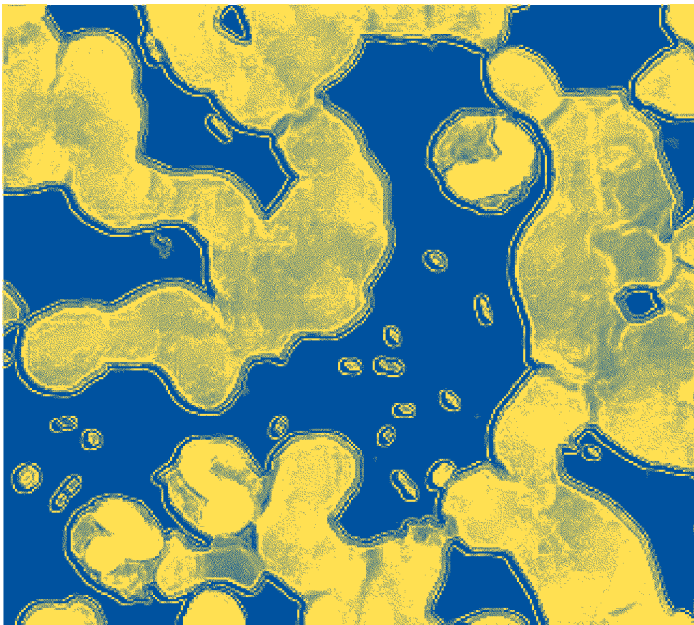


Preparing for and Responding to Bioterrorism

Information for Primary Care Clinicians



Plague and Botulism

Developed by

Jennifer Brennan Braden, MD, MPH

Jeffrey S. Duchin, MD

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*This manual and the accompanying MS Powerpoint® slides are current as of July 2002. Please refer to <http://nwcphp.org/bttrain/> for updates to the material.

Last Revised July 2002

Acknowledgements

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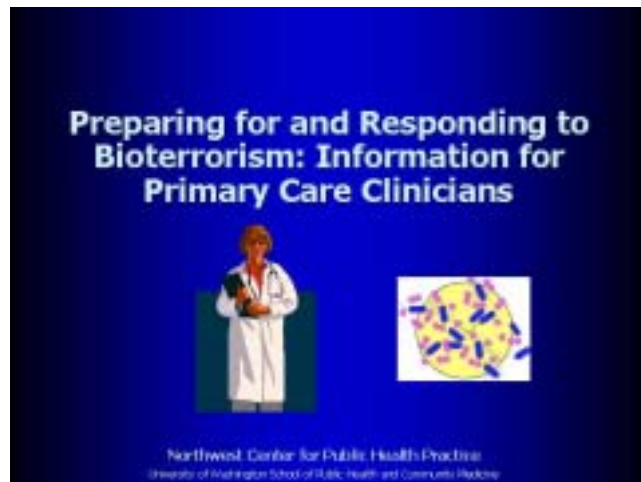
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About This Course



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

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

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

How to Use This Manual

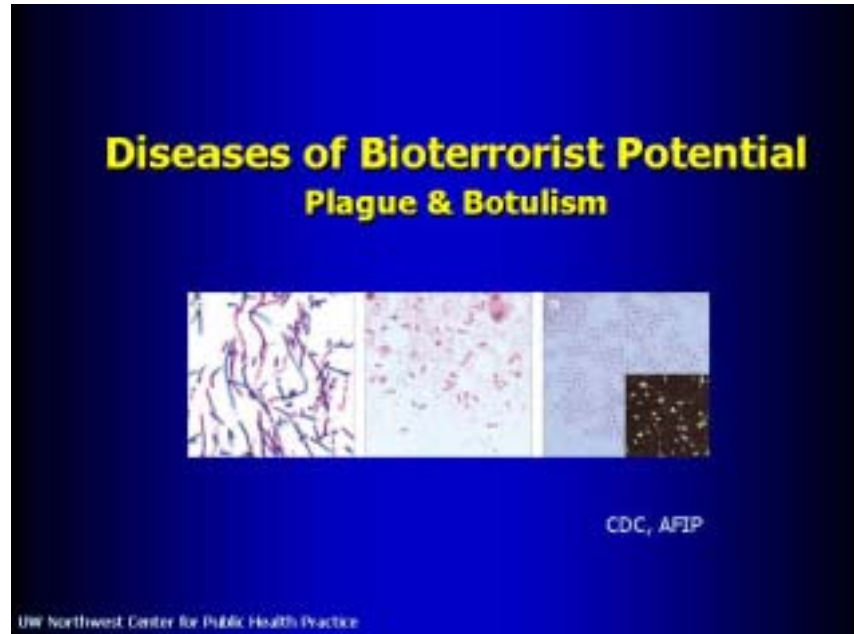
This manual provides the instructor with additional useful information related to the accompanying MS PowerPoint® slides. The manual and slides are divided into four major sections: Introduction to Bioterrorism, Bioterrorism Preparedness and Response, Diseases of Bioterrorist Potential, and Psychological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

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

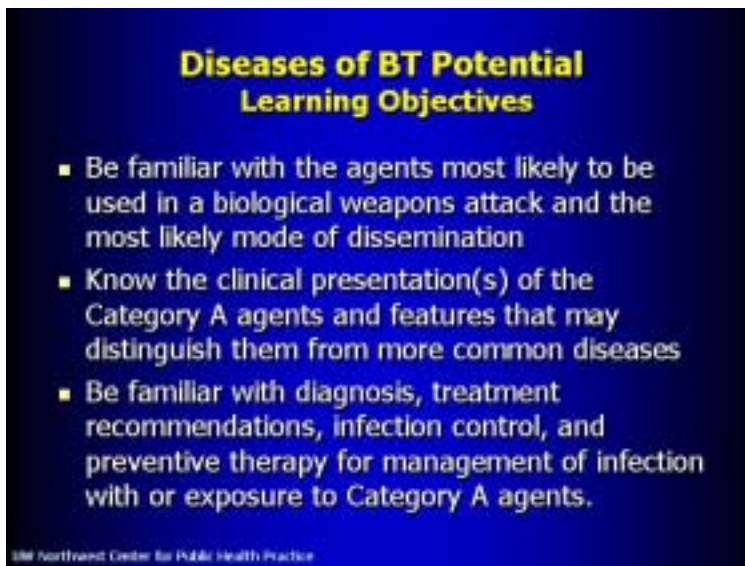
The slide set can be presented in its entirety, in subsections, or as an overview, depending on the level of detail included. The entire course was intended to be presented in a six- to seven-hour block of time, divided into one- to three-hour blocks according to instructor/audience preference. For instructors who want to present a less detailed “overview” course, suggestions for more abbreviated presentations are incorporated into the modules. These latter options are built into the slide set and can be accessed by going to “Custom Shows” (under the “Slide Show” option on the MS PowerPoint® task bar).

Diseases of Bioterrorist Potential

The photo shows, from left to right, gram stains of *Bacillus anthracis* (anthrax), *Yersinia pestis* (plague), and *Francisella tularensis* (tularemia). The source for the first two photos is the CDC, and for the gram stain of *F. tularensis*, the Armed Forces Institute of Pathology



Learning Objectives (Slide 4)



**Diseases of BT Potential
Learning Objectives**

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

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The learning objectives for this session are:

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

Section 1: Biological Agents of Highest Concern

(Slides 6-10)

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

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

Category B agents are of the next highest level of concern and are listed in slides 8 and 9. These agents are moderately easy to disseminate and produce lower mortality and moderate morbidity.

