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Bioterrorism and Biodefense

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KEY CONCEPTS

- Bioterrorism continues to pose a global threat due to ongoing geopolitical conflicts.

- Early recognition of bioterrorism is critical to preserving individual and public health. Agents of bioterrorism concern are prioritized according to their potential to cause high mortality and major impact on public health (category A); to be associated with moderate morbidity (category B); or to represent emerging threats and future concerns (category C).

- Clinical syndromes caused by agents of bioterrorism must be differentiated from those due to other, naturally occurring infectious diseases.

- Biodefense represents the range of public health responses that can prevent or mitigate the effects of bioterrorism and of outbreaks of naturally occurring, emerging infectious diseases.

Introduction

Bioterrorism, the deliberate use of microbial agents or their toxins as weapons against noncombatants outside the setting of armed conflict is conceptually analogous to biologic warfare in a combat theater. 'Biodefense' represents the range of responses, including surveillance, diagnostic, therapeutic and preventive measures employed to mitigate the impact of not only bioterrorism threat agents but of outbreaks of naturally occurring, emerging infectious diseases as well. Since the multifocal anthrax attacks that followed the catastrophic events on September 11, 2001 in the USA, ongoing, geopolitical turmoil and escalating conflicts around the world have ensured that bioterrorism will remain a persistent global concern.

Biologic weapons have been used against both military and civilian targets throughout history. Although the development or use of biologic weapons was banned by an international Convention in 1972,[1] multiple signatories, including the former Soviet Union and Iraq, violated the terms and spirit of the agreement. The accidental release of aerosolized anthrax spores from a military plant in Sverdlovsk in 1979, resulting in at least 68 human deaths from inhalational anthrax, verified the existence of an active Soviet offensive biologic weapons program.

Threat Assessment

Biologic agents are considered weapons of mass destruction (WMD) because their use may result in large-scale morbidity and mortality. In a World Health Organization-sponsored model of the hypothetical casualty estimates from the intentional release of 50 g of aerosolized anthrax spores upwind from a population center of 500 000 (analogous to a medium-sized metropolitan area), nearly 200 000 people might be killed or incapacitated by the event.[2]

Biologic weapons possess unique properties among all WMD. Unlike other weapons, most biologic agents are associated with a clinical latency period of days to weeks, during which time exposed individuals are asymptomatic, making early detection difficult. Additionally, specific antimicrobial therapy and/or vaccines are available for the treatment and prevention, respectively, of illness caused by biologic weapons; casualties from other forms of WMD can generally only be treated by decontamination, trauma mitigation, and supportive care.

Due to heightened global tensions, bioterrorism is a credible threat and a potential tool for political coercion. Several events over the past three decades signal a shift in terrorism trends: the intentional contamination of restaurant salad bars with *Salmonella* by a religious cult trying to influence a local election in The Dalles, Oregon in 1984;[3] the revelations that Aum Shinrikyo, the Japanese cult responsible for the sarin gas attack in the Tokyo subway system in 1995 experimented on multiple occasions with aerosolizing anthrax from downtown Tokyo rooftops; the findings of massive quantities of weaponized biologic agents in Iraq following the first Gulf War;[4] and the domestic anthrax attacks in the USA in 2001.

The aims of bioterrorism are similar to those of other forms of terrorism: to cause morbidity and mortality among civilian populations, disruption of societal fabric, and exhaustion or diversion of resources.[5] Terrorist goals may be achieved without furthering all of these aims but simply by a perceived credible threat of action or by a small-scale agent deployment. The anthrax attacks in 2001 evoked fear and anxiety and diverted public health and healthcare resources away from other critical activities despite the limited number of casualties associated with the event. Thus, agents of bioterrorism may be viewed as 'weapons of mass terror'.

Biologic weapons offer other, significant advantages to terrorists:
- they are relatively inexpensive to acquire as compared with conventional or nuclear weaponry;
- they can be deployed in a stealth fashion due to a variable clinical latency period, thus allowing the perpetrator opportunity to escape if desired;
- person-to-person transmission may amplify their effective range; and
- they evoke anxiety and panic in a population that is, in some instances, out of proportion to their physical effects.

The technology for bioterrorism is 'dual use', i.e. it can serve legitimate functions such as vaccine or pharmaceutical production as readily as biologic weapons production, thus affording credible cover for rogue nations. For large-scale bioterrorism, biologic agents must undergo complex processes of production, cultivation, chemical modification and weaponization. Therefore, state sponsorship or direct support from organizations with significant resources and infrastructure would predictably be required to incite such events.[5] However, some threat agents may be acquired by terrorist groups on the black market.[6] Additionally, the anthrax attacks in the USA in late 2001 illustrated the devastating results that can be achieved with relatively primitive delivery methods, e.g. high-speed mail-sorting equipment and mailed letters.

