

Chapter 13

Natural and Intentional Epidemics

OBJECTIVES

1. Predict how the medical response to an outbreak is likely to differ from the response to a conventional disaster.
2. Recognize the importance of early notification of public health officials for cases that raise suspicion of a new outbreak.
3. Recognize the additional challenges of caring for critically ill patients who are contagious with an organism that can easily spread to health professionals and other patients.
4. Describe the environmental and personal protective equipment (PPE) necessary for contact, droplet, and airborne precautions.

I. INTRODUCTION

Both natural and deliberate outbreaks from exposure to serious pathogens (or toxins) may cause large numbers of victims who will require critical care. Moreover, such a scenario will tax hospitals' capabilities for laboratory diagnosis of cases, distribution of postexposure prophylaxis, epidemiologic tracking of the scale and geographic scope of the event and medical management of patients. The response to an outbreak versus another type of disaster will most likely result in a delay in detection, secondary spread of contagious pathogens and post-exposure prophylaxis. Consequently, it is important to recognize these differences in order to provide the most appropriate situational and medical response.

II. OUTBREAKS MAY DIFFER FROM OTHER DISASTERS

The primary way in which an intentional outbreak differs from other disasters is a delay in detection that could be caused by a multitude of circumstances. A covert

release of a biological agent may initially go undetected. Additionally, most agents have an incubation period of at least a few days until symptoms occur. Due to travel patterns, patients may present to a number of hospitals in a larger geographical range than is associated with a natural outbreak, which is typically isolated to a specific geographic location. While some of the symptoms and signs may mimic those commonly seen in everyday medical practices, others are nonspecific (eg, fever, shortness of breath, multilobar pneumonia or acute respiratory distress syndrome (ARDS) for pneumonic plague).

Aside from the added issue of fear, another way in which an intentional outbreak differs from other disasters is the secondary spread of contagious pathogens in a hospital setting. The pathogen could be transmitted from person-to-person before appropriate infection control (IC) measures are instituted. Additionally, an outbreak differs from other disasters in the potential need for postexposure prophylaxis, and it may require prophylaxis and/or immunization to be administered to HCWs as well as the community-at-large. (Not all diseases will have that aspect of a response.)

III. EARLY ACTIONS

Clinicians who suspect that an individual has a rare biologic disease should contact the appropriate public action officials immediately. Although most clinicians prefer receiving a confirmation about their suspicions before obtaining consultations, there is no time to do so under these circumstances. Confirmation may be delayed due to either the lack of available tests or rapid diagnostic ones (eg, blood cultures that can

take several hours to days to yield a result) or the inability of the hospital laboratory to confirm certain diagnoses.

There are several reasons for notifying public health officials early on. First and foremost, they can notify other clinicians, who will be on heightened alert for individuals presenting with suspicious signs and symptoms. This, in turn, may allow for the earlier identification and treatment of victims. Second, notifying officials may allow for earlier confirmation of the outbreak, especially if diagnostic tests are unavailable at most hospitals as public health officials have access to confirmatory laboratory tests that hospitals may not. Finally, early notification will allow more time to mobilize public health distribution of postexposure prophylaxis or initiate other infection control or public health measures (such as quarantine) to individuals who have been exposed but are not yet ill and perform epidemiologic investigations and interventions. For some diseases, there is a small window of opportunity for large-scale prophylaxis and huge logistical barriers for distributing large quantities of countermeasures.

Notifying public officials early on also can result in the implementation of appropriate infection control (IC) measures at other hospitals. This includes isolating patients as soon as there is suspicion of a contagious disease.

IV. INFECTION CONTROL

Hospitals are high-risk areas for secondary spread of contagious diseases for several reasons. Ill patients may be more contagious than others at least at certain stages of the disease. There may be a higher concentration of contagious patients in a hospital versus the community-at-large. Infected hospitalized patients may be more likely to

spread disease due to higher pathogen shedding, aerosol generating procedures and interventions, as well as frequent staff contact with the patient and their sputum, stool and other bodily fluids. Also, initially uninfected hospitalized patients may be more susceptible to secondary spread of infection as a result of comorbidities and effective immunosuppression.

For these reasons, it is critical to implement and strictly adhere to the use of standard IC precautions, and in some cases, isolation precautions or even quarantining victims suspected of having been exposed to an intentional release of a biologic disease. Isolation (symptomatic/exposed) is likely to have large impact on controlling spread of diseases. Appropriate infection control precautions implemented during care for symptomatic persons are consistently successful at reducing transmission in hospitals. A quarantine (asymptomatic/exposed) is a high logistical burden.

Appropriate IC precautions implemented during care for symptomatic persons are consistently successful at reducing transmission in hospitals. For instance, there was a nearly 80% reduction in risk of infection for critical care nurses who consistently wore a mask while caring for severe acute respiratory distress syndrome (SARS) patients during the 2003 outbreak in Toronto.

Similarly, the use of isolation precautions for symptomatic patients with suspected or confirmed exposure to outbreak-related illnesses may have a large impact on controlling the spread of disease.

The IC measures prescribed should be based on how the pathogens are transmitted from person-to-person.

A. MODES OF TRANSMISSION

There are 3 modes of transmission. The first is contact; this may be direct or indirect. Direct contact means pathogens are transmitted directly from one person to another. Indirect contact means that pathogens are transmitted through a contaminated intermediate such as medical equipment, stethoscopes and/or bed linens.

The second mode of transmission is a droplet. Respiratory droplets ($> 5\mu\text{m}$) are transmitted a short distance (eg, $< 3\text{-}6$ feet) from the infected person to the conjunctivae, nasal mucosa or oropharynx of another. The droplets are transmitted through activities such as talking, coughing and sneezing.

Airborne transmission is the third mode. This involves a droplet nuclei ($< 5\mu\text{m}$) from the infected person transmitted over potential longer distances to the oropharynx or lower respiratory tract. This type of transmission occurs when pathogens that can survive in the air are inhaled by a new host.

B. INFECTION CONTROL PRECAUTIONS

All patients who are have suspected or confirmed cases of outbreak-related illnesses should be managed using standard IC precautions. Such precautions prevent the direct contact with all body fluids including blood, secretions and excretions (whether or not they contain visible blood), mucous membranes and nonintact skin including rashes.

Standard precautions should be used when any contact with a patient's blood or body fluid is anticipated. The number one standard precaution that should be routinely practiced by HCWs is handwashing or hand hygiene. The PPE required for standard precautions include gloves, a face shield or surgical mask with eye protection and a gown. As outlined below in **Table 2**, there are no additional environmental precautions that must be taken beyond the standard regulatory requirements.

Table 2: Standard Precautions

- Wash hands after patient contact.
- Wear gloves when touching blood, body fluids, secretions, excretions and contaminated items.
- Wear a mask and eye protection, or a face shield during procedures likely to generate splashes or sprays of blood, body fluids, secretions or excretions.
- Handle used patient-care equipment and linen in a manner that prevents the transfer of microorganisms to people or equipment.
- Use care when handling sharp objects and use a mouthpiece or other ventilation device as an alternative to mouth-to-mouth resuscitation when practical.
- Standard precautions are employed in the care of ALL patients.