Biological Agents of Highest Concern Category A Agents

- “Easily disseminated,” infectious via aerosol
- Susceptible civilian populations
- Cause high morbidity and mortality
- Person-to-person transmission
- Unfamiliar to physicians – difficult to diagnose/treat
- Cause panic and social disruption
- Previous development for BW

Biological Agents of Highest Concern Category A Agents

- Variola major (Smallpox)
- *Bacillus anthracis* (Anthrax)
- *Yersinia pestis* (Plague)
- *Francisella tularensis* (Tularemia)
- Botulinum toxin (Botulism)
- Filoviruses & Arenaviruses (Viral hemorrhagic fevers)
- Report ANY suspected illness due to these agents to Public Health immediately.

Biological Agents of 2nd Highest Concern Category B Agents

- *Coxiella burnetii* (Q-fever)
- *Brucella* species (brucellosis)
- *Burkholderia mallei* (glanders)
- Alphaviruses (Venezuelan, Western and Eastern encephalomyelitis viruses)
- Ricin toxin from *Ricinus communis* (castor bean)
- Epsilon toxin from *Clostridium perfringens*
- *Staphylococcus enterotoxin B*

Biological Agents of 2nd Highest Concern
Food- or Water-borne Category B Agents

- *Salmonella species*
- *Shigella dysenteriae*
- *Escherichia coli* 0157:H7
- *Vibrio cholera*
- *Cryptosporidium parvum*

A subset of the Category B agents includes food- and water-borne agents. These agents more commonly produce disease outbreaks from a non-deliberate source and may also be employed in a biological attack.

Biological Agents of 3rd Highest Concern
Category C Agents

- Emerging pathogens that could be engineered for mass dissemination in the future
 - Nipah virus
 - Hantaviruses
 - Tick-borne hemorrhagic fever viruses
 - Tickborne encephalitis viruses
 - Yellow fever
 - Multidrug-resistant tuberculosis

CDC, Northwest Center for Public Health Practice

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

The Laboratory Response Network

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

Level A – Most clinical labs are Level A and include public health and hospital labs with a certified biological safety cabinet as a minimum.

Level B – State and local public health labs with BSL-2 facilities that incorporate BSL-3 practices

Level C – BSL-3 facilities with the capability to perform nucleic acid amplification, molecular typing, toxicity testing (Washington Public Health Laboratories, for example)

Level D – Possess BSL-3 and BSL-4 biocontainment facilities and include CDC and USAMRIID labs. Level B/C labs can register for the LRN and then have password-protected access to information over the Web.

Plague (Slides 12-34)

Summary of Key Points

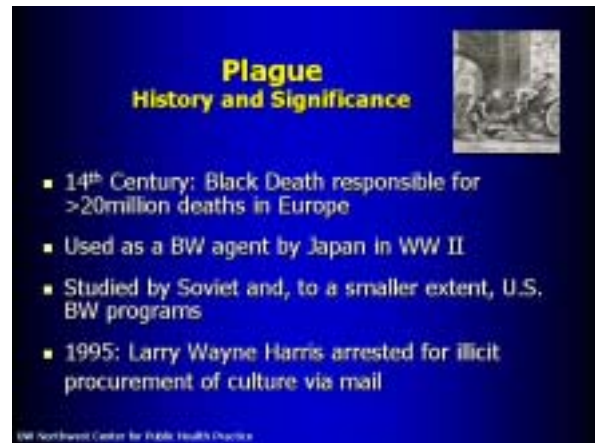
(Listed in slides 32-33)

1. The most likely presentation in a BT attack is pneumonic plague.
2. In addition to the epidemiologic clues noted in module 1 (Introduction to Bioterrorism), clinical clues suggesting pneumonic plague include an abrupt onset of pneumonia with bloody sputum and a fulminant course.
3. Unlike other forms of plague, pneumonic plague is transmitted person to person, and thus respiratory droplet precautions are indicated in suspected cases until 48 hours after the initiation of antibiotic therapy.

Microbiology, History, and Epidemiology (Slides 12-14)

The picture in slide 12 ("Plague in 1665" by S. Wale) depicts plague victims being collected and loaded on a cart.

Naturally occurring plague is transmitted to rats and other rodents following the bite of an infected flea. When the natural rat reservoir is unavailable, fleas will bite humans, as was the case historically during plague epidemics. The resulting form of plague – bubonic plague – is the most common naturally occurring form and is different from that expected in the event of a bioterrorist attack. Although the Japanese used plague-infected fleas as a biowarfare weapon during WW II to create a bubonic plague epidemic, this is not as efficient a weapon as a plague aerosol.




Plague
History and Significance

- 14th Century: Black Death responsible for >20million deaths in Europe
- Used as a BW agent by Japan in WW II
- Studied by Soviet and, to a smaller extent, U.S. BW programs
- 1995: Larry Wayne Harris arrested for illicit procurement of culture via mail

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Plague Epidemiology

- Caused by *Yersinia pestis*
- About 10-15 cases/year U.S.
 - Mainly SW states
- Human plague occurs from bite of an infected flea (bubonic)
- Only pneumonic form of plague is spread person-to-person
 - Last case of person-to-person transmission in U.S. occurred in 1924

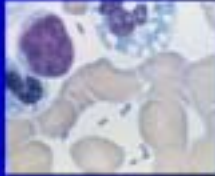


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Currently, a bioterrorist attack is more likely to employ aerosolization of *Y. pestis*, and victims of the attack will present with pneumonic plague. Plague bacilli are killed by sunlight and estimated to remain viable in an aerosol for no longer than one hour following release (Inglesby, et al., JAMA 2000; 283:2281-90).

Yersinia Pestis

- Gram negative, non-motile, non-spore-forming bacillus
- Resistant to freezing temperature and drying, killed by heat and sunlight



Source: Centers for Disease Control and Prevention, Division of Field Epidemiology, Severe Disease, Field Office, CDC

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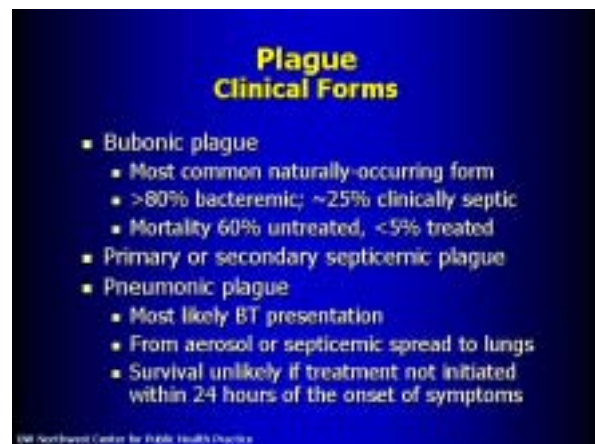
Yersinia pestis, a gram negative bacillus, is the causative agent of plague. Slide 14 shows a peripheral blood smear of a patient with septicemic plague and illustrates the bipolar (“safety pin”) staining characteristically seen in Gram, Wright, and Giemsa stains of *Y. pestis*. It should be noted, however, that bipolar staining is not always observed, and the absence does not necessarily rule out plague.

