F tularensis*.[7,26]

Correlates of protective immunity appear about 2 weeks following natural infection or vaccination. Given the short incubation period of tularemia and incomplete protection of current vaccines against inhalational tularemia, vaccination is not recommended for postexposure prophylaxis. The working group recommends use of the live vaccine strain only for laboratory personnel routinely working with *F tularensis*.

TREATMENT

Contained Casualty Situation

Adults. In a contained casualty situation, in which logistics permit individual medical management, the working group recommends parenteral antimicrobial therapy for tularemia (TABLE 2). Streptomycin is the drug of choice.[49,74,90,91] Gentamicin, which is more widely available and may be used intravenously, is an acceptable alternative.[49,74,90-93] Treatment with aminoglycosides should be continued for 10 days. Tetracyclines and chloramphenicol are also used to treat tularemia[49,74,90]; however, relapses and primary treatment failures occur at a higher rate with these bacteriostatic agents than with aminoglycosides, and they should be given for at least 14 days to reduce chance of relapse.[27,74,90] Fluoroquinolones, which have intracellular activity, are promising candidates for treating tularemia. Ciprofloxacin, which is not labeled for use in tularemia, has been shown to be active against *F tularensis* in vitro[94] and in animals[95] and has been used to successfully treat tularemia in both adults and children.[90,94,96,97] Treatment with ciprofloxacin should be continued for 10 days. In persons beginning treatment with parenteral doxycycline, ciprofloxacin, or chloramphenicol, therapy can be switched to oral antibiotic administration when clinically indicated. Very limited experiences in treating tularemia patients with β-lactam and macrolide antibiotics have been reported, and treatment failures have occurred.[98] Use of β-lactam and macrolide antibiotics in treating tularemia is neither FDA-approved nor recommended by the working group.

Children. In children, streptomycin or gentamicin is recommended by the working group as first-line treatment in a contained casualty situation (Table 2). Doxycycline, ciprofloxacin (≤1 g/d), and chloramphenicol can be used as alternatives to aminoglycosides. Fluoroquinolones have been reported to cause cartilage damage in immature animals and are not FDA-approved for use in children. However, short courses of these agents have not been associated with arthropathy in pediatric patients, and the potential risks of their use must be weighed against their benefits in treating serious infections.[96,99,100]

Mass Casualty Situation

Doxycycline and ciprofloxacin, administered orally, are the preferred choices for treatment in the mass casualty setting, for both adults and children (TABLE 3). The ciprofloxacin dosage for children should not exceed 1 g/d. In a mass casualty situation, the working group believes the benefits to children from short courses of doxycycline or fluoroquinolones (Table 3) outweigh the risks of their use.

Since it is unknown whether drug-resistant organisms might be used in a bioterrorist event, antimicrobial susceptibility testing of isolates should be conducted quickly and treatments altered according to test results and clinical responses.

Antibiotics for treating patients infected with tularemia in a bioterrorism scenario are included in a national pharmaceutical stockpile

maintained by the CDC, as are ventilators and other emergency equipment needed to respond to situations of large numbers of critically ill persons that strip local and state resources.[30]

Management of Special Groups

Pregnant Women. In a contained casualty situation, short courses of gentamicin are likely to pose a low risk to fetuses when used to treat tularemia in pregnant women (Table 2). Rare cases of fetal nerve deafness and renal damage have been reported with other aminoglycosides but have not been reported with gentamicin. The benefits of gentamicin in treating pregnant women with tularemia are expected to outweigh any potential risk to fetuses. In a mass casualty situation, oral ciprofloxacin is considered the best alternative to gentamicin for pregnant women (Table 3).

Immunosuppressed Persons. There is scant experience in treating tularemia in immunocompromised patients. However, considering the greater occurrence in immunocompetent patients of tularemia relapses and treatment failures following use of bacteriostatic antimicrobial agents compared with aminoglycosides, streptomycin or gentamicin should be used when possible to treat patients with known immune dysfunction in either contained casualty or mass casualty situations (Table 2).

POSTEXPOSURE ANTIBIOTIC RECOMMENDATIONS

Persons beginning treatment with streptomycin, gentamicin, doxycycline, or ciprofloxacin in the incubation period of tularemia and continuing treatment daily for 14 days might be protected against symptomatic infection. In studies of aerosol challenge with infective doses of the virulent SCHU S-4 strain of *F tularensis*, each of 8 volunteers given oral dosages of tetracycline, 1 g/d for 28 days, and each of 8 volunteers given tetracycline, 2 g/d for 14 days, were fully protected when treatment was begun 24 hours following challenge.[27] Two of 10 volunteers given tetracycline, 1 g/d for only 5 days, developed symptomatic tularemia after antibiotic treatment was stopped.

In the unlikely event that authorities quickly become aware that an *F tularensis* biological weapon has been used and are able to identify and reach exposed persons during the early incubation period, the working group recommends that exposed persons be prophylactically treated with 14 days of oral doxycycline or ciprofloxacin (Table 3). In a circumstance in which the weapon attack has been covert and the event is discovered only after persons start to become ill, persons potentially exposed should be instructed to begin a fever watch. Persons who develop an otherwise unexplained fever or flulike illness within 14 days of presumed exposure should begin treatment as outlined in Tables 2 and 3.