Source: U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID). Available at: <http://www.usamriid.army.mil/education/bluebook/appxb.doc>

Expanded precautions incorporate standard precautions with additional IC measures for contact, droplet and/or airborne infection. The extra precautions are determined by the mechanism of transmission.

Contact precautions should be used for diseases that can be spread through touching an infected patient or an object touched by the patient. The PPE required for contact precautions include a gown and gloves. Regarding environmental precautions, one should place the patient in a private room, if possible, limit his/her movement and use dedicated patient care equipment (eg, stethoscope) for that patient (**Table 3**).

Table 3: Contact Precautions

Standard Precautions plus:

- Place the patient in a private room or cohort them with someone with the same infection if possible.
- Wear gloves when entering the room. Change gloves after contact with infective material.
- Wear a gown when entering the room if contact with patient is anticipated or if the patient has diarrhea, a colostomy or wound drainage not covered by a dressing.
- Limit the movement or transport of the patient from the room.
- Ensure that patient-care items, bedside equipment, and frequently touched surfaces receive daily cleaning.
- Dedicate use of noncritical patient-care equipment (such as stethoscopes) to a single patient, or cohort of patients with the same pathogen. If not feasible, adequate disinfection between patients is necessary.

Conventional Diseases requiring Contact Precautions: MRSA, VRE, Clostridium difficile, RSV, parainfluenza, enteroviruses, enteric infections in the incontinent host, skin infections (SSSS, HSV, impetigo, lice, scabies), hemorrhagic conjunctivitis.

Biothreat Diseases requiring Contact Precautions: Viral Hemorrhagic Fevers.

Source: U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID). Available at: <http://www.usamriid.army.mil/education/bluebook/appxb.doc>

Droplet precautions should be used for diseases that can spread via respiratory droplets. The PPE required are the same for standard precautions with the addition of a surgical mask and eye protection. Environmental actions include placing the patient in a private room, if possible, and limiting his/her movement. Special air handling and ventilation measures are *not* necessary (**Table 4**).

Table 4: Droplet Precautions

Standard Precaution plus:

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

Conventional Diseases requiring Droplet Precautions: Invasive Haemophilus influenzae and meningococcal disease, drug-resistant pneumococcal disease, diphtheria, pertussis, mycoplasma, GABHS, influenza, mumps, rubella, parvovirus.

Source: U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID). Available at: <http://www.usamriid.army.mil/education/bluebook/appxb.doc>

Airborne infection isolation precautions should be used for diseases that can be spread through the air by droplet nuclei over long distances. The required PPE include the particulate respirator mask (N95) (or higher) or powered air-purifying respirator (PAPR), a gown, and gloves. The latter two items are only necessary if contact is anticipated. From an environmental perspective, one should place the patient in a room that is at a lower pressure than the hospital ward, has > 6-12 air exchanges per hour, a discharge of air to the outdoors that does not communicate directly with the discharge of another patient room or is re-circulated through a monitored HEPA system (**Table 5**).

Table 5: Airborne Precautions

Standard Precautions plus:

- Place the patient in a private room that has monitored negative air pressure, a minimum of 6 air changes/hour, and appropriate filtration of air before it is discharged from the room.
- Wear respiratory protection when entering the room.
- Limit movement and transport of the patient. Place a mask on the patient if they need to be moved.

Conventional Diseases requiring Airborne Precautions: Measles, Varicella, Pulmonary Tuberculosis.

Biothreat Diseases requiring Airborne Precautions: Smallpox.

Source: U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID). Available at: <http://www.usamriid.army.mil/education/bluebook/appxb.doc>

Failure to control the spread of disease is the biggest risk for hospitals becoming non-functional during an outbreak. Consequently, hospitals must stock enough PPE to handle an unexpected outbreak. For example, Sunnybrook Hospital in Ontario used 18,000 N95 masks daily during the peak of the 2003 SARS outbreak. Currently there is a limit to the number of N95 masks that can be purchased by institutions due to manufacturing limitations. The Institute of Medicine recently published a document addressing the data for re-using N95s if a shortage exists. Additionally,

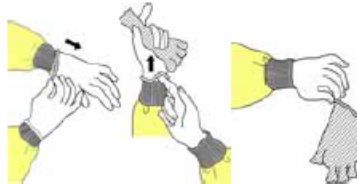
even if there are adequate PPE supplies, the proper donning and removal of PPE to avoid self-contamination must be strictly adhered to (**Figure 1**).

REMOVING PPE

Remove PPE at doorway before leaving patient room or in anteroom; remove respirator outside of room

GLOVES

- Outside of gloves are contaminated!
- Grasp outside of glove with opposite gloved hand; peel off
- Hold removed glove in gloved hand
- Slide fingers of ungloved hand under remaining glove at wrist



GOGGLES/FACE SHIELD

- Outside of goggles or face shield are contaminated!
- To remove, handle by "clean" head band or ear pieces
- Place in designated receptacle for reprocessing or in waste container



GOWN

- Gown front and sleeves are contaminated!
- Unfasten neck, the waist ties
- Remove gown using a peeling motion; pull gown from each shoulder toward the same hand
- Gown will turn inside out
- Hold removed gown away from body, roll into a bundle and discard into waste or linen receptacle



MASK OR RESPIRATOR

- Front of mask/respirator is contaminated – DO NOT TOUCH!
- Grasp bottom then top ties/elastics and remove
- Discard in waste container



Figure 1: Removing Personal Protective Equipment

V. BIOWEAPONS AGENTS

A number of natural or modified pathogens and toxins may be used to intentionally injure or kill. A working group of experts led by the Centers for Disease Control and Prevention (CDC) has identified 3 categories[‡] of agents that are potential threats for bioterrorism.

Category A agents are the highest priority category because they can be easily disseminated or transmitted person-to-person, cause high mortality and morbidity rates, and could potentially cause public panic and social disruption.

Category A agents include the following:

- *Bacillus anthracis* (anthrax)
- Botulinum toxin (botulism)
- *Yersinia pestis* (plague)
- *Variola major* (smallpox)
- *Francisella tularensis* (tularemia)
- Hemorrhagic fever viruses (filoviruses, such as Ebola and Marburg, and arenaviruses such as Lassa and Machupol)

Category B agents are in the second highest priority group. They are moderately easy to disseminate and cause moderate morbidity and low mortality. They also require additional surveillance measures. Category B agents include the following:

- *Brucella* species (brucellosis)
- *Burkholderia* species (glanders and melioidosis)

[‡] Not all pathogens that could be intentionally used to cause human disease are included in these categories.

- Coxiella burnetti (Q fever)
- Staphylococcal enterotoxin B
- Viral encephalitis (alphaviruses)

An additional list of Category B agents include pathogens that are food- or waterborne, presenting a threat to the food and water supply.