Clinical Presentation (Slides 15-22)

Key Points

1. Bubonic, pneumonic, and septicemic plague each begin with the acute onset of a nonspecific febrile illness.
2. Pneumonia (without buboes) is the most likely presentation of plague in a BT attack.
3. Pneumonic plague progresses rapidly to respiratory failure and death if not treated early.

Slides 15-22 describe the three clinical forms of plague and their presentations. All three forms begin with the acute onset of fever, chills, myalgia, and malaise.





**Plague
Clinical Forms**

- Bubonic plague
 - Most common naturally-occurring form
 - >80% bacteremic; ~25% clinically septic
 - Mortality 60% untreated, <5% treated
- Primary or secondary septicemic plague
- Pneumonic plague
 - Most likely BT presentation
 - From aerosol or septicemic spread to lungs
 - Survival unlikely if treatment not initiated within 24 hours of the onset of symptoms

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Bubonic Plague

- Incubation: 2-8 days
- Sudden onset nonspecific symptoms: fever, chills, malaise, myalgias, headache
- Nausea/vomiting/abdominal pain in some cases
- Liver and spleen often tender and palpable

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Source: CDC/MSD

The two photos in slide 16 are from the CDC National Center for Infectious Disease, Division of Vector-borne Diseases. The photo on the left shows an ulcerated flea bite caused by *Yersinia pestis*; the photo on the right shows an inguinal bubo in a person with bubonic plague.

Bubonic Plague

- Regional lymphadenitis (buboes)
 - Swollen, very painful lymph nodes
 - Typically inguinal, femoral, axillary, or cervical
 - Erythema overlying skin
 - May have surrounding edema
 - Concurrent with or shortly after onset of other symptoms
- Cutaneous findings (~25% of patients)
 - Possible papule, vesicle, or pustule at inoculation site
 - Purpuric lesions – late

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Bubonic plague involves infection, inflammation, and marked tenderness of the regional lymph nodes draining the inoculation (bite) site. Bacteria gain access to the bloodstream and cause septicemia and endotoxemia with associated complications. Most cases of naturally occurring plague are bubonic plague.

Septicemic plague can be primary, or secondary to bubonic or pneumonic plague. Septicemic plague is frequently complicated by shock and disseminated intravascular coagulation (DIC).

Septicemic Plague

- Primary occurs in absence of buboes
- Secondary from bubonic or pneumonic disease
- Presentation similar to other gram negative septicemias with endotoxin production

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Slide 19 illustrates gangrene secondary to thrombosis of acral blood vessels in septicemic plague (giving the name *Black Death* to fatal cases during previous plague pandemics).

Septicemic Plague

- Can cause DIC, vascular necrosis, and purpura
- Gangrene of acral digits = Black Death (late complication)
- Secondary pneumonia, meningitis may occur



Source: Centers for Disease Control and Prevention, Division of Vector-Borne Infectious Diseases, Fort Collins, CO

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Pneumonic Plague
Clinical Presentation

- Incubation: 1-6 days (usually 2-4 days)
- Acute onset of fever with cough and dyspnea, chest pain
- Hemoptysis characteristic; watery or purulent sputum also possible
- Prominent GI symptoms may be present, including nausea, vomiting, diarrhea, and abdominal pain

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Pneumonic Plague
Clinical Presentation

- Other symptoms include headache, chills, malaise, myalgias
- Rarely, cervical bubo present
- Rapid progression to respiratory failure and shock


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Pneumonic plague is the most likely form expected after a BT attack. Approximately 12 percent of cases of septicemic plague also result in pneumonic involvement. Since a BT attack is most likely to occur via an aerosol release, it is unlikely that the patient with pneumonic plague in this scenario will have a bubo. Pneumonic plague may present as a severe community-acquired pneumonia with chest pain, dyspnea, and cough. Gastrointestinal symptoms may be prominent, and the disease progresses rapidly; both features are also consistent with inhalational anthrax. Unlike inhalational anthrax, patients with pneumonic plague usually have bloody sputum and are infectious.

Pneumonic Plague: Radiological and Lab Findings

Pneumonic Plague
Radiological & Lab Findings

- CXR: variable, but frequently bilateral infiltrates, patchy or consolidated
- Leukocytosis w/bandemia (PMNs)
- Often fibrin split products; liver enzymes may be ↑



Source: Centers for Disease Control and Prevention, Division of Field Epidemiology, Infectious Diseases, April 2001, 22

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Slide 22 shows a chest radiograph of a patient with primary pneumonic plague. The bilateral infiltrates seen here are common in pneumonic plague, but CXR findings are variable and nonspecific. Laboratory findings are also nonspecific and reflect a systemic inflammatory response, multi-organ failure, DIC, and sepsis.

Key Points, Slides 23-28

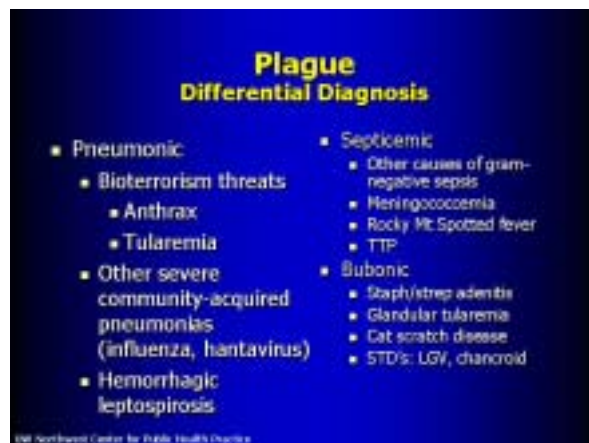
1. The differential diagnosis of pneumonic plague includes other causes of severe pneumonia and sepsis.
2. Clinical and epidemiologic clues are important in the diagnosis of pneumonic plague.
3. Clinicians should not wait for laboratory confirmation of diagnosis to initiate treatment or contact public health authorities.
4. Droplet precautions should be instituted in the case of pneumonic plague.

Differential Diagnosis

The differential diagnosis of plague is listed in slide 23 and includes other causes of lymphadenopathy, severe pneumonia, and sepsis.

Pneumonic

Pneumonic plague can be differentiated from viral pneumonia and pneumonic tularemia by its more fulminant course. Patients with pneumonic plague also usually have bloody sputum, whereas this is either absent or infrequent in community-acquired pneumonia, pneumonic tularemia, and inhalational anthrax. Characteristic mediastinal lymphadenopathy and hemorrhagic necrosis of lymph nodes is seen on CT in anthrax cases. Leptospirosis may present with hemoptysis and could be confused with plague. Conjunctival suffusion is often present in leptospirosis, and fever may be diphasic. Thrombocytopenia is common in hantavirus pulmonary syndrome, but hemorrhagic manifestations and hemoptysis are usually absent.



Bubonic Plague

Staph/strep adenitis – This occurs more commonly in children. Constitutional symptoms other than fever are usually not present.

Glandular tularemia – This has a similar presentation and reservoir to plague, but tularemia tends to have a more gradual course.

Cat scratch disease – A red papular lesion is found at the inoculation site in 50-90%; >90% have a history of cat scratch/lick/bite in the 3-14 days before appearance of the papule. If fever is present at all, it is low-grade

Sexually transmitted diseases: Lymphogranuloma venereum (LGV), chancroid -- history of sexual exposure is present. Lymphadenopathy is preceded by a primary lesion in both cases and may still be present at the onset of lymphadenopathy in chancroid.