In the laboratory, persons who have had potentially infective exposures to *F tularensis* should be administered oral postexposure antibiotic prophylaxis if the risk of infection is high (eg, spill, centrifuge accident, or needlestick). If the risk is low, exposed persons can be placed on a fever watch and treated if they develop symptoms.

Postexposure prophylactic antibiotic treatment of close contacts of tularemia patients is not recommended since human-to-human transmission of *F tularensis* is not known to occur.

INFECTION CONTROL

Isolation is not recommended for tularemia patients, given the lack of human-to-human transmission. In hospitals, standard precautions[101] are recommended by the working group for treatment of patients with tularemia.

Microbiology laboratory personnel should be alerted when tularemia is clinically suspected. Routine diagnostic procedures can be performed in biological safety level 2 (BSL-2) conditions. Examination of cultures in which *F tularensis* is suspected should be carried out in a biological safety cabinet. Manipulation of cultures and other activities involving infectious materials with a potential for aerosol or droplet production (centrifuging, grinding, vigorous shaking, growing cultures in volume, animal studies) require BSL-3 conditions.[102] When *F tularensis* is presumptively identified in a routine BSL-2 clinical laboratory (level A), specimens should be forwarded to a BSL-3 laboratory (level B) (eg, a state public health laboratory) for confirmation of agent and other studies, such as antimicrobial susceptibility testing.[11] Bodies of patients who die of tularemia should be handled using standard precautions. Autopsy procedures likely to cause aerosols, such as bone sawing, should be avoided. Clothing or linens contaminated with body fluids of patients infected with *F tularensis* should be disinfected per standard precautions protocols.[101]

ENVIRONMENTAL DECONTAMINATION AND PROTECTION

Under natural conditions, *F tularensis* may survive for extended periods in a cold, moist environment. The working group lacks information on survival of intentionally dispersed particles but would expect a short half-life due to desiccation, solar radiation, oxidation and other environmental factors, and a very limited risk from secondary dispersal. In circumstances of a laboratory spill or intentional use in which authorities are concerned about an environmental risk (eg, inanimate surfaces wet with material thought to contain *F tularensis*), decontamination can be achieved by spraying the suspected contaminant with a 10% bleach solution (1 part household bleach and 9 parts water). After 10 minutes, a 70% solution of alcohol can be used to further clean the area and reduce the corrosive action of the bleach. Soap water can be used to flush away less hazardous contaminations. Persons with direct exposure to powder or liquid aerosols containing *F tularensis* should wash body surfaces and clothing with soap water. Standard levels of chlorine in municipal water sources should protect against waterborne infection.[60] Following an urban release, the risk to humans of acquiring tula-

remia from infected animals or arthropod bites is considered minimal and could be reduced by educating the public on simple avoidance of sick or dead animals and on personal protective measures against biting arthropods.

ADDITIONAL RESEARCH

Simple, rapid, and reliable diagnostic tests that could be used to identify persons infected with *F tularensis* in the mass exposure setting need to be developed. Further methods should be designed to rapidly define the molecular genetic characteristics of organisms, especially as they may relate to engineered attributes, such as enhanced virulence and resistance to antimicrobial agents or normally lethal environmental conditions. Complete sequencing and analysis of the genome of natural strains of *F tularensis* would provide an archival base for understanding genetic variants, functions of genes, and mechanisms of action useful in developing means to protect against *F tularensis*. Research is also needed to develop accurate and reliable procedures to rapidly detect *F tularensis* in environmental samples.

New technologies should be explored for developing active (eg, DNA-based) or passive (eg, monoclonal antibody–based) vaccines for rapid preexposure or postexposure protection.

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Chapter 29

VIRAL HEMORRHAGIC FEVERS

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INTRODUCTION

The concept of a viral hemorrhagic fever (VHF) syndrome is useful in clinical medicine. VHF syndrome can be described as an acute febrile illness characterized by malaise, prostration, generalized signs of increased vascular permeability, and abnormalities of circulatory regulation. Bleeding manifestations often occur, especially in the more severely ill patients, but this does not result in a life-threatening loss of blood volume. Rather, these signs are the result of damage to the vascular endothelium and are an index of how severe the disease is in specific target organs.

The viral agents that cause VHFs are taxonomically diverse; they are all ribonucleic acid (RNA) viruses and are transmitted to humans through contact with infected animal reservoirs or arthropod vectors. They are all natural infectious disease threats although their geographical ranges may be tightly circumscribed. The recent advent of jet travel coupled with human demographics increase the opportunity for humans to contract these infections.

The VHF agents are all highly infectious via the aerosol route, and most are quite stable as respirable aerosols. This means that they satisfy at least one criterion for being weaponized, and some clearly have the potential to be biological warfare threats. Most of these agents replicate in cell culture to concentrations sufficiently high to produce a small terrorist weapon, one suitable for introducing lethal doses of virus into the air intake of an airplane or office building. Some replicate to even higher concentrations, with obvious potential ramifications. Since the VHF agents cause serious diseases with high morbidity and mortality, their existence as endemic disease threats and as potential biological warfare weapons suggests a formidable potential impact on unit readiness. Further, returning troops may well be carrying exotic viral diseases to which the civilian population is not immune, a major public health concern.