Category C agents, the third highest priority, include emerging pathogens that could be engineered for mass dissemination because of their availability, ease of production and dissemination, as well as potential high morbidity and mortality rates.

They include the following emerging pathogens:

- Nipah virus
- Hantaviruses
- Multidrug-resistant tuberculosis

VI. CLUES THAT BIOTERRORISM HAS OCCURRED

Certain epidemiologic clues may help clinicians recognize that a bioterror attack has occurred. They include:

- An influx of patients presenting with similar signs and symptoms (eg, previously healthy or young persons presenting with critical illness)
- Uncommon findings in patients with common symptoms (eg, mediastinal lymphadenopathy, pleural effusions and fever in patient presenting with shortness of breath)
- Persons presenting with diseases in urban areas that are usually only seen in rural areas
- Persons presenting with zoonotic diseases prior to any animals dying off

Public health officials may have additional clues provided by deployed programs for environmental sampling and syndromic surveillance to identify a bioweapons agent release on civilians, but these programs are still in their infancy and their ability to lead to earlier responses remains controversial. In the meantime, clinicians will most likely provide the initial information that an event has occurred.

VII. SELECT CATEGORY A BIOLOGIC AGENTS

A. BACILLUS ANTHRACIS (ANTHRAX)

Anthrax is caused by the gram-positive, spore-forming, nonmotile *Bacillus* species. The disease occurs in humans via 3 major routes: inhalational, cutaneous, and gastrointestinal (GI). Anthrax infections are not transmitted person-to-person.

1. INHALATIONAL ANTHRAX

Infection begins with the inhalation of anthrax spores, which deposit into alveolar spaces in the 1- to 5- μ m range. The spores are ingested by alveolar macrophages and then transported through lymphatics to hilar and mediastinal lymph nodes. There, the surviving spores germinate into vegetative bacilli, which in turn produce toxins that results in hemorrhage, edema in the lymph nodes and mediastinum.

The incubation period of the 11 inhalation anthrax cases that occurred in the US in 2001 was 4-6 days, with the median being 4 days. However, the incubation period of

the inhalational anthrax epidemic in Sverdlovsk, Russia, in 1979, following an unintentional release of the spores from a bioweapons factory was 2-43 days. Infection has been reported to occur in humans up to 60 days following exposure.

Patients initially present with a number of nonspecific symptoms and signs including fever, nausea and vomiting, drenching sweats and fatigue. During the following days, untreated patients may develop neurologic abnormalities, such as seizures and altered mentation, as well as hypoxemic respiratory failure and circulatory collapse. Radiographic manifestations include mediastinal adenopathy and large pleural effusions.

The presence of abnormal findings on either chest x-rays or computed tomography (CT) scan is an important clue in diagnosing inhalational anthrax. In the 2001 anthrax attacks, 10 of the 11 inhalational cases had abnormal chest x-rays as did 8 patients for whom CT scans were performed. Abnormalities included widened mediastinum, massive pleural effusions and air bronchograms. The chest x-ray in **Figure 2** shows widened mediastinum, right hilar mass, right pleural effusion and right perihilar air-space disease. A noncontrast chest CT in **Figure 3** reveals enlarged hyperdense lymph nodes in the mediastinum and the left hilum, with bilateral pleural effusions.

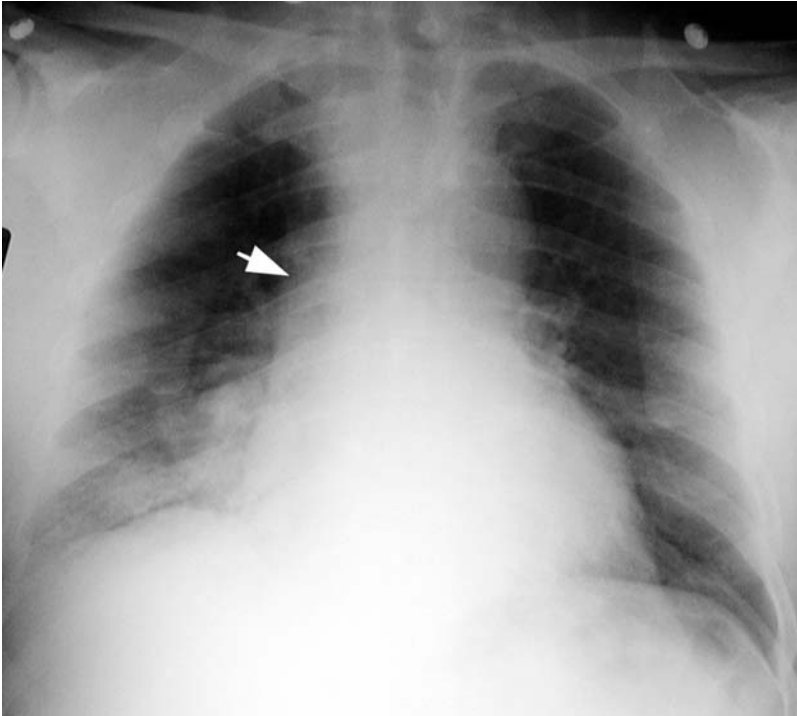


Figure 2: Chest x-ray showing widened mediastinum, right hilar mass, right pleural effusion, and right perihilar air-space disease.

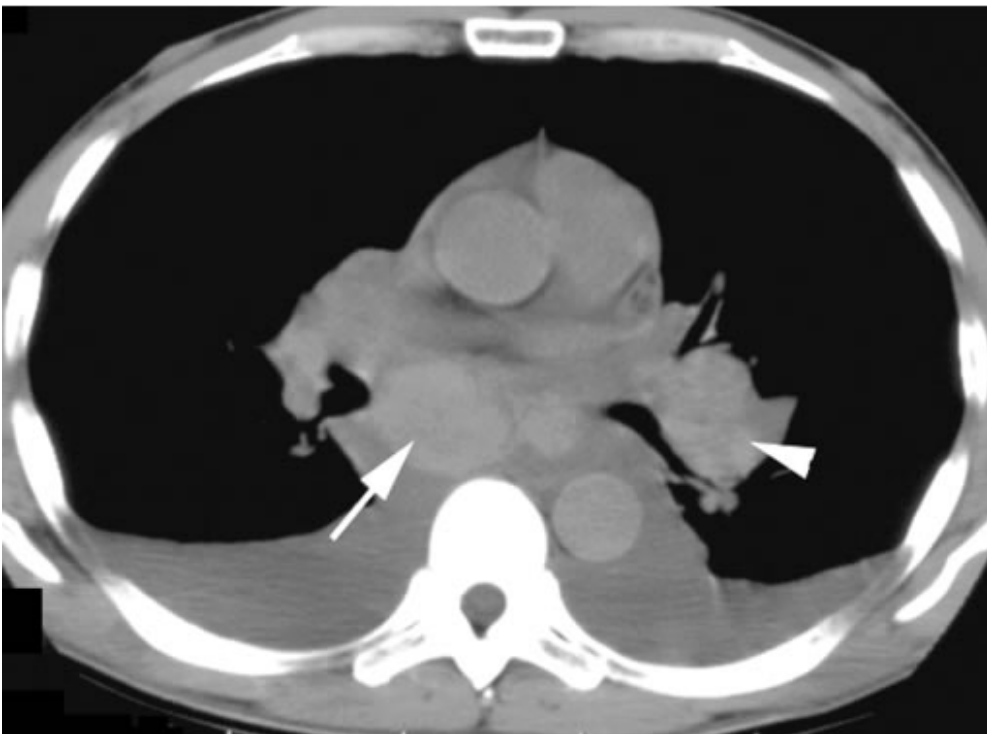


Figure 3: A noncontrast chest CT reveals enlarged hyperdense lymph nodes in the mediastinum and the left hilum, with bilateral pleural effusions.