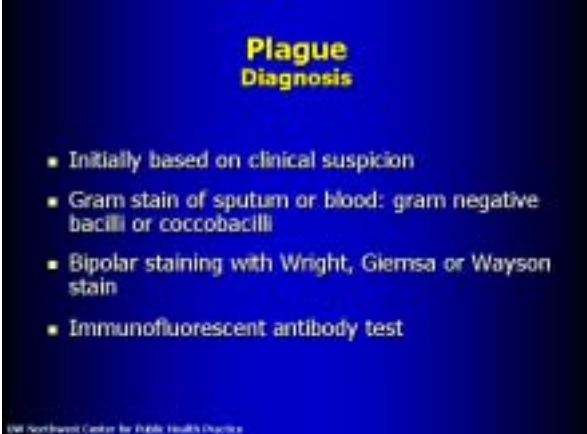
Septicemic Plague

Rocky Mountain Spotted Fever – The rash has a characteristic progression: maculopapular rash on extremities ->palms&soles->rest of body; a petechial rash follows on or after day six in 40-60%.

Thrombotic/Idiopathic Thrombocytopenic Purpura – Patients with ITP are usually systemically well; patients with TTP are acutely ill, accompanied by neurological signs.

Diagnosis (Slides 24-25)

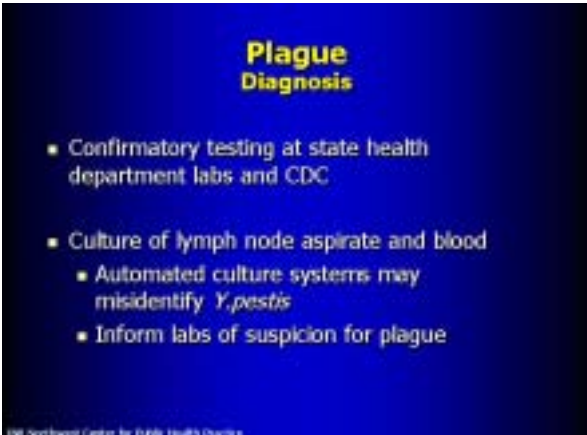
Diagnosis of pneumonic plague is primarily based on clinical suspicion (abrupt onset of pneumonia, bloody sputum, epidemiologic clues as described in Module 1 [Introduction to Bioterrorism]). If a patient is suspected of having plague, the local or state health department should be contacted immediately. The Washington Public Health Laboratory can report preliminary results within four hours (including indirect fluorescent antibody testing), but final culture results may take days. Pneumonic plague is likely to be fatal if not treated within 24 hours of infection, and thus clinicians should not wait for confirmation to initiate treatment.



**Plague
Diagnosis**

- Initially based on clinical suspicion
- Gram stain of sputum or blood: gram negative bacilli or coccobacilli
- Bipolar staining with Wright, Giemsa or Wayson stain
- Immunofluorescent antibody test

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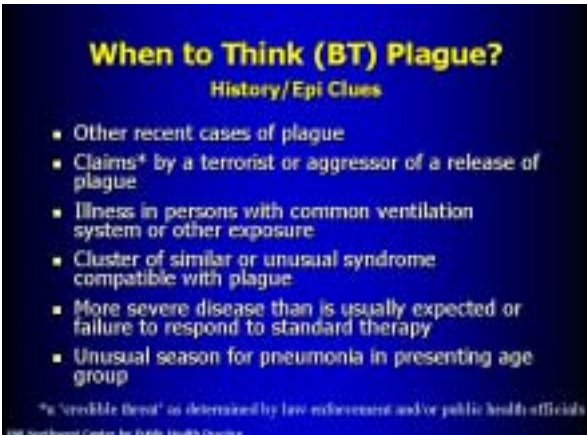
**Plague
Diagnosis**

- Confirmatory testing at state health department labs and CDC
- Culture of lymph node aspirate and blood
 - Automated culture systems may misidentify *Y. pestis*
 - Inform labs of suspicion for plague

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When to think plague?

Slide 26 highlights epidemiological and patient history clues that can assist the clinician in determining when to suspect plague and how to prioritize the medical evaluation. The presence of these clues may lead the clinician to look for a critical agent as a potential source of disease in the patient.



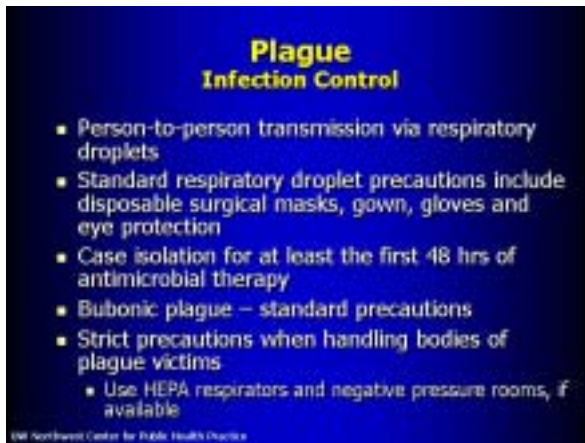
When to Think (BT) Plague?
History/Epi Clues

- Other recent cases of plague
- Claims* by a terrorist or aggressor of a release of plague
- Illness in persons with common ventilation system or other exposure
- Cluster of similar or unusual syndrome compatible with plague
- More severe disease than is usually expected or failure to respond to standard therapy
- Unusual season for pneumonia in presenting age group

*"credible threat" as determined by law enforcement and/or public health officials

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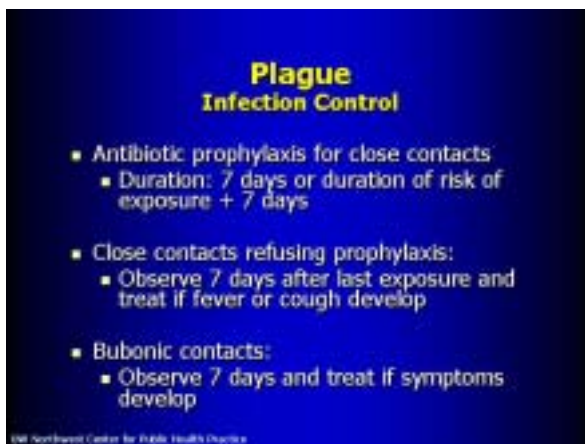
Infection Control (Slides 27-28)



Plague Infection Control

- Person-to-person transmission via respiratory droplets
- Standard respiratory droplet precautions include disposable surgical masks, gown, gloves and eye protection
- Case isolation for at least the first 48 hrs of antimicrobial therapy
- Bubonic plague – standard precautions
- Strict precautions when handling bodies of plague victims
 - Use HEPA respirators and negative pressure rooms, if available

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Plague Infection Control

- Antibiotic prophylaxis for close contacts
 - Duration: 7 days or duration of risk of exposure + 7 days
- Close contacts refusing prophylaxis:
 - Observe 7 days after last exposure and treat if fever or cough develop
- Bubonic contacts:
 - Observe 7 days and treat if symptoms develop

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Person-to-person transmission of pneumonic plague is thought to occur via respiratory droplets. Patient isolation, standard respiratory droplet precautions, and disposable surgical masks are recommended to prevent transmission for at least the first 48 hours of antimicrobial therapy (Bolyard, et al, Am J Infect Control, 1998;26:289-354). Patients should wear surgical masks during transport. Exposed persons refusing antibiotic prophylaxis should be closely watched for development of fever or cough for seven days after last exposure and treated immediately if either occur. Microbiology lab personnel should be alerted when specimen testing from suspected or confirmed plague cases is requested. Bodies of patients who have died of plague should be handled with strict precautions. Aerosol generation procedures should be avoided, and appropriate high-efficiency particulate respirators and negative pressure rooms employed if such procedures are necessary.