EPIDEMIOLOGICAL OVERVIEW

The VHF agents are a taxonomically diverse group of RNA viruses whose major characteristics are summarized in Table 29-1. Four virus families contribute pathogens to the group of VHF agents: the *Arenaviridae, Bunyaviridae, Filoviridae,* and *Flaviviridae.* Despite their diverse taxonomy, all these viruses share some common characteristics. They are all relatively simple RNA viruses, and they all have lipid envelopes. This renders them relatively susceptible to detergents, as well as to low-pH environments and household bleach. Conversely, they are quite stable at neutral pH, especially when protein is present. Thus, these viruses are stable in blood for long periods, and can be isolated from a patient's blood after weeks of storage at refrigerator or even at ambient temperatures.

These viruses tend to be stable and highly infectious as fine-particle aerosols. These characteristics have great significance in not only the natural transmission cycle for arenaviruses and bunyaviruses (from rodents to man) but also make nosocomial transmission a concern. As a group, the viruses are also linked to the ecology of their vectors or reservoirs, whether rodents or arthropods. In that regard, most of these reservoirs tend to be rural, and a patient's history of being in a rural locale is an important factor to consider when reaching a diagnosis. Human-to-human spread is possible, but pandemics are unlikely.

The *Arenaviridae*

The arenaviruses are classified into the Old World and New World groups. All the arenaviruses are maintained in nature by a life-long association with a rodent reservoir. Rodents spread the virus to humans, and outbreaks can usually be related to some perturbation in the ecosystem that brings man into contact with the rodents.

Lassa virus causes Lassa fever, a major febrile disease of West Africa, where it is associated with 10% to 15% of adult febrile admissions to the hospital and perhaps 40% of nonsurgical deaths.[1] In addition, Lassa fever is a pediatric disease and the cause of high mortality in pregnant women. While nosocomial infections do occur, most Lassa virus infections can be traced to contact with the carrier rodent, *Mastomys natilensis.*

The Junin virus that causes Argentine hemorrhagic fever is carried by a field mouse, *Calomys colosus,* and is associated with agricultural activities in the pampas of Argentina, where 300 to 600 cases have occurred every year since 1955.[2] In Bo-

TABLE 29-1

RECOGNIZED VIRAL HEMORRHAGIC FEVERS OF HUMANS

Virus *Family* *Genus*	Disease (Virus)	Natural Distribution	Source of Human Infection		Incubation (Days)
			Usual	Less Likely	
Arenaviridae					
Arenavirus	Lassa fever	Africa	Rodent	Nosocomial	5–16
	Argentine HF (Junin)	South America	Rodent	Nosocomial	7–14
	Bolivian HF (Machupo)	South America	Rodent	Nosocomial	9–15
	Brazilian HF (Sabia)	South America	Rodent	Nosocomial	7–14
	Venezuelan HF (Guanarito)	South America	Rodent	Nosocomial	7–14
Bunyaviridae					
Phlebovirus	Rift Valley fever	Africa	Mosquito	Slaughter of domestic animal	2–5
Nairovirus	Crimean-Congo HF	Europe, Asia, Africa	Tick	Slaughter of domestic animal; nosocomial	3–12
Hantavirus	HFRS (Hantaan and related viruses)	Asia, Europe; possibly worldwide	Rodent		9–35
Filoviridae					
Filovirus	Marburg and Ebola HF	Africa	Unknown	Nosocomial	3–16
Flaviviridae					
Flavivirus (Mosquito–borne)	Yellow fever	Tropical Africa, South America	Mosquito		3–6
	Dengue HF	Asia, Americas, Africa	Mosquito		Unknown for dengue HF, but 3–5 for uncomplicated dengue
(Tick–borne)	Kyasanur Forest disease	India	Tick		3–8
	Omsk HF	Soviet Union	Tick	Muskrat–contaminated water	3–8

HF: hemorrhagic fever; HFRS: hemorrhagic fever with renal syndrome

livia, Machupo virus is the agent associated with Bolivian hemorrhagic fever,[3] a disease that was associated with outbreaks in the 1960s but only with sporadic disease subsequently. Guanarito virus is a newly described arenavirus, first recognized in association with an outbreak of VHF involving several hundred patients in Venezuela beginning in 1989.[4] More recently, yet another VHF arenavirus has been recognized: Sabia virus was associated with a fatal VHF infection in Brazil in 1990, followed by a severe laboratory infection in Brazil in 1992 and another laboratory infection in the United States in 1994.[5]

The *Bunyaviridae*

Among the bunyaviruses, the significant human pathogens include the phlebovirus Rift Valley fever (RVF) virus, which causes Rift Valley fever. This major African disease is frequently associated with unusual increases in mosquito populations.[6] Rift Valley fever is also a disease of domestic livestock, and human infections have resulted from contact with infected blood, especially around slaughter houses.

A nairovirus, Crimean-Congo hemorrhagic fever (C-CHF) virus is carried by ticks, and has been

associated with sporadic, yet particularly severe, VHF in Europe, Africa, and Asia.[7] Crimean-Congo hemorrhagic fever has frequently occurred as small, hospital-centered outbreaks, owing to the copious hemorrhage and highly infective nature of this virus via the aerosol route.