The most useful microbiologic test to diagnose inhalational anthrax is the standard blood culture. The bacteria may even be visible on Gram stain of peripheral blood. The problem is that detection is delayed because aerobic blood cultures can take several hours to 1 day to yield results and blood cultures may be sterilized after even 1 dose of antibiotics is administered. Definitive diagnosis could be confirmed by polymerase chain reaction (PCR) and/or phase lysis but only through the Laboratory Response Network (LRN), the network of state and local public health, federal, military and international labs established by the CDC to respond to bioterrorism events.

Sputum is rarely helpful in diagnosing inhalational anthrax due to a lack of vegetative bacilli communicating with the airways. Serum transaminases may be elevated, and pleural fluid sampling may demonstrate hemorrhagic specimens with markedly elevated red blood cell counts. Nasal swabs have no role in clinical diagnosis as their predictive value is untested in humans.

Good communication between clinicians and the microbiology lab is essential because current routine clinical lab procedures do not necessarily further identify *Bacillus* species to exclude *B anthracis* unless specifically requested. Furthermore, these microbiology specimens may be labeled as “contaminants” and discarded by some labs. Therefore, all suspect specimens should be fully processed, especially if the aforementioned clinical pattern fits.

Given the rapid development of symptoms and the delay of treatment associated with higher mortality, the early administration of antibiotic is critical. Therefore, individuals in high-risk groups who develop fever or evidence of systemic disease should be provided therapy as soon as possible, even if it means treatment begins while awaiting test results. The circumstances surrounding the outbreak will dictate the recommended therapy. For example, in a contained casualty setting, that is, a situation in which a modest number of patients require treatment, **Table 6** shows the recommended therapy.

Table 6: Inhalation and GI Anthrax

- Adults (including pregnant women):
 - Ciprofloxacin 400 mg IV q 12 hours

OR

- Doxycycline 100 mg IV q 12
- May use additional agents such as rifampin (for intracellular activity) and clindamycin (theoretical anti-toxin effect)

If, however, there is an influx of individuals requiring treatment following a bioterrorist attack or for the purpose of postexposure prophylaxis, the recommended treatment switches to oral therapy as a feasible option (**Table 7**). Both oral and intravenous (IV) therapy should be continued for 60 days.

Table 7: Recommended Prophylactic Regimens

Adults (including pregnant woman)

Ciprofloxacin 500 mg po bid for 60 days

OR doxycycline 100 mg po bid for 60 days (if strain is susceptible and not for pregnant women)

Other supportive treatment, including mechanical ventilation, tube thoracostomy and vasopressors, may be required in severe cases. Six of the 11 patients with inhalational anthrax in 2001 survived with aggressive medical interventions.

However, none of the patients who required mechanical ventilation survived despite the aggressive care. Other supportive treatment options include drainage of pleural effusions, which may improve oxygenation and reduce toxin burden. Also, antimicrobial resistance patterns may require different antibacterial strategies, such as the use of 2 or 3 antibiotics in combination. This would be a reasonable therapeutic approach if, for example, an engineered strain of *B anthracis* resistant to certain antibiotics would be used in a bioterror attack. Antimicrobial resistant patterns may require different antibacterial strategies. Additional countermeasure treatments are in development but are currently unavailable.

One vaccine is currently mandated for all US military personnel. However, vaccine supplies are limited. Guidelines for determining administration of postexposure prophylaxis to civilian populations in the wake of an intentional release of *B anthracis* aerosol is a matter left up to public health officials. Logistics of identifying exposed individuals and distributing large amounts of antibiotic are very complex.

2. CUTANEOUS ANTHRAX

In cutaneous anthrax, spores enter the skin through previous cuts and abrasions. After germinating in the skin tissues, the spores produce toxin that results in local edema. In **Figure 4**, an initially pruritic macule or papule enlarges into a round ulcer

by the second day. Subsequently, 1- to 3-mm vesicles may appear and begin discharging clear or serosanguinous fluid containing numerous organisms.



Figure 4: Round Ulcer

The papular lesion progresses from this vesicular stage to become a depressed black eschar, which falls off in 1 to 2 weeks without leaving a permanent scar (**Figure 5**). Although lymphangitis and painful lymphadenopathy can occur with associated systemic symptoms including fever, malaise and headache, the lesion itself is often painless.



Figure 5: Depressed black eschar

In 2001, 11 confirmed or probable cases of cutaneous anthrax resulted from exposure to letters contaminated with *B anthracis*. The incubation period ranged between 1 and 10 days, with the mean at 5 days.

Cutaneous anthrax can be diagnosed through Gram stain and sputum culture, the same means used for diagnosing inhalational anthrax. The only difference is that, in the case of cutaneous anthrax, a punch biopsy with silver staining and immunohistochemical testing may be necessary for individuals who have received prior antibiotics. An aerobic blood culture could be used for diagnosis as well. Definitive diagnosis should be confirmed by PCR through the LRN.

Recommended treatment for cutaneous anthrax is oral fluoroquinolone or doxycycline to be used until antibiotic susceptibility is proven. Amoxicillin is an

acceptable alternative if the other antibiotics are contraindicated as is the case for pregnant or lactating women, individuals who are younger than 18 years of age or antibiotic intolerant. Conservative clinical management (per the inhalational anthrax treatment guidelines in Table 3 of *JAMA* article) is recommended for cutaneous lesions associated with extensive edema or those located on the head and neck. While antibiotic therapy does not appear to change the course of eschar formation, it does decrease the likelihood of systemic disease.

The reported case fatality rate (due to systemic dissemination) is 20% without treatment. That drops to <1% with treatment.

3. GI ANTHRAX

The rarest of the disease forms, naturally occurring GI anthrax could potentially occur if it were delivered in a food or water vehicle, although evidence of this actually happening is lacking. Rapid motility of food and water through the GI tract has led some experts to question whether spores actually cause the disease or whether it is caused by ingesting vegetative bacilli from poorly cooked infected meat.

The incubation period is between 2 and 7 days following ingestion of contaminated meat.