Treatment and Prophylaxis (29-31)

Key Points

1. Gentamicin and streptomycin are preferred antibiotics for pneumonic plague in a contained casualty setting; duration of treatment should be 10 days.
2. Doxycycline and ciprofloxacin are alternate antibiotics for contained casualties and are preferred for pneumonic plague in a mass casualty setting or for prophylaxis.
3. Antibiotic resistance patterns should be taken into consideration in choosing therapy.
4. Antibiotic prophylaxis for close contacts of cases, and those exposed to plague aerosol, should be continued for seven days beyond the time of exposure.

Current treatment recommendations for patients with pneumonic plague are listed in slides 29 and 30. Note that these recommendations were created by the Working Group on Civilian Biodefense and assume a deliberate source of infection. In the event of a BT attack of plague, clinicians should be alert to current recommendations made by CDC for patient management (<http://www.bt.cdc.gov>).

Treatment of pneumonic plague in a mass casualty setting should be continued for ten days, whereas post-exposure prophylaxis need only be given for seven days following the end of the exposure period.

Recommendations for Treatment of Patients With Pneumonic Plague in a Contained Casualty Setting*

- **Adults**
 - Streptomycin 1gm IM BID x 10d
 - Gentamicin 5mg/kg IM/IV qd, or 2mg/kg loading followed by 1.7mg/kg IM/IV TID x 10d
- **Children**
 - Streptomycin 15mg/kg IM BID x 10d (max 2g/d)
 - Gentamicin 2.5mg/kg IM/IV TID x 10d
- **Pregnant women – gentamicin, doxycycline, ciprofloxacin**
- **Alternates: ciprofloxacin, doxycycline, chloramphenicol**

*Working Group on Civilian Biodefense consensus based recommendations
Source: www.bt.cdc.gov

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Recommendations for Treatment of Patients With Pneumonic Plague in Mass Casualty Settings and for Postexposure Prophylaxis*

- **Adults & Pregnant women**
 - Doxycycline 100mg po BID x 7-10d
 - Ciprofloxacin 500mg po BID x 7-10d
- **Children <45kg**
 - Doxycycline 2.2mg/kg po BID x 7-10d (if 45+ kg, give adult dosage)
 - Ciprofloxacin 20mg/kg po BID x 7-10d
- **Alternate: Chloramphenicol**

*Working Group on Civilian Biodefense consensus based recommendations
Source: www.bt.cdc.gov

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Plague
Other Treatment/Prophylactic Measures

- Supportive Care –e.g., IV crystalloids; heparin & pressor agents rarely needed
- Buboes – aspiration, and not I&D, recommended
- Vaccine - none currently available
 - Old killed whole cell vaccine effective against bubonic, not pneumonic form
 - F1-V antigen vaccine in development at USAMRIID

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Supportive care, including hemodynamic monitoring, correction of fluid imbalance and acid-base disturbances, and relief of pressure in painful buboes, if present, is indicated. For the latter, aspiration and not incision and drainage is recommended to avoid unnecessary potential for contamination.

Plague
Summary of Key Points

- The most likely presentation in a BT attack is pneumonic plague.
- In addition to the epidemiologic clues noted in Module 1 (Introduction to Bioterrorism), clinical clues suggesting pneumonic plague include an abrupt onset of pneumonia with bloody sputum and a fulminant course.

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Summary of Key Points

Plague
Summary of Key Points

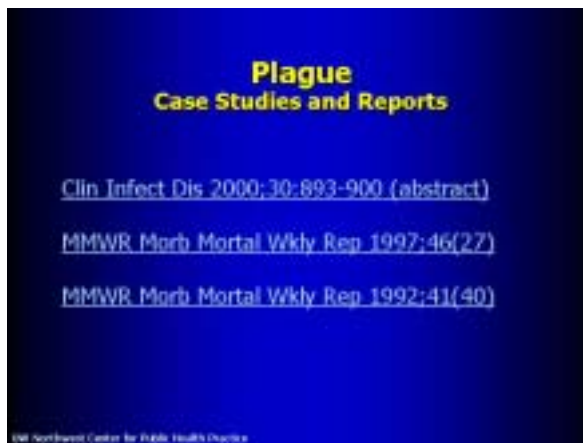
- Unlike other forms of plague, pneumonic plague is transmitted person to person, and thus respiratory droplet precautions are indicated in suspected cases until 48 hours after the initiation of antibiotic therapy.

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Case Studies and Reports

This slide contains links to case studies and reports on plague. Note that these are not BT-related cases.

Navigation Slide (slide 35)



Botulism (Slides 36-57)

Summary of Key Points:

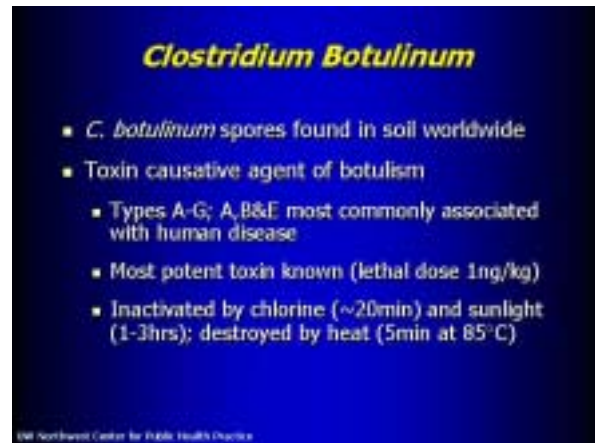
1. Botulism presents as symmetric bilateral weakness or paralysis with cranial nerve abnormalities and a clear sensorium.
2. Inhalational botulism does not occur naturally, and any potential cases suggest a deliberate source of infection.
3. Gastrointestinal symptoms may not occur with inhalational botulism or with food-borne botulism (e.g., resulting from deliberate contamination of the food supply).
4. A careful dietary and activity/travel history is important when evaluating potential botulism cases.
5. An outbreak occurring with a common geographic factor, but with no common food exposure, would suggest a deliberate aerosol exposure.
6. Botulinum antitoxin must be administered as soon as possible for optimum results.
7. Contact your local health department for any suspicion of botulism.

Key Points, Slides 36-44

1. Naturally occurring forms of botulism include infant, food-borne, and wound botulism.
2. A bioterrorist attack with botulinum toxin is most likely to be via aerosol (inhalational botulism) or possibly through contamination of the food supply.
3. Botulism presents as a symmetric descending flaccid paralysis, regardless of the mode of infection.

Microbiology, Epidemiology, and Pathogenesis (Slides 36-40)

Botulism is caused by botulism toxin, a zinc protease produced by *Clostridium botulinum*. *C. botulinum*, a ubiquitous soil bacteria, produces hardy spores that survive for extended periods in the environment. Vegetative cells germinated from spores produce toxin under anaerobic conditions. Several toxin types, A-G, have been classified based on reactivity with specific antitoxins, but all have similar effects. Types A, B, and E are most often associated with human disease. The toxin is easily inactivated by heat, sunlight, and chlorine. Contamination of the water supply is thus unlikely (this would also require a large, impractical amount to achieve a high enough concentration in the water). Contamination of untreated beverages and food is possible and could result in disease if not heated sufficiently prior to consumption.