Numerous attributes contribute to the effectiveness of a biologic weapon:
- availability or ease of large-scale production;
- ease of dissemination, especially by the aerosol route;
- stability in storage and delivery;
- transmission characteristics; and
- clinical virulence.

The last refers to the reliability with which the pathogen causes mortality, morbidity or social disruption. The Centers for Disease Control and Prevention (CDC) have prioritized biologic agent threats based upon the aforementioned characteristics,[7,8] thus influencing current preparedness strategies (Table 75-1). Category A agents, the highest priority, are associated with high mortality and the greatest potential for major impact on public health. Category B agents are

TABLE 75-1	**Agents of Concern for Use in Bioterrorism**
Highest Priority: Category A (Based Upon Potential Mortality, Morbidity, Virulence, Transmissibility, Aerosol Feasibility and Psychosocial Implications of an Attack)	
Microbe/Toxin	**Disease**
Bacillus anthracis	Anthrax: inhalational, cutaneous
Variola virus	Smallpox and its variants
Yersinia pestis	Plague: pneumonic, bubonic, septicemic
Clostridium botulinum toxin	Botulism
Francisella tularensis	Tularemia: pneumonic, typhoidal
Viral hemorrhagic fevers	
Filoviruses	Ebola, Marburg
Arenaviruses	Lassa fever, South American hemorrhagic fevers
Bunyaviruses	Rift Valley fever, Crimean-Congo hemorrhagic fever
Flaviviruses	Dengue
Moderately High Priority: Category B (Based Upon Potential Morbidity, Aerosol Feasibility, Dissemination Characteristics and Diagnostic Difficulty)	
Microbe/Toxin	**Disease**
Coxiella burnetii	Q fever
Brucella spp.	Brucellosis
Burkholderia mallei	Glanders
Burkholderia pseudomallei	Melioidosis
Alphaviruses (e.g. EEE, VEE)	Viral encephalitides
Ricinus communis toxin	Ricin intoxication
Staphylococcal enterotoxin B	Staphylococcal toxin illness
Salmonella spp., *Shigella dysenteriae, Escherichia coli* O157:H7, *Vibrio cholerae, Cryptosporidium parvum, Listeria monocytogenes, Campylobacter jejuni, Yersinia enterocolitica*	Food- and water-borne gastroenteritis
Rickettsia prowazekii	Epidemic typhus
Chlamydia psittaci	Psittacosis
Epsilon toxin of *Clostridium perfringens*	*C. perfringens* intoxication
Emerging Threat Agents: Category C (Based Upon Potential For Production And Dissemination, Availability, Morbidity/Mortality)	
Microbe/Toxin	**Disease**
Hantaviruses	Viral hemorrhagic fevers
Flaviviruses	Yellow fever, West Nile virus
Mycobacterium tuberculosis	Multidrug-resistant tuberculosis
Nipah virus	Systemic flu-like illness
Miscellaneous: (Other Examples of Candidate Threat Agents that Possess some Elements of Bioterrorism Concern)	
Genetically engineered vaccine- and/or antimicrobial-resistant category A or B agents	
HIV-1	
Adenoviruses	
Influenza	
Rotaviruses	
Molecular hybrid pathogens (e.g. smallpox–plague, smallpox–ebola)	
Severe acute respiratory syndrome coronavirus	

EEE, eastern equine encephalomyelitis; VEE, Venezuelan equine encephalomyelitis.
Adapted from Patrozou E., Artenstein A.: Bioterrorism. In: Schlossberg D., ed. Clinical infectious diseases, *3rd ed. New York: Cambridge University Press; 2008:865-877.*

'incapacitating' because of their potential for moderate morbidity but relatively low mortality. Most category A and B agents have been experimentally weaponized in the past. Category C agents include emerging threats and pathogens that are potentially effective weapons. With the burgeoning fields of molecular biology and genomics, future risk scenarios may have to contend with genetically altered, designer pathogens that may be equipped with enhanced virulence, such as antimicrobial resistance or augmented toxin production, or modifications that enhance dissemination, such as prolonged aerosol stability (see Table 75-1).