Patients with naturally occurring GI anthrax experience nausea, vomiting and fever followed by severe abdominal pain. The disease rapidly progresses to bloody diarrhea and hematemesis. Additionally, patients may develop massive ascites and severe sepsis.

Like inhalational and cutaneous anthrax, diagnosis of GI anthrax can be obtained through Gram stain and sputum culture. Some experts recommend using the same treatment regimen for GI anthrax as inhalational anthrax because mortality rates for the former could be as high as 50%.

B. YERSINIA PESTIS (PLAGUE)

Plague is an acute bacterial disease caused by the nonmotile, gram-negative bacillus, *Y. pestis*, which is usually transmitted by infected fleas. The result is very enlarged lymph nodes (bubo) and severe sepsis. Most people infected in this manner develop bubonic plague. However, a small percentage of people may develop sepsis without bubo formation, which is known as primary septicemic plague, the form most likely to be seen after an intentional release, especially if it occurs in areas where bubonic plague is not endemic. Although it is rare, some patients with bubonic or septicemic plague develop pneumonia, which is termed secondary pneumonic plague. Patients with pneumonic plague can transmit it through respiratory droplets to another person, the latter of whom is considered to have primary pneumonic plague, even though he/she does not develop buboes.

Typically patients experiencing naturally occurring plague develop symptoms of bubonic plague 2 to 8 days after being bitten by the infected flea. Similarly, the incubation period of aerosol exposure resulting in primary pneumonic plague ranges from 1 to 6 days but is usually between 2 and 4 days.

Symptoms, which appear suddenly include fever, dyspnea and cough with chest pain. Prominent GI symptoms, such as nausea, vomiting, abdominal pain and diarrhea, may be present. Sputum is watery or bloody; purulent sputum is less

common. Buboes are not present in this form of plague except for rare cervical buboes after ingestion of plague bacteria. The disease progresses quickly with sepsis and respiratory failure occurring in 1 to 2 days.

On average, 13 cases of bubonic plague occur each year in the US. Typically it occurs in rural areas since it is endemic in certain wild animal populations. Most cases occur in the summer.

A positive sputum or blood gram stain shows gram-negative bacilli, or sometimes coccobacillus, in a bipolar or "safety pin" staining (**Figure 6**). Colonies of *Y. Pestis*, a member of the Enterobacteriaceae family, typically require 48 hours for observable growth, but they are initially much smaller than other members of the Enterobacteriaceae family and may be overlooked.

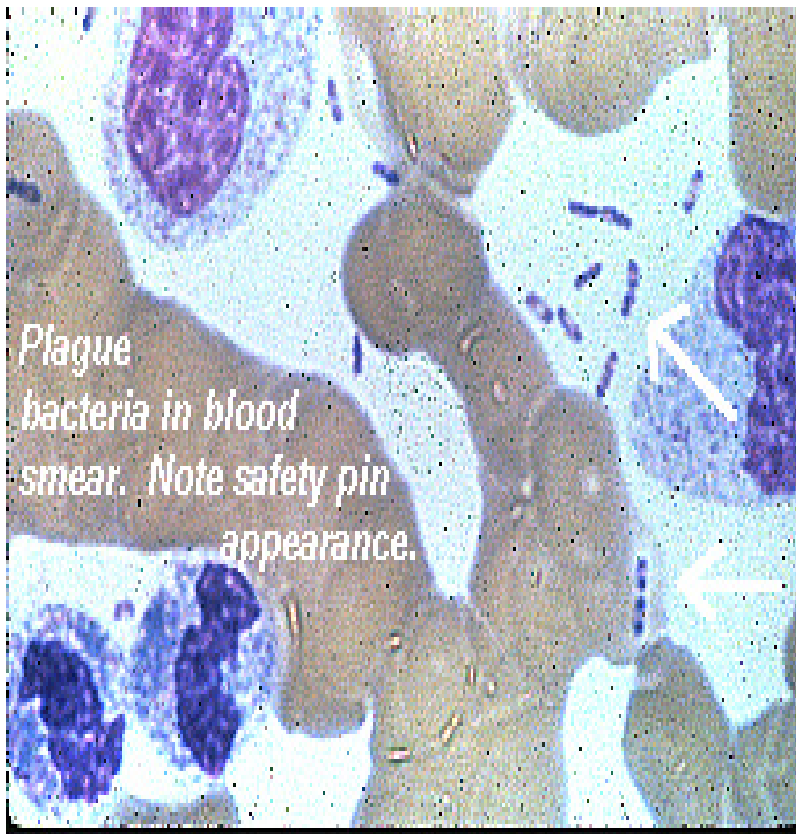
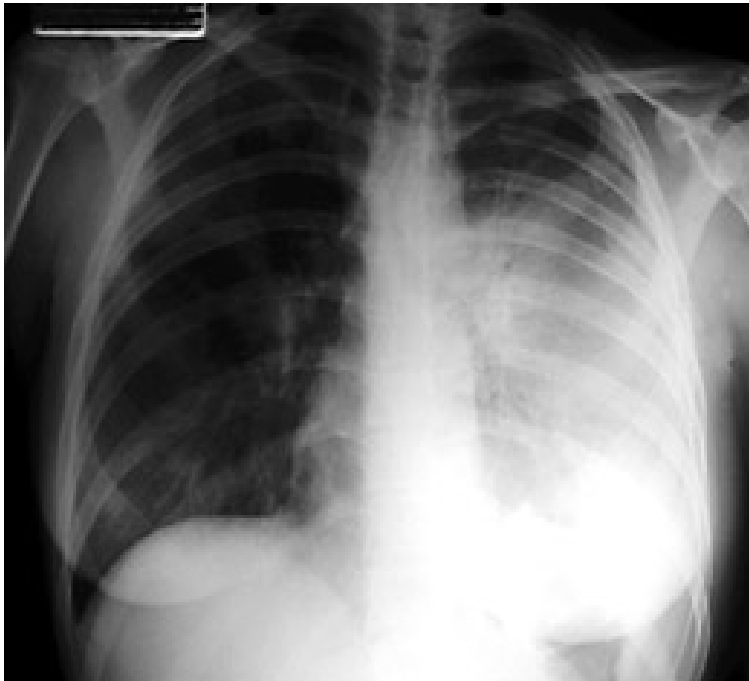


Figure 6: "Safety Pin" staining

Plague 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. Identification may take up to 6 days. Direct fluorescent antibody testing, if available, may be positive. Other definitive tests, available through some state health departments and the LRN, include an IgM enzyme immunoassay, antigen detection and PCR. No widely available rapid diagnostic tests exist, and serum agglutination testing may require serial titers since antibodies to the F1 antigen may be initially negative.

Chest radiographs would demonstrate findings consistent with a serious pneumonia or acute respiratory distress syndrome (ARDS). For example, in **Figure 7**, the chest radiograph of a patient with primary pneumonic plague shows extensive consolidation in left lung.

**Figure 7: Pneumonic Plague (Diagnosis)**

Standard therapy is 10 days with a single IV antibiotic, switching to oral therapy when patients improve (**Table 8**). Therapy should not be delayed while waiting for confirmation of diagnosis, as mortality jumps from 15% if treated early to between 50% and 90% if untreated.