Clostridium Botulinum

- *C. botulinum* spores found in soil worldwide
- Toxin causative agent of botulism
 - Types A-G; A, B&E most commonly associated with human disease
 - Most potent toxin known (lethal dose 1ng/kg)
 - Inactivated by chlorine (~20min) and sunlight (1-3hrs); destroyed by heat (5min at 85°C)

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Botulism & Bioterrorism

- Weaponized by former U.S. and Soviet offensive BW programs
- Iran, Iraq, N. Korea, Syria believed to have developed/be developing toxin as a weapon
- Therapeutic botox: impractical BT weapon
 - Dipsied vial of type A only 0.3% estimated human lethal inhalational dose
- Aerosol use or food supply sabotage most likely

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Botulinum toxin has been studied extensively for use as a biological weapon. Although botulism is rarely fatal when treated early and appropriately, prolonged ventilatory support is often necessary. An outbreak could thus severely task the health care system's resources. The need for significant supportive care and the relative availability of botulinum spores (spores can be found worldwide in soil) make botulinum toxin a likely biological weapon.

Botulism Clinical Forms



- Food-borne
 - Toxin produced anaerobically in improperly processed or canned, low-acid foods contaminated by spores
- Wound
 - Toxin produced by organisms contaminating wound
- Infant
 - Toxin produced by organisms in intestinal tract
- Inhalation botulism
 - No natural* occurrence, developed as BW weapon

*3 accidental cases in veterinary personnel, W. Germany, 1962

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Clostridium Botulinum Epidemiology

- Approximately 100 reported cases botulism/year in the U.S.
 - Infant most common (72%)
 - Food-borne not common
- Incubation (food-borne): 12-72 hrs (range 2hr-6d)
 - Dose dependent
 - Could be less following a BT attack
- No person-to-person transmission
- Death 60% untreated; <5% treated

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Clostridium Botulinum Pathogenesis

- Toxin absorbed into circulation via mucosal surface or wound, not intact skin
- Binds acetylcholine receptor irreversibly and blocks release of acetylcholine into neuromuscular junction

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Food-borne botulism results from production of toxin in foods contaminated with botulism spores that are canned or processed under conditions favorable for toxin production. Wound botulism results from toxin production by spores contaminating devitalized tissue. Infant botulism is the most common form reported in the U.S. and results from toxin production by organisms residing in the intestinal tract. All forms of botulism occur from the absorption of toxin into the circulation through mucosal surfaces or wounds.


The incubation period for food-borne botulism is 12-72 hours and is dose-dependent. Inhalational botulism does not occur naturally and should always suggest a deliberate source. It is likely that the incubation period for botulism following an aerosol exposure would be less than that following a food-borne exposure. No person-to-person spread occurs, and no special infection control precautions are indicated for botulism cases.

Toxin does not penetrate intact skin. Once absorbed, the toxin irreversibly binds at the neuromuscular junction, preventing the release of acetylcholine and muscle contraction.

Clinical presentation (Slides 41-44)

The classic clinical presentation of botulism is described in slides 41-44. Note that the gastrointestinal symptoms of botulism are actually thought to result from other bacterial metabolites in food and, thus, may not be present in either an aerosol attack or in a deliberate contamination of the food supply with a purified form of the toxin.

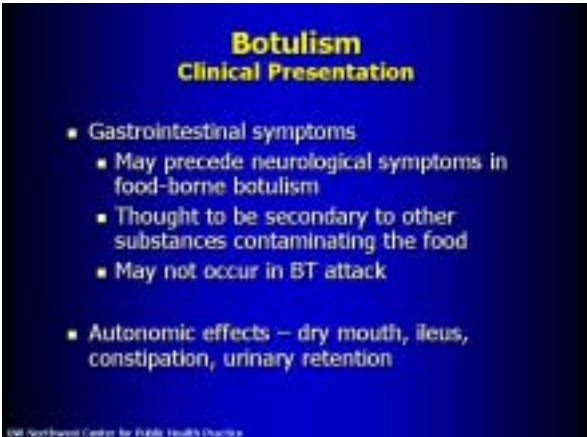
Botulism presents as an afebrile, symmetric descending flaccid paralysis beginning in the bulbar musculature. Symptoms (slide 43) include diplopia, blurry vision, dysphagia, dysarthria, fatigue, dizziness, dyspnea, and gastrointestinal symptoms. The latter may be absent in both aerosol exposure to purified toxin and naturally occurring food-borne cases.



**Botulism
Clinical Presentation**

- Acute, afebrile, symmetric descending flaccid paralysis
 - Always begins in bulbar musculature --> cranial nerve palsies
 - Skeletal muscle paralysis follows
 - Respiratory failure can occur in as little as 24 hrs
- Clear sensorium: sensation and mental status normal
- Afebrile patient

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**Botulism
Clinical Presentation**

- Gastrointestinal symptoms
 - May precede neurological symptoms in food-borne botulism
 - Thought to be secondary to other substances contaminating the food
 - May not occur in BT attack
- Autonomic effects – dry mouth, ileus, constipation, urinary retention

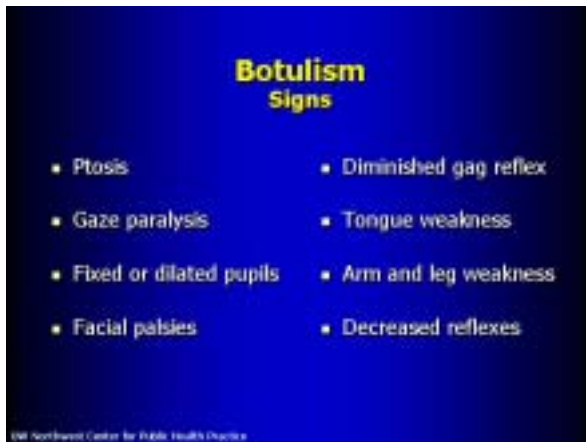
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**Botulism
Symptoms**

- Diplopia
- Blurry vision
- Dysphagia
- Dysarthria
- Fatigue
- Dizziness
- Dyspnea
- GI symptoms

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Signs of botulism (slide 44) include alert mental status, ptosis, gaze paralysis, fixed or dilated pupils, facial palsies, diminished gag reflex, tongue weakness, arm and leg weakness, and decreased reflexes. Sensory changes are not present and suggest other etiologies. One exception is paresthesias secondary to hyperventilation, which can result from anxiety. Gag and cough reflexes, control of secretions, oxygen saturation, vital capacity, and inspiratory force should be monitored in cases that are still progressing. Progressive paralysis results in failure to control secretions and ventilatory failure, requiring airway intubation and mechanical ventilation.