Hantaviruses, unlike the other bunyaviruses, are not transmitted via infected arthropods; rather, they infect man via contact with infected rodents and their excreta. Hantavirus disease was described prior to World War II in Manchuria along the Amur River, and later among United Nations troops during the Korean War, where it became known as Korean hemorrhagic fever.[8] The prototype virus from this group, Hantaan, is the cause of Korean hemorrhagic fever as well as the severe form of hemorrhagic fever with renal syndrome (HFRS). Hantaan virus is borne in nature by the striped field mouse, *Apodemus agrarious*.

Hantaan virus is still active in Korea, Japan, and China. Seoul virus causes a milder form of HFRS, and may be distributed worldwide. There are a number of other hantaviruses that are associated with HFRS, including Puumala virus, which is associated with chronically infected bank voles (*Clethrionomys glareolus*). Recently in the United States, a new hantavirus (Sin nombre virus) has been associated with the hantavirus pulmonary syndrome (HPS).[9]

The *Filoviridae*

The *Filoviridae* includes the causative agents of Ebola and Marburg hemorrhagic fevers. These filoviruses have an exotic, threadlike appearance when observed via electron microscopy. Marburg virus was first recognized in 1967 when a lethal epidemic of VHF occurred in Marburg, Germany, among laboratory workers exposed to the blood and tissues of African green monkeys that had been imported from Uganda; secondary transmission to medical personnel and family members also occurred.[10] In all, 31 patients became infected, 9 of whom died. Subsequently, Marburg virus has been associated with sporadic, isolated, usually fatal cases among residents and travelers in southeast Africa.[11]

Ebola viruses are taxonomically related to Marburg viruses; they were first recognized in association with explosive outbreaks that occurred almost simultaneously in 1976 in small communities in Zaire[12] and Sudan.[13] Significant secondary transmission occurred through reuse of unsterilized needles and syringes and nosocomial contacts. These independent outbreaks involved serologically distinct viral strains. The Ebola–Zaire outbreak involved 277 cases and 257 deaths (92% mortality), while the Ebola–Sudan outbreak involved 280 cases and 148 deaths (53% mortality). Sporadic cases occurred subsequently. In 1989, a third strain of Ebola virus appeared in Reston, Virginia, in association with an outbreak of VHF among cynomolgus monkeys imported to the United States from the Philippines.[14] Hundreds of monkeys were infected (with high mortality) but no human cases occurred, although four animal caretakers seroconverted without overt disease. Recently, small outbreaks involving new strains of Ebola virus occurred in human populations in Côte d'Ivorie in 1994 and Gabon in 1995; a larger outbreak involving the Ebola-Zaire strain involved more than 300 people, with 75% mortality, in Zaire in 1995.[15]

Very little is known about the natural history of any of the filoviruses. Animal reservoirs and arthropod vectors have been aggressively sought without success.

The *Flaviviridae*

Finally, the flaviviruses include the agents of yellow fever, found throughout tropical Africa and South America; and dengue, found throughout the Americas, Asia, and Africa, both transmitted by mosquitoes.[16] Both yellow fever and dengue have had major impact on military campaigns and military medicine. The tick-borne flaviviruses include the agents of Kyasanur Forest disease, which occurs in India,[17] and Omsk hemorrhagic fever, which occurs in the former Soviet Union.[18] Both diseases have a biphasic course; the initial phase includes a prominent pulmonary component, followed by a neurological phase with central nervous system manifestations.

CLINICAL FEATURES OF THE VIRAL HEMORRHAGIC FEVER SYNDROME

The VHF syndrome develops to varying degrees in patients infected with these viruses. The exact nature of the disease depends on viral virulence and strain characteristics, routes of exposure, dose, and host factors. For example, dengue hemorrhagic fever is typically seen only in patients previously exposed to heterologous dengue serotypes.[19] The target organ in the VHF syndrome is the vascular bed;

correspondingly, the dominant clinical features are usually a consequence of microvascular damage and changes in vascular permeability.[20] Common presenting complaints are fever, myalgia, and prostration; clinical examination may reveal only conjunctival injection, mild hypotension, flushing, and petechial hemorrhages. Full-blown VHF typically evolves to shock and generalized bleeding from the mucous membranes, and often is accompanied by evidence of neurological, hematopoietic, or pulmonary involvement. Hepatic involvement is common, but a clinical picture dominated by jaundice and other evidence of hepatic failure is seen in only a small percentage patients with Rift Valley fever, Crimean-Congo hemorrhagic fever, Marburg hemorrhagic fever, Ebola hemorrhagic fever, and yellow fever. Renal failure is proportional to cardiovascular compromise, except in HFRS caused by hantaviruses, where it is an integral part of the disease process; oliguria is a prominent feature of the acutely ill patient.[8] VHF mortality may be substantial, ranging from 5% to 20% or higher in recognized cases. Ebola outbreaks in Africa have had particularly high case fatality rates, from 50% up to 90%.[12,13]

The clinical characteristics of the various VHFs are somewhat variable. For Lassa fever patients, hemorrhagic manifestations are not pronounced, and neurological complications are infrequent, occurring only late and in only the most severely ill group. Deafness is a frequent sequela of severe Lassa fever. For the South American arenaviruses, (Argentine and Bolivian hemorrhagic fevers), neurological and hemorrhagic manifestations are much more prominent. RVF virus is primarily hepatotropic; hemorrhagic disease is seen in only a small proportion of cases. In recent outbreaks in Egypt, retinitis was a frequently reported component of Rift Valley fever.[21]

Unlike Rift Valley fever, where hemorrhage is not prominent, Crimean-Congo hemorrhagic fever infection is usually associated with profound disseminated intravascular coagulation (DIC) (Figure 29-1). Patients with Crimean-Congo hemorrhagic fever may bleed profusely; and since this occurs during the acute, viremic phase, contact with the blood of an infected patient is a special concern: a number of nosocomial outbreaks have been associated with C-CHV virus.