Table 8: Plague Treatment

- Adults
 - Streptomycin 1G IM BID

OR

- Gentamicin 5mg/kg IV or IM q24
- Alternatives include:
 - Ciprofloxacin 400 mg IV q12
 - Doxycycline 100 mg IV q12
 - Chloramphenicol 25 mg/kg IV QID

- Children
 - Streptomycin 15 mg/kg IM BID

OR

- Gentamicin 2.5 mg/kg IV or IM TID
- Alternatives
 - Ciprofloxacin 15 mg/kg IV q12
 - Doxycycline 2.2 mg/kg IV q12
 - (if children are >45 kg, use adult dose)
 - Chloramphenicol 25 mg/kg IV QID

Supportive critical care is likely to be necessary for many symptomatic persons who do not receive postexposure prophylaxis. Common complications that will require such care include ARDS, disseminated intravascular coagulation, shock and multiorgan failure.

Clinicians should practice IC precautions, including droplet precautions, as person-to-person transmission can occur by respiratory droplets. That means HCWs must wear surgical masks (N95 and PAPRs are not necessary unless transmission is by droplet nuclei) when they are in close proximity to contagious patients. Additionally, lab personnel should be notified since secondary transmission within lab settings has occurred.

Clinicians who suspect an outbreak of pneumonic plague should contact local health authorities immediately so that the latter can initiate case-finding and postexposure prophylaxis because the window of opportunity to successfully treat ill patients is so narrow. Moreover, postexposure prophylaxis is likely to prevent disease or reduce severity of illness. Postexposure prophylaxis should be administered 7 days in a mass casualty setting or to close contacts (within 2 meters) of an infected patient. Recommended regimens are oral doxycycline or ciprofloxacin at standard doses for 7 days. If a fever $>38.5^{\circ}\text{C}$ is present or cough develops, then one should initiate therapy with the preferred IV agent, either streptomycin or gentamicin.

Neither routine vaccination nor postexposure prophylaxis of civilian populations for plague is currently recommended.

C. BOTULINUM TOXIN (BOTULISM)

Clostridium botulinum is an anaerobic gram-positive bacillus that, in combination with two other species, produces one of the most potent known neurotoxins: botulinum toxin. Once botulism toxin is absorbed, it is carried by the bloodstream to peripheral cholinergic synapses where it binds irreversibly. Then it presynaptically inhibits the release of acetylcholine, thus blocking neuromuscular transmission.

Botulinum toxin exists in 7 antigen types, A through G. Types C, D and G do not cause natural disease in humans. The 3 naturally occurring forms of botulinum toxin are foodborne, wound and infant. A fourth man-made form is the result of aerosolized botulinum toxin.

It only takes minute quantities acquired by ingestion, inhalation or absorption to cause death from botulinum toxin. The disease is not contagious, and only direct exposure to the toxin is a threat. After release in aerosol form, the toxin is inactivated in the air in 12 hours. Sunlight inactivates it in 1 to 3 hours.

The incubation period is dependent on the amount and type of botulinum toxin absorbed. It ranges from 24 hours to several days for inhalational botulism and half that for foodborne botulism.

Patients present with initial signs of symmetric cranial neuropathies such as drooping eyelids, difficulty swallowing or speaking, weakened jaw clench and blurred or double vision. They are, however, alert, oriented and afebrile. As the disease progresses,

paralysis descends symmetrically and can cause airway obstruction or respiratory muscle paralysis. If the transmission occurred by inhalation, GI symptoms such as cramping, nausea, vomiting and diarrhea usually associated with foodborne botulism may be absent.

Botulism can be diagnosed by using the following clinical triad: symmetric cranial neuropathies with descending paralysis, afebrile and clear sensorium. The disease, however, is frequently misdiagnosed as myasthenia gravis, the Miller-Fisher variant of Guillan-Barre syndrome, tick paralysis, atropine poisoning and paralytic shellfish/puffer fish poisoning.

Diagnostic testing may help identify other similar conditions instead of providing a definitive diagnosis of botulism. For example, the edrophonium or "Tensilon" test may show up only transiently positive in botulism but may be helpful in distinguishing it from myasthenia gravis. Measuring for cerebrospinal fluid protein levels may be beneficial, but these levels are generally normal in botulism. An electromyogram demonstrating an incremental response with repetitive stimulation at 50 HZ may suggest botulism when the conduction velocity and sensory nerves are normal. Another option is to detect *Clostridium* from clinical specimens including serum, gastric contents or vomitus, feces or return from sterile water enema and wound tissue (for naturally occurring wound botulism). Confirmation usually requires the mouse bioassay, which involves exposing mice to samples and those given polyvalent and specific antitoxin survive, but results take several days. Samples must be collected prior to the patient receiving antitoxin. Among 309 persons with clinically diagnosed botulism reported to the CDC between 1975 and 1988: 51% of stool cultures for *C. botulinum* were positive, 37% of serum botulinum toxin testing

was positive and 23% of stool botulinum toxin testing was positive. Overall, at least 1 of the aforementioned tests was positive for 65% of all patients.

Most lab testing cannot be performed at hospitals and specimens must be sent to Level D labs in the LRN. Laboratories must be notified of suspicion regarding botulism, since samples can be potentially harmful to lab personnel.

Botulinum toxin can be treated with an equine antitoxin (trivalent A,B,E) available from the CDC. It has been effective in animal experiments if given early in the course of inhalation botulism. Recommendations call for a 10 mL vial diluted 1:10 in normal saline and administered by slow IV infusion. Additional doses are not required as the amount of neutralizing antibody far exceeds the highest serum toxin levels found in foodborne botulism. The antitoxin has been known to cause hypersensitivity reactions in approximately <10% of patients. Consequently, skin testing for horse serum sensitivity is recommended prior to administration. If there is an intentional release of a toxin not neutralized by the trivalent antitoxin, other treatments including heptavalent antitoxin or monoclonal antibodies may be available.

Additional supportive therapies include feeding by enteral tube or parenteral nutrition, treatment of secondary infections and intensive care often including mechanical ventilation. For example, airway and ventilatory support should be implemented if forced vital capacity is low, even if the patient's pCO₂ has not yet risen. Ventilatory failure can be prolonged, requiring mechanical ventilation for a few months. One should position patients with diaphragmatic weakness in reverse Trendelenburg, which may improve ventilation. While the use of antitoxin is unlikely to reverse weakness, it may halt further progression. Antibiotic use does not directly affect the toxin, but it does treat the resulting nosocomial infections. If this care is

available, fatality rates should be <5%. Without treatment, mortality rates are high as death is generally the result of the loss of airway protection and/or ventilatory failure.

The hospital epidemiologist or IC practitioner should be contacted about a suspected botulism toxin outbreak as standard precautions should be used when caring for patients. Additionally, all materials suspected of containing toxin should be handled with caution, although decontamination is not an issue unless patients are grossly contaminated.