Bioterrorism Recognition

Bioterrorism is insidious; with the absence of advance warning or specific intelligence information, clinical illness will be manifest before the circumstances of a release event are known. Affected individuals will therefore initially be seen in healthcare settings, in contrast to scenarios involving conventional weaponry or a natural disaster in which police, firefighters, paramedics and other emergency services personnel are first responders. Physicians and other healthcare workers must therefore maintain a high index of suspicion for suggestive epidemiologic clues and clinical features to enhance early recognition, management and communication of information to minimize the deleterious effects of bioterrorism on individual patients and on the public health.

Early recognition is hampered for several reasons:

- Potential targets of terrorists are widespread and somewhat unpredictable.
- Immediate recognition of a common source outbreak from a bioterrorist event might be missed secondary to a clinical latency period following exposure and casualties are likely to present for medical attention in diverse locations and at varying times.[9] This illustrates the critical importance of surveillance, data sharing and real-time communication.
- Initial symptoms of bioterrorism-associated diseases may be nonspecific. In the absence of a known exposure, many mildly symptomatic individuals may either not seek medical attention or may be misdiagnosed with a nonspecific, 'flu-like' illness. However, once beyond the early stages, many of these illnesses progress rapidly and treatment may be less effective.
- Most of the diseases caused by agents of bioterrorism are rarely, if ever, seen in clinical practice. Therefore, physicians are likely to be inexperienced with their clinical characteristics.
- By definition, agents of bioterrorism have been laboratory-manipulated and may therefore not demonstrate the classic clinical features of naturally occurring infection. This was illustrated by differences in the clinical manifestations of inhalational anthrax in the USA in October 2001 as compared with historical accounts of naturally occurring disease.[10]

Early identification of bioterrorism may be facilitated by the recognition of certain epidemiologic and clinical clues:

- Clustering of patients with common clinical syndromes, especially unusual or known to be associated with bioterrorism agents, should prompt notification of public health authorities.
- The recognition of a single case of a rare or non-endemic infection in the absence of a travel history or other potential natural exposure.
- Unusual epidemiologic patterns of disease, such as atypical age distributions, unexpected clinical severity, or concurrent illness in human and animal populations. For some agents of bioterrorism and several naturally occurring, emerging infectious diseases, evidence supports the potential role of animals as early warning sentinels of an attack or as markers of persistent exposure risks to humans.[11]

Infectious diseases specialists are uniquely suited to play pivotal roles in the recognition, investigation, and mitigation of bioterrorism, based on:

- an understanding of epidemiologic principles and risk assessment;
- expertise in specific threat agents, their clinical presentations and diagnostic approaches;
- knowledge of communicability and infection control principles; and
- an understanding of the tenets of treatment and prophylaxis of infectious diseases.

Threat Agents

This section will describe the highest priority, category A agents. Extensive descriptions of specific pathogens can be found in related chapters in this text (cross-referenced in Table 75-2) and in other sources.[12,13]

TABLE 75-2	Epidemiologic Characteristics for Selected Category A and B Bioterrorism-Associated Diseases			
Disease	Incubation Period Range (Days)	Person-to-Person Transmission	Infection Control Precautions For Patients	Case Fatality Rate
Inhalational anthrax (see Chapter 134)	2–43*	No	Standard	Untreated 100% Treated 45%
Cutaneous anthrax (see Chapter 134)	1–12	No	Standard	Untreated 20% Treated <1%
Botulism (see Chapter 22)	12–72 hours	No	Standard	6%
Primary pneumonic plague (see Chapter 126)	1–6	Yes	Droplet	Untreated 100% Treated ~50%
Bubonic plague (see Chapter 126)	2–8	No	Standard	Untreated 60% Treated <5%
Smallpox	7–19	Yes	Contact and airborne	Unvaccinated 30% Vaccinated 3%
Tularemia pneumonia (see Chapter 127)	1–21	No	Standard	Untreated 60% Treated <4%
Viral hemorrhagic fevers (see Chapter 132)	2–21	Yes	Contact and airborne	Marburg 25% Ebola 80% Other forms 2–30%
Viral encephalitides (see Chapter 20)	1–14	No	Standard	10–35%
Q fever (see Chapter 187)	2–41	No	Standard	3%
Brucellosis (see Chapter 129)	5–60	No	Standard	Untreated 5%
Glanders	1–21	Yes	Contact and droplet	Untreated – approaches 100% Treated – low

*Based on limited data from human outbreaks; experimental animal data support clinical latency periods of up to 100 days.
Adapted from Patrozou E., Artenstein A.: Bioterrorism. In: Schlossberg D., ed. Clinical infectious diseases, 3rd ed. New York: Cambridge University Press; 2008:865-877.

TABLE 75-3	**Syndromic