The picture for diseases caused by hantaviruses is evolving, especially now in the context of HPS syndrome. The pathogenesis of HFRS may be somewhat different; immunopathological events seem to be a major factor. When patients present with HFRS, they are typically oliguric. Surprisingly, the oliguria occurs while the patient's viremia is resolving and they are mounting a demonstrable antibody response. This has practical significance in that renal dialysis can be started with relative safety.

Fig. 29-1. Massive cutaneous ecchymosis associated with late-stage Crimean-Congo hemorrhagic fever virus infection, 7 to 10 days after clinical onset. Ecchymosis is indicative of multiple abnormalities in the coagulation system, coupled with loss of vascular integrity. Epistaxis and profuse bleeding from puncture sites, hematemesis, melena, and hematuria often accompany spreading ecchymosis, which may occur anywhere on the body as a result of needlesticks or other minor trauma. The sharply demarcated proximal border of this patient's lesion is not explained. Photograph: Courtesy of Robert Swanepoel, PhD, DTVM, MRCVS, National Institute of Virology, Sandringham, South Africa.

For the diseases caused by filoviruses, little clinical data from human outbreaks exist. Although mortality is high, outbreaks are rare and sporadic. Marburg and Ebola viruses produce prominent maculopapular rashes, and DIC is a major factor in their pathogenesis. Therefore, treatment of the DIC should be considered, if practicable, for these patients.

Among the flaviviruses, yellow fever virus is, of course, hepatotropic: black vomit caused by hematemesis has been associated with this disease. Patients with yellow fever develop clinical jaundice and die with something comparable to hepatorenal syndrome. Dengue hemorrhagic fever and shock are uncommon, life-threatening complications of dengue, and are thought—especially in children—to result from an immunopathological mechanism triggered by sequential infections with different dengue viral serotypes.[19] Although this is the general epidemiological pattern, dengue virus may also rarely cause hemorrhagic fever in adults and in primary infections.[22]

DIAGNOSIS

The natural distribution and circulation of VHF agents are geographically restricted and mechanistically linked with the ecology of the reservoir species and vectors. Therefore, a high index of suspicion and elicitation of a detailed travel history are critical in making the diagnosis of VHF. Patients with arenaviral or hantaviral infections often recall having seen rodents during the presumed incubation period, but, since the viruses are spread to humans by aerosolized excreta or environmental contamination, actual contact with the reservoir is not necessary. Large mosquito populations are common during the seasons when RVF virus and the flaviviruses are transmitted, but a history of mosquito bite is sufficiently common to be of little assistance in making a diagnosis, whereas tick bites or nosocomial exposure are of some significance when Crimean-Congo hemorrhagic fever is suspected. History of exposure to animals in slaughterhouses should raise suspicions of Rift Valley fever and Crimean-Congo hemorrhagic fever in a patient with VHF. When large numbers of military personnel present with VHF manifestations in the same geographical area over a short period of time, medical personnel should suspect either a natural outbreak (in an endemic setting) or possibly a biowarfare attack (particularly if the virus causing the VHF is not endemic to the area).

VHF should be suspected in any patient presenting with a severe febrile illness and evidence of vascular involvement (subnormal blood pressure, postural hypotension, petechiae, hemorrhagic diathesis, flushing of the face and chest, nondependent edema) who has traveled to an area where the etiologic virus is known to occur, or where intelligence suggests a biological warfare threat. Signs and symptoms suggesting additional organ system involvement are common (headache, photophobia, pharyngitis, cough, nausea or vomiting, diarrhea, constipation, abdominal pain, hyperesthesia, dizziness, confusion, tremor), but they rarely dominate the picture. A macular eruption occurs in most patients who have Marburg and Ebola hemorrhagic fevers; this clinical manifestation is of diagnostic importance.

Laboratory findings can be helpful, although they vary from disease to disease and summarization is difficult. Leukopenia may be suggestive, but in some patients, white blood cell counts may be normal or even elevated. Thrombocytopenia is a component of most VHF diseases, but to a varying extent. In some, platelet counts may be near normal, and platelet function tests are required to explain the bleeding diathesis. A positive tourniquet test has been particularly useful in diagnosing dengue hemorrhagic fever, but this sign may be associated with other hemorrhagic fevers as well. Proteinuria or hematuria or both are common in VHF, and their absence virtually rules out Argentine hemorrhagic fever, Bolivian hemorrhagic fever, and hantaviral infections. Hematocrits are usually normal, and if there is sufficient loss of vascular integrity perhaps mixed with dehydration, hematocrits may be increased. Liver enzymes such as aspartate aminotransferase (AST) are frequently elevated. VHF viruses are not primarily hepatotropic, but livers are involved and an elevated AST may help to distinguish VHF from a simple febrile disease.