Differential Diagnosis (Slides 45-46)

The differential diagnosis for botulism is listed in slides 45-46. Clinical history and physical exam are the most important tools in differentiating botulism from other similar syndromes. The occurrence of clusters of cases would be suggestive of botulism over alternative diagnoses. Prominent cranial nerve palsies disproportionate to milder weakness and hypotonia below the neck, symmetrical involvement, and absence of sensory nerve damage distinguish botulism from other causes of flaccid paralysis (Arnon et al., JAMA 2001;285:1059-1070). Consultation with a neurologist is recommended to help with complicated diagnoses. Common conditions that may be confused with botulism include Guillain-Barre syndrome (especially the variant Miller-Fisher syndrome), myasthenia gravis, and stroke. Other common misdiagnoses include intoxication with depressants, Lambert-Eaton Syndrome, and tick paralysis.

Botulism Differential Diagnosis	
Condition	Features that distinguish condition from botulism
Guillain-Barre and variants	H/o 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

Source: Arnon et al. JAMA 2001;285:1059-1070

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Botulism Differential Diagnosis	
Condition	Features that distinguish condition from botulism
Intoxication w/depressants	H/o exposure; excessive drug levels in body fluids
Lambert-Eaton syndrome	Increased strength w/sustained contraction; evidence of lung carcinoma; EMG findings similar to botulism
Tick paralysis	Paresthesias; ascending paralysis; tick attached to skin

Source: Arnon et al. JAMA 2001;285:1059-1070

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Diagnosis and Treatment (Slides 47-52)

Key Points

1. Botulism is a clinical diagnosis – public health should be notified and treatment initiated before confirmatory testing.
2. Confirmatory laboratory testing by a BSL-2 laboratory (state and some local public health labs) should be done for suspected cases.
3. Treatment of botulism includes early administration of antitoxin, careful monitoring of respiratory status, and possibly ventilatory support.

Botulism Diagnosis

- Mouse bioassay: available at CDC and certain public health labs
 - In King County, call Public Health – Seattle & King County: (206) 296-4774
- EMG findings – nonspecific but may be helpful
 - Normal nerve conduction velocity and sensory nerve function; brief small amplitude motor potentials, facilitation with repetitive stimulation

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Suspected cases of botulism should be reported immediately to the local and state health department. In Washington, botulism testing is available at the State Public Health Laboratories. Laboratory testing is done with a mouse bioassay in which anti-toxin protects the mouse from toxin in the clinical sample. Blood (>30cc for adults in a “tiger” or red-top tube), stool, gastric aspirate or vomitus, and left-over food samples are appropriate specimens for testing.

Botulism Diagnosis

- Exclusionary tests to rule out other causes
 - Normal CSF
 - Edrophonium (“Tensilon test”)
 - Reverses paralysis in myasthenia gravis
 - May have false positive with botulism
 - Normal imaging
 - Evaluate for presence of ticks

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Electromyogram (EMG), CSF analysis, CT scan of the brain, and the edrophonium chloride (anticholinesterase) test can be used to evaluate for other common conditions that may be confused with botulism: Guillain-Barre syndrome (especially the variant Miller-Fischer syndrome), stroke, and myasthenia gravis.

Trivalent (A, B, E) botulinum antitoxin prevents binding of additional toxin subsequent to its administration but does not reverse the action of already-bound toxin. Antitoxin is most useful early in the course of illness while progression is occurring. Experts advise it be withheld if the patient is improving from maximal paralysis. Recovery depends on the regeneration of new motor axons and may take weeks to months.

Specific treatment with antitoxin must be initiated as soon as possible, since antitoxin does not reverse the effects of bound toxin and will have little to no benefit once maximal toxin binding has occurred and the clinical progression has stabilized. Recent data describe a 6 percent death rate from food-borne botulism. Many cases require intensive care, prolonged mechanical ventilation, and extensive rehabilitation. In addition to antitoxin, ventilation, and supportive care including nutrition through tube or parenteral feeding, fluid balance, and treatment of complications (e.g. pneumonia and other infections, pressure ulcers) must be provided.

Specimen Collection *C. botulinum*

In Washington, call local (in King County: (206) 296-4774) or State Department of Health (206-361-2914) for prior approval.

Serum	Collect 10-15 ml serum as soon as possible after the onset of symptoms and before administration of antibiotics; use red top or separator type tubes; ship cold
Feces	10-50 g of stool should be collected in sterile container; sterile enema water minus material (2fl oz) o.k.; ship cold
Food sample	Food should be left in original container if possible or placed in a sterile unbreakable container. Place containers in leak-proof plastic bags. Do not freeze. Ship cold
Wound or tissue	Place in an airtight collection device. Transport at room temperature.
Gastric contents/vomit (>0gms)	Ship same as serum

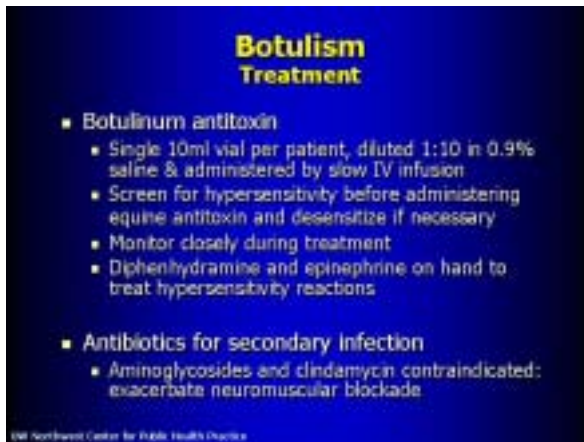
Source: CDC, 2004 A-2716, "Best Practices for Lymphatic System", Michigan Department of Community Health, Washington State Department of Health, Public Health Laboratory

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Botulism Treatment

- Ventilatory assistance and supportive care
 - Recovery depends on regeneration of new motor axons and may take weeks to months
- Botulinum antitoxin
 - Most effective if given early; does not reverse action of already-bound toxin
 - Trivalent equine product against types A, B, and E currently available from CDC
 - Heptavalent (A-G) antitoxin - investigational
 - Monovalent human anti-serum for infant botulism - investigational

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The currently licensed antitoxin is effective against the three most commonly occurring toxins – A, B & E. A botulism outbreak resulting from a BT attack could potentially occur with toxins C, D, F, or G. The current recommended dose is one 10 ml vial per patient (providing between 5500 and 8500 IU of each type-specific antitoxin) diluted 1:10 in 0.9 % saline and administered by slow IV infusion. This dose greatly exceeds the amount of toxin present in serum of food-borne botulism cases. If necessary in the context of large exposures to toxin, neutralization of toxin can be determined by re-checking the serum for toxin after treatment.

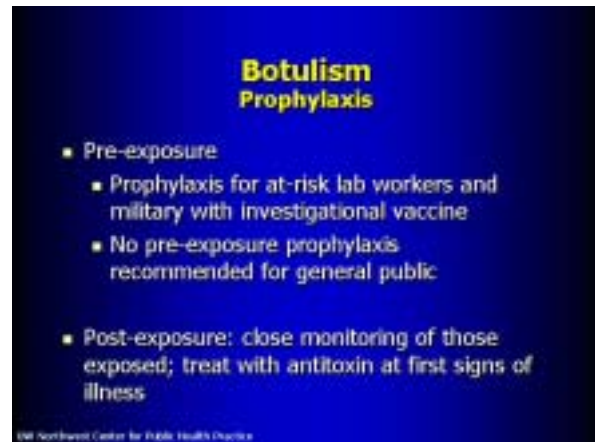
Adverse effects of botulism antitoxin include a spectrum of hypersensitivity reactions to equine antiserum: urticaria, serum sickness, and anaphylaxis.