Clinicians who suspect an outbreak of botulism also should contact public health officials early on. A number of temporally related cases of acute paralysis is indicative of an outbreak, which represents a potential public health emergency because, in the case of foodborne botulism, the contaminated food could be ingested by other individuals. While naturally occurring outbreaks of botulinum toxin do occur, some telltale signs point to suspicion for bioterrorism. Scenarios that suggest intentional release of the toxin include the following: outbreaks within a geographically related population that lacks a common food exposure outbreaks involving an unusual toxin type (non A, B E, and maybe F) typically not implicated in human disease multiple simultaneous outbreaks without a common source and outbreaks of a large number of cases of acute flaccid paralysis with prominent bulbar palsies.

There is a limited amount of available antitoxin. Currently, lab workers at high risk of exposure and the military troops receive an investigational pentavalent, but mass pre-exposure immunization or post-exposure prophylaxis for asymptomatic individuals is neither feasible nor desirable at this time.

D. VARIOLA MAJOR (SMALLPOX)

Smallpox is an acute viral illness caused by the Variola virus. This deoxyribonucleic acid virus is a member of the genus Orthopoxvirus in the Poxviridae family. It is transmitted via respiratory droplets as well as contact with skin lesions and items contaminated with drainage from lesions. Additionally, scabs contain viral particles that may be contagious.

There are primarily two forms of the virus: *Variola major* and *Variola minor*. *V. major*, which is the more severe form, is most likely to be seen during an intentional release.

The incubation period for *V. major* ranges from 7 to 17 days, with an average of 12 days following exposure.

Initial symptoms, which occur prior to eruption of the associated skin rash, include fever, rigors, backache and headache. These signs last 2 to 4 days and then oropharyngeal enanthem appears approximately 1 day prior to a nonspecific erythematous skin rash begins (**Table 8**).

Table 8: Ordinary Smallpox – Onset of Rash

Days from onset of rash (exanthem)

0-1: Macules on face/forehead. Spreads to proximal limbs than distal limbs
and trunk within ~ 24 hours

2-3: Papules

3-5: Vesicles (may be umbilicated)

6-12: Pustules (deep in dermis)

13-20: Crusts

This centrifugal rash first appears in the mouth and throat, specifically on the buccal and pharyngeal surfaces. The lesions become pustular, are umbilicate and are deeply seated in the dermis. Typically, they are more concentrated on the face and limbs than the trunk or extremities, and they sometimes involve the palms and soles. Lesions appear and progress in the same stages in a particular part of the body. These characteristics are contrary to Varicella in which lesions on any given part of the body (but rarely on the palms and soles) vary in their stages of development and begin on the trunk and move outward. Sometime after 8 or 10 days, scabs form at the site of the pustules. Approximately 10 days later, the scabs fall off and in their place are light-colored or depigmented areas. Over a period of many weeks, the skin gradually returns to its normal appearance. However, scars may remain on the face.

The aforementioned description is seen in > 90% of smallpox cases. Less common forms of the disease include hemorrhagic smallpox, which is uniformly fatal, typically has a shorter incubation period and does not result in the classic smallpox rash. Instead, death follows development of a hemorrhagic rash. In the malignant or flat form of smallpox, the disease begins classically but does not progress to pustules. Instead, the rash is confluent and may desquamate.

Initial diagnosis can be made clinically with the characteristic syndrome. Screening criteria for *V. major* criteria are as follows: fever < 101 for 1 to 4 days prior to rash prostration, headache, backache, chills, vomiting and/or abdominal pain and deep, firm, round and well-circumscribed lesions located on the same body part in the same stage. Screening criteria for *V. minor* are as follows: lesions concentrated on

face and distal extremities; lesions first appear on oropharynx, face, or forearms; macules that slowly evolve to papules and then pustules, taking 1 to 2 days for each stage; toxic patient appearance and lesions on palms and soles.

Patients at high risk of having smallpox will meet all 3 major criteria. Patients at moderate risk of having the virus will demonstrate either febrile prodrome and 1 other major criteria or febrile prodrome and > 4 minor criteria. This algorithm, however, may miss early ordinary smallpox as well as atypical smallpox features (flat and hemorrhagic). Still, a Level D lab in the LRN will be needed to rule out other viruses. The smallpox rash is commonly confused with varicella, allergic contact dermatitis or erythema multiforme with bullae. Although lab confirmation is essential for initial cases, once an epidemic is established it is unnecessary.

Rapid initial confirmation by electron microscopy will determine the presence of an orthopox but is not specific to smallpox. Polymerase chain reaction testing with Variola-specific primers can confirm smallpox. Guidelines for sample collection for testing are available on the CDC's Web site at <http://www.bt.cdc.gov/agent/smallpox/response-plan/files/guide-d.pdf>.

Because routine vaccination and production of vaccine for smallpox was discontinued in the US in 1972 following worldwide eradication of the disease, there is no known effective therapy. Currently, supportive care is the mainstay of therapy for smallpox. That includes fluid and electrolyte therapy, treatment for bacterial superinfections, supplemental oxygenation and ventilatory support and disseminated intravascular coagulation. Cidofovir may be beneficial as it has shown activity against other pox viruses in animal studies and *in vitro* activity against Variola virus, the agent of smallpox. In the event of an outbreak, it may be administered under an

Investigational New Drug protocol. Vaccination with Vaccinia will not help patients symptomatic with smallpox. It will, however, reduce transmission of Variola to patients misdiagnosed as having smallpox.

Historically, mortality rates of unvaccinated individuals have been 30%. However, that was before the introduction of modern critical care. Nowadays, mortality may be lower depending on the availability of supportive critical care during an outbreak.

Clinicians who suspect patients are infected with smallpox should isolate them immediately and get expert consultation. One should isolate patients from the onset of fever until the separation of scabs; patients may not be contagious during the prodromal stage, but early rash may be difficult to detect. Once the rash begins, patients are contagious through the scab formation stages of the disease. Also, those with cough during the first week of rash may be most likely to transmit the virus through droplet nuclei. Additionally, fomite transmission has been documented. Patients should be isolated in a room with airborne infection isolation capabilities. Both contact and airborne precautions should be used in addition to standard precautions.

Immediate notification of public health officials about the suspicion of smallpox is essential for mobilizing efforts for postexposure therapy. One likely strategy used would be ring vaccination, which involves isolating confirmed and suspected cases with tracing, vaccination and close surveillance of contacts, as well as vaccinating individuals within the contact's household. This strategy is more desirable than mass vaccination because it is designed to protect individuals at greatest risk for contracting the disease and forming a buffer of immune persons to prevent the spread.