For much of the world, the major differential diagnosis is malaria. It must be borne in mind that parasitemia in patients partially immune to malaria does not prove that symptoms are due to malaria. Typhoid fever and rickettsial and leptospiral diseases are major confounding infections; nontyphoidal salmonellosis, shigellosis, relapsing fever, fulminant hepatitis, and meningococcemia are some of the other important diagnoses to exclude. Ascertaining the etiology of DIC is usually surrounded by confusion. Any condition leading to DIC could be mistaken for diseases such as acute leukemia, lupus erythematosus, idiopathic or thrombotic thrombocytopenic purpura, and hemolytic uremic syndrome.

Definitive diagnosis in an individual case rests on specific virological diagnosis. Most patients have readily detectable viremia at presentation (the exception is those with hantaviral infections). Infectious virus and viral antigens can be detected and identified by a number of assays using fresh or frozen serum or plasma samples. Likewise, early immunoglobulin (Ig) M antibody responses to the VHF-causing agents can be detected by enzyme-linked immunosorbent assays (ELISA), often during the acute illness. Diagnosis by viral cultivation and identification requires 3 to 10 days for most (longer for the hantaviruses); and, with the exception of dengue, specialized microbiologic containment is required for safe handling of these viruses.[23] Appropriate precautions should be observed in collection, handling, shipping, and processing of diagnostic samples.[24] Both the Centers for Disease Control and Prevention (CDC, Atlanta, Georgia.) and the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID, Fort Detrick,

Frederick, Maryland.) have diagnostic laboratories operating at the maximum Biosafety Level (BL-4; see Chapter 19, The U.S. Biological Warfare and Biological Defense Programs, for further discussion of BLs). Viral isolation should not be attempted without BL-4 containment.

In contrast, most antigen-capture and antibody-detection ELISAs for these agents can be performed with samples that have been inactivated by treatment with β-propiolactone (BPL).[25] Likewise, diagnostic tests based on reverse transcriptase polymerase chain reaction (RT-PCR) technology are safely performed on samples following RNA extraction using chloroform and methanol. RT-PCR has been successfully applied to the real-time diagnosis of most of the VHF agents.[26,27] When isolation of the infectious virus is difficult or impractical, RT-PCR has proven to be extremely valuable; for example, with HPS, where the agent was recognized by PCR months before it was finally isolated in culture.[9]

When the identity of a VHF agent is totally unknown, isolation in cell culture and direct visualization by electron microscopy, followed by immunological identification by immunohistochemical techniques is often successful.[14] Immunohistochemical techniques are also useful for retrospective diagnosis using formalin-fixed tissues, where viral antigens can be detected and identified using batteries of specific immune sera and monoclonal antibodies.

Although intensive efforts are being directed toward the development of simple, qualitative tests for rapid diagnosis in the field, definitive diagnosis for these diseases today requires, at a minimum, an ELISA capability coupled with specialized immunological reagents, supplemented (ideally) with an RT-PCR capability.

MEDICAL MANAGEMENT

Patients with VHF syndrome require close supervision, and some will require intensive care. Since the pathogenesis of VHF is not entirely understood and availability of specific antiviral drugs is limited, treatment is largely supportive. This care is essentially the same as the conventional care provided to patients with other causes of multisystem failure. The challenge is to provide this support while minimizing the risk of infection to other patients and medical personnel.

Supportive Care

Patients with VHF syndrome generally benefit from rapid, nontraumatic hospitalization to prevent unnecessary damage to the fragile capillary bed. Transportation of these patients, especially by air, is usually contraindicated because of the effects of drastic changes in ambient pressure on lung water balance. Restlessness, confusion, myalgia, and hyperesthesia occur frequently and should be managed by reassurance and other supportive measures, including the judicious use of sedative, pain-relieving, and amnestic medications. Aspirin and other antiplatelet or anticlotting-factor drugs should be avoided.

Secondary infections are common and should be sought and aggressively treated. Concomitant malaria should be treated aggressively with a regimen known to be effective against the geographical strain of the parasite; however, the presence of malaria, particularly in immune individuals, should not preclude management of the patient for VHF syndrome if such is clinically indicated.

Intravenous lines, catheters, and other invasive techniques should be avoided unless they are clearly indicated for appropriate management of the patient. Attention should be given to pulmonary toilet, the usual measures to prevent superinfection, and the provision of supplemental oxygen. Immunosuppression with steroids or other agents has no empirical and little theoretical basis, and is contraindicated except possibly for HFRS.

The diffuse nature of the vascular pathological process may lead to a requirement for support of several organ systems. Myocardial lesions detected at autopsy reflect cardiac insufficiency antemortem. Pulmonary insufficiency may develop, and, particularly with yellow fever, hepatorenal syndrome is prominent.[16]

Treatment of Bleeding

The management of bleeding is controversial. Uncontrolled clinical observations support vigorous administration of fresh frozen plasma, clotting factor concentrates, and platelets, as well as early use of heparin for prophylaxis of DIC. In the absence of definitive evidence, mild bleeding manifestations should not be treated at all. More-severe hemorrhage indicates that appropriate replacement therapy is needed. When definite laboratory evidence of DIC becomes available, heparin therapy should be employed if appropriate laboratory support is available.