Patients should be screened for hypersensitivity to horse serum according to instructions in the package insert before receiving the equine antitoxin and desensitized if necessary. Patients should be closely monitored during treatment, and diphenhydramine and epinephrine should be on hand during administration of antitoxin to treat hypersensitivity reactions. Aminoglycosides and clindamycin exacerbate neuromuscular blockade and should not be used to treat secondary infections in botulism patients (antibiotics have no known direct effect on the botulinum toxin).

Prophylactic use of botulism antitoxin for potentially exposed but asymptomatic persons is not recommended. Asymptomatic persons who may have been exposed to botulism toxin should be under medical observation and treated at the first signs of illness. An investigational pentavalent botulism toxoid vaccine has been used by the military and for certain laboratory workers, but is not available for general use and is not effective in post-exposure prophylaxis.

Decontamination

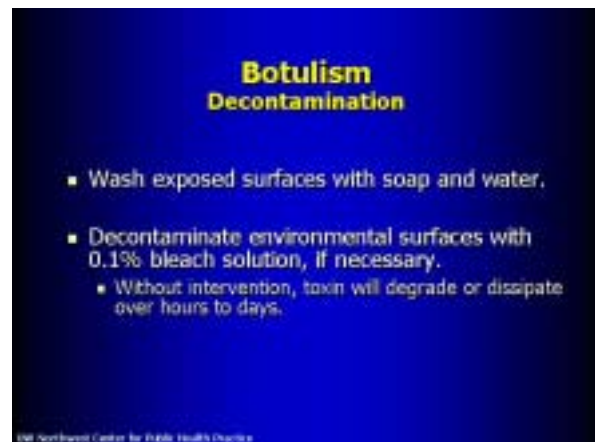
After exposure to botulinum toxin, clothing and skin should be washed with soap and water. The toxin will degrade or dissipate in the environment over hours to days. Hypochlorite bleach solution, 0.1%, can be used if necessary to clean contaminated surfaces.



Botulism Prophylaxis

- Pre-exposure
 - Prophylaxis for at-risk lab workers and military with investigational vaccine
 - No pre-exposure prophylaxis recommended for general public
- Post-exposure: close monitoring of those exposed; treat with antitoxin at first signs of illness

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Botulism Decontamination

- Wash exposed surfaces with soap and water.
- Decontaminate environmental surfaces with 0.1% bleach solution, if necessary.
 - Without intervention, toxin will degrade or dissipate over hours to days.

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Summary of Key Points

Botulism
Summary of Key Points

- Botulism presents as symmetric bilateral weakness or paralysis with cranial nerve abnormalities and a clear sensorium.
- Inhalational botulism does not occur naturally, and any potential cases suggest a deliberate source of infection.

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Botulism
Summary of Key Points

- An outbreak occurring with a common geographic factor, but with no common food exposure, would suggest a deliberate aerosol exposure.
- Botulinum antitoxin must be administered as soon as possible for optimum results.
- Contact your local health department for any suspicion of botulism.

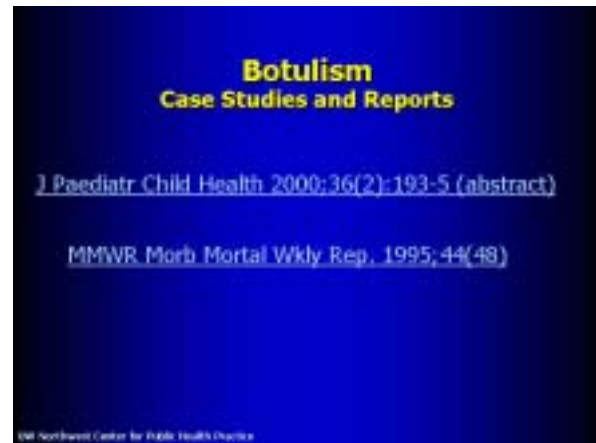
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Botulism
Summary of Key Points

- Gastrointestinal symptoms may not occur with inhalational botulism or with food-borne botulism (e.g., resulting from deliberate contamination of the food supply).
- A careful dietary and activity/travel history is important when evaluating potential botulism cases.

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Case Studies and Reports



Summary: Category A Critical Agents

Summary - Category A Critical Agents

Disease	Infectious Dose in Man	Infective Dose* (Animals)	Incubation Period	Duration of Illness	Signs, Case Fatality
Botulinum toxin	ns	0.0001-0.0010 spores	1-6 days	3-8 days (usually fatal if untreated)	High
Pneumonic Plague	High	100-500 organisms	2-9 days	1-6 days, usually fatal	High unless treated within 12-24 hours; moderate if untreated
Tularemia	ns	10-50 organisms	3-10 days (average 5-8)	2-3 weeks	High to moderate
Smallpox	High	Assumed low (10-100 organisms)	7-17 days (average 12)	4 weeks	High to moderate
Viral Hemorrhagic Fevers	Moderate	1-10 organisms	2-21 days	Length between 1-60 days	High for 20% or more, moderate with 50%
Bubonic	ns	0.001 µg/kg or 1 LD ₅₀ for type A	1-5 days	Deaths in 24-72 hours, 100% mortality if not treated	High without respiratory support

*Infectious dose may be less in certain circumstances

Modified from: [USAMRIID's Medical Management of Biological Emergencies Handbook](#)

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**Summary
Category A Critical Agents**

- Decontamination of exposed persons
 - Showering or washing thoroughly with soap and water adequate for most; bleach not necessary
- Infection control
 - Standard precautions – all cases
 - Airborne and contact precautions – smallpox and viral hemorrhagic fevers
 - Droplet precautions – pneumonic plague

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Resources

Resources

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

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Resources

- Office of the Surgeon General: Medical Nuclear, Biological and Chemical Information <http://www.nbc-med.org>
- St. Louis University Center for the Study of Bioterrorism and Emerging Infections – fact sheets and links <http://bioterrorism.slu.edu>
- Public Health - Seattle & King County <http://www.metrokc.gov/health>

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Resources

- American College of Physicians – links to BT resources, including decision support tools and palm documents <http://www.acponline.org>
- Self-Assessment (case scenarios – chemical and biological) http://www.acponline.org/bioterror/self_assessment.htm
- MMWR Rec. and Rep. Case definitions under public health surveillance. 1997;46(RR-10):1-55

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In Case of An Event...

**In Case of An Event...
Web Sites with Up-to-Date Information and Instructions**

- Centers for Disease Control and Prevention
<http://www.bt.cdc.gov/EmContact/index.asp>
- Saint Louis University, CSB & EI
<http://bioterrorism.slu.edu/hotline.htm>
- WA State Local Health Departments/Districts
<http://www.doh.wa.gov/LHJMap/LHJMap.htm>
- Level A Lab Protocols: Presumptive Agent ID
<http://www.bt.cdc.gov/LabIssues/index.asp>

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

**In Case of An Event...
Web Sites with Up-to-Date Information and Instructions**

- FBI Terrorism Web Page
<http://www.fbi.gov/terrorism/terrorism.htm>
- WA State Emergency Mgt Division – Hazard Analysis Update
<http://www.wa.gov/wsem>
- Mail Security
<http://www.usps.com/news/2001/press/serviceupdates.htm>
- Links to your state health department
<http://www.astha.org/state.html>
- NIOSH – Worker Safety and Use of PPE
<http://www.cdc.gov/niosh/emres01.html>

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