Additionally, the CDC Working Group recommends that in an outbreak setting, all HCWs and patients in the hospital be vaccinated. Vaccination with Vaccinia is most effective when it is administered within 3 to 4 days post-exposure to prevent development of smallpox or lessen the severity of the disease in persons who become ill. The decision to distribute post-exposure prophylaxis would be left up to public health officials. Although mass vaccination may be an option in some situations, few countries currently have adequate supplies of vaccine to respond to an outbreak. Even fewer have the ability to successfully perform ring vaccination. Due to the threat of smallpox being used as a biological weapon, production of new vaccine has been initiated and research studies examining methods of diluting current vaccine stocks are underway.

E. VIRAL HEMORRHAGIC FEVERS

Viral hemorrhagic fevers (VHFs) refer to the viruses from various families that cause fever and bleeding diathesis. Those that pose the greatest threat as bioweapon agents are Ebola and Marburg viruses (Filoviridae), Lassa and New World viruses (Arenaviridae), Yellow Fever, Omsk hemorrhagic fever, and Kyasanur Forest disease (Flaviviridae) and Crimean Congo, Rift Valley, and Hantavirus (Bunyaviridae).

The predominant modes of transmission appear to be contact and droplet respiratory spread. However, airborne transmission cannot be ruled out because of nosocomial cases reported in African outbreaks.

The VHFs share some similarities. For example, the incubation period is typically 5 to 10 days but can range from 2 to 21 days.

Early symptoms are an abrupt onset of fever (except for Arenaviruses that have a more gradual onset), myalgia and headache. These are followed by nausea, vomiting, abdominal pain, diarrhea, chest pain, cough and pharyngitis. The characteristics of rash vary among the VHF. Initially, patients may have only conjunctival infection, mild hypotension and flushing. Approximately 5 days into the illness, a truncal maculopapular rash develops. Bleeding manifestations occur later and may include petechiae, ecchymoses and frank hemorrhage (including mucosal and conjunctival hemorrhage) with neurologic and pulmonary involvement (**Figure 8a**).





Figure 8:

Source: Borio, JAMA, 2002

The World Health Organization recommends notifying public health authorities if patients present with fever < 21 days in a severely ill patient without a previous risk factor for hemorrhage who has 2 of the following symptoms: hemorrhagic rash or purpuric rash, epistaxis, hematemesis, hemoptysis or hematochezia.

Thrombocytopenia and leucopenia are common, as are proteinuria and hematuria. Viral hemorrhagic fevers are often confused with malaria, typhoid fever, rickettsial infections, meningococemia, idiopathic or thrombotic thrombocytopenic purpura, or acute leukemia.

Currently, most labs are not equipped to provide rapid diagnostic tests for any of these viruses. Therefore, testing must be performed in Level D labs in the LRN. Plans

are underway to equip select public health labs with standard diagnostic reagents, expediting confirmation of cases in the event of an outbreak. Methods of diagnosis include antigen detection by antigen-capture enzyme-linked immunosorbent assay (ELISA), IgM antibody detection by antibody-capture ELISA, RT-PCR and viral isolation. In the event of a bioterrorist attack with a VHF, diagnosis will initially be based on clinical judgment.

With no antiviral drugs approved for the treatment of VHFs, the mainstay of treatment is supportive. Hemodynamic support for shock and blood product replacement is often necessary. Intravenous ribavirin reduces mortality for the VHFs in the Arenaviruses and Bunyavirus families. It should be started immediately in an outbreak setting until the specific causative agent is identified. Specific immune globulin therapy from convalescent serum or equine sources has been used with some success in endemic areas but would be difficult to obtain and use empirically before the specific VHF is identified.

Mortality rates are dependent on the type of virus, availability of treatment (including its response to ribavirin) and availability of supportive care. They can be as high as 90% in cases of Ebola virus, for example.

With the prevention of secondary transmission of great concern, HCWs should use strict contact and droplet precautions as well as airborne infection isolation (at least until the HVF is identified) when treating patients and handling corpses. One should double-bag lab specimens and decontaminate the outer bag before removal. Either autoclave excreta and other contaminated materials or decontaminate them using a liberal application of hypochlorite or phenolic disinfectants. Corpses, which should be

handled minimally, should be sealed in a leakproof material and promptly buried or cremated. Post-exposure prophylaxis for VHF are currently unavailable.

Outbreaks need not be intentional, as seen in the recent avian to human influenza transmission. In 1999, there were 2 reported cases in Hong Kong resulting in 1 death. Between January 2004 and December 2005, 88 cases were reported in Vietnam, Cambodia and Thailand, resulting in 51 deaths. Even a small outbreak can be imported. Travel to developed countries from remote areas is possible as was the case in a Lassa fever fatality in New Jersey in 2004. A number of unprotected exposures to contagious people are plausible and likely unless there is a paradigm shift for protecting HCWs and patients on a daily basis.

The critical care community must plan and prepare now to handle outbreaks of infectious disease. A key component of that is staff education. Every HCW should know the CDC Emergency Response Hotline (770-488-7100) and when to use it. Hospitals should ensure that staff has the most current information regarding diagnosis, treatment and prophylaxis regimens for infectious disease outbreaks, all of which are subject to change as new information emerges.

KEY POINTS

1. The medical response to an outbreak will differ from that to a conventional disaster due to a delay in detection, secondary spread of contagious pathogens and the need for post-exposure prophylaxis.

2. Notifying public health officials as soon as an intentional outbreak is suspected will allow for earlier identification and treatment of victims, confirmation of the outbreak and distribution of post-exposure prophylaxis, if applicable.
3. The primary challenge that health professionals face when caring for critically ill patients contagious with an outbreak-related illness involve using the most appropriate IC measures to minimize the risk of secondary spread.

SUGGESTED READINGS

1. APIC Bioterrorism Working Group. April 2002 Interim Bioterrorism Readiness Planning Suggestions. www.apic.org/Content/NavigationMenu/PracticeGuidance/Topics/Bioterrorism/APIC_BTWG_BTRSugg.pdf. Accessed June 21, 2006.
2. Arnon SS, Schechter R, Inglesby TV, et al. Botulinum toxin as a biological weapon: medical and public health management. *JAMA*. 2001;285(8):1059-1070.
3. Borio L, Inglesby TV, Peters CJ, et al. Hemorrhagic fever viruses as biological weapons: medical and public health management. *JAMA*. 2002;287(18):2391-2405.
4. Garner JS and the 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.
5. Henderson DA, Inglesby TV, Barlett JG, et al. Smallpox as a biological weapon: medical and public health management. *JAMA*. 1999;281(22):2127-2137.
6. Inglesby TV, O'Toole T, Henderson DA, et al. Anthrax as a biological weapon, 2002: updated recommendations for management. *JAMA*. 2002; 287(17):2236-2252.
7. Inglesby TV, Dennis DT, Henderson DA, et al. Plague as a biological weapon: medical and public health management. *JAMA*. 2000;283(17):2281-2290.
8. Loeb M, McGeer A, Henry B, et al: SARS among critical care nurses, Toronto. *Emerg Infect Dis* 2004; 10(2):251-255.
9. Farmer JC, Jimenez EJ, Rubinson L, Talmor DS. Fundamentals of Disaster Management, Second Edition. 2003.