Treatment of Hypotension and Shock

Management of hypotension and shock is difficult. Patients often are modestly dehydrated from heat, fever, anorexia, vomiting, and diarrhea, in any combination. There are covert losses of intravascular volume through hemorrhage and increased vascular permeability.[28] Nevertheless, these patients often respond poorly to fluid infusions and readily develop pulmonary edema, possibly due to myocardial impairment and increased pulmonary vascular permeability. Asanguineous fluids—either colloid or crystalloid solutions—should be given, but cautiously. Although it has never been evaluated critically for VHFs, dopamine would seem to be the agent of choice for patients with shock who are unresponsive to fluid replacement. α-Adrenergic vasoconstricting agents have not been clinically helpful except when emergent intervention to treat profound hypotension is necessary. Vasodilators have never been systematically evaluated. Pharmacological doses of corticosteroids (eg, methylprednisolone 30 mg/kg) provide another possible but untested therapeutic modality in treating shock.

Particular Problems With Dengue and Hantaviral Infections

Two hemorrhagic fevers should be clearly separated from the other VHF diseases. Severe consequences of dengue infection are largely due to systemic capillary leakage syndrome and should be managed initially by brisk infusion of crystalloid, followed by albumin or other colloid if there is no response.[29]

Severe hantaviral infections have many of the management problems of the other hemorrhagic fevers but will culminate in acute renal failure with a subsequent polyuria during the patient's recovery. Careful fluid and electrolyte management, and often renal dialysis, are necessary for optimal treatment.

Isolation and Containment

Patients with VHF syndrome generally have significant quantities of virus in their blood, and perhaps in other secretions as well (with the exceptions of dengue and classic hantaviral disease). Well-documented secondary infections among contacts and medical personnel not parenterally exposed have occurred. Thus, caution should be exercised in evaluating and treating patients with suspected VHF syndrome. Over-reaction on the part of medical personnel is inappropriate and detrimental to both patient and staff, but it is prudent to provide isolation measures as rigorous as feasible.[30] At a minimum, these should include the following:

- stringent barrier nursing;
- mask, gown, glove, and needle precautions;
- hazard-labeling of specimens submitted to the clinical laboratory;
- restricted access to the patient; and
- autoclaving or liberal disinfection of contaminated materials, using hypochlorite or phenolic disinfectants.

For more intensive care, however, increased precautions are advisable. Members of the patient care team should be limited to a small number of selected, trained individuals, and special care should be directed toward eliminating all parenteral exposures. Use of endoscopy, respirators, arterial catheters, routine blood sampling, and extensive laboratory analysis increase opportunities for aerosol dissemination of infectious blood and body fluids. For medical personnel, the wearing of flexible plastic hoods equipped with battery-powered blowers provides excellent protection of the mucous membranes and airways.

Specific Antiviral Therapy

Ribavirin is a nonimmunosuppressive nucleoside analogue with broad antiviral properties,[31] and is of proven value for some of the VHF agents. Ribavirin reduces mortality from Lassa fever in high-risk patients,[32] and presumably decreases morbidity in all patients with Lassa fever, for whom current recommendations are to treat initially with ribavirin 30 mg/kg, administered intravenously, followed by 15 mg/kg every 6 hours for 4 days, and then 7.5 mg/kg every 8 hours for an additional 6 days.[30] Treatment is most effective if begun within 7 days of onset; lower intravenous doses or oral administration of 2 g followed by 1 g/d for 10 days also may be useful.

The only significant side effects have been anemia and hyperbilirubinemia related to a mild hemolysis and reversible block of erythropoiesis. The anemia did not require transfusions or cessation of therapy in the published Sierra Leone study[32] or in subsequent unpublished limited trials in West

Africa. Ribavirin is contraindicated in pregnant women, but, in the case of definite Lassa fever, the predictability of fetal death and the need to evacuate the uterus justify its use. Safety of ribavirin in infants and children has not been established.

A similar dose of ribavirin begun within 4 days of disease is efficacious in patients with HFRS.[33] In Argentina, ribavirin has been shown to reduce virological parameters of Junin virus infection (ie, Argentine hemorrhagic fever), and is now used routinely as an adjunct to immune plasma. However, ribavirin does not penetrate the brain and is expected to protect only against the visceral, not the neurological phase of Junin infection.

Small studies investigating the use of ribavirin in the treatment of Bolivian hemorrhagic fever and Crimean-Congo hemorrhagic fever have been promising, as have preclinical studies for Rift Valley fever.[33] Conversely, ongoing studies conducted at USAMRMC predict that ribavirin will be ineffective against both the filoviruses and the flaviviruses. No other antiviral compounds are currently available for the VHF agents.

Interferon alpha has no role in therapy, with the possible exception of Rift Valley fever,[34] where fatal hemorrhagic fever has been associated with low interferon responses in experimental animals. However, as an adjunct to ribavirin, exogenous interferon gamma holds promise in treatment of arenaviral infections.

IMMUNOPROPHYLAXIS AND IMMUNOTHERAPY

Passive immunization has been attempted for treatment of most VHF infections. This approach has often been taken in desperation, owing to the limited availability of effective antiviral drugs. Anecdotal case reports describing miraculous successes are frequently tempered by more systematic studies, where efficacy is less obvious. For all VHF viruses, the benefit of passive immunization seems to be correlated with the concentration of neutralizing antibodies, which are readily induced by some—but not all—of these viruses.

Passive Immunization

Antibody therapy (ie, passive immunization) also has a place in the treatment of some VHFs. Argentine hemorrhagic fever responds to therapy with two or more units of convalescent plasma that contain adequate amounts of neutralizing antibody (or an equivalent quantity of immune globulin), provided that treatment is initiated within 8 days of onset.[35] Antibody therapy is also beneficial in the treatment of Bolivian hemorrhagic fever. Efficacy of immune plasma in treatment of Lassa fever[36] and Crimean-Congo hemorrhagic fever[37] is limited by low neutralizing antibody titers and the consequent need for careful donor selection.

In the future, engineered human monoclonal antibodies may be available for specific, passive immunization against the VHF agents. In HFRS, a passive immunization approach is contraindicated for treatment, since an active immune response is usually already evolving in most patients when they are first recognized, although plasma containing neutralizing antibodies has been used empirically in prophylaxis of high-risk exposures.

Active Immunization

The only established and licensed virus-specific vaccine available against any of the hemorrhagic fever viruses is yellow fever vaccine, which is mandatory for travelers to endemic areas of Africa and South America. For prophylaxis against Argentine hemorrhagic fever (AHF) virus, a live-attenuated Junin vaccine strain (Candid #1) was developed at USAMRMC and is available as an Investigational New Drug (IND). Candid #1 was proven to be effective in Phase III studies in Argentina, and plans are proceeding to obtain a New Drug license. This vaccine also provides some cross-protection against Bolivian hemorrhagic fever in experimentally infected primates. Two IND vaccines were developed at USAMRMC against Rift Valley fever; an inactivated vaccine that requires three boosters, which has been in use for 20 years; and a live-attenuated RVF virus strain (MP-12), which is presently in Phase II clinical trials.

For Hantaan virus, a formalin-inactivated rodent brain vaccine is available in Korea, but is not generally considered acceptable by U.S. standards. Another USAMRMC product, a genetically engineered vaccinia construct, expressing hantaviral structural proteins, is in Phase II safety testing in U.S. volunteers. For dengue, a number of live attenuated strains for all four serotypes are entering Phase II efficacy testing. However, none of these vaccines in Phase I or II IND status will be available as licensed products in the near term. For the remaining VHF agents, availability of effective vaccines is more distant.

SUMMARY

The VHF agents are a taxonomically diverse group of RNA viruses that cause serious diseases with high morbidity and mortality. Their existence as endemic disease threats or their use in biological warfare could have a formidable impact on unit readiness. Significant human pathogens include the arenaviruses (Lassa, Junin, and Machupo viruses, the agents of Lassa fever and Argentinean and Bolivian hemorrhagic fevers, respectively). Bunyavirus pathogens include RVF virus, the agent of Rift Valley fever; C-CHF virus, the agent of Crimean-Congo hemorrhagic fever; and the hantaviruses. Filovirus pathogens include Marburg and Ebola viruses. The flaviviruses are arthropod-borne viruses and include the agents of yellow fever, dengue, Kyasanur Forest disease, and Omsk hemorrhagic fever.

The dominant clinical features of VHF are a consequence of microvascular damage and changes in vascular permeability. Patients commonly present with fever, myalgia, and prostration. Full-blown VHF syndrome typically evolves to shock and generalized mucous membrane hemorrhage, and often is accompanied by evidence of neurological, hematopoietic, or pulmonary involvement. A viral hemorrhagic fever should be suspected in any patient who presents with a severe febrile illness and evidence of vascular involvement (subnormal blood pressure, postural hypotension, petechiae, easy bleeding, flushing of the face and chest, nondependent edema), and who has traveled to an area where the virus is known to occur, or where intelligence suggests a biological warfare threat.

Definitive diagnosis rests on specific virological diagnosis, including detection of viremia or IgM by ELISA at presentation. Diagnosis by viral cultivation and identification requires 3 to 10 days or longer and specialized microbiologic containment. Appropriate precautions should be observed in collection, handling, shipping, and processing of diagnostic samples. It is prudent to provide isolation measures that are as rigorous as feasible.

Patients with viral hemorrhagic fevers generally benefit from rapid, nontraumatic hospitalization to prevent unnecessary damage to the fragile capillary bed. Aspirin and other antiplatelet or anticlotting-factor drugs should be avoided. Secondary and concomitant infections including malaria should be sought and aggressively treated. The management of bleeding includes administration of fresh frozen plasma, clotting factor concentrates and platelets, and early use of heparin to control DIC. Fluids should be given cautiously, and asanguineous colloid or crystalloid solutions should be used. Multiple organ system support may be required.

Ribavirin is an antiviral drug with efficacy for treatment of the arenaviruses and bunyaviruses. Passively administered antibody is also effective in therapy of some viral hemorrhagic fevers. The only licensed vaccine available for VHF agents is for yellow fever. Experimental vaccines exist for Junin, RVF, hantaan, and dengue viruses, but these will not be licensed in the near future.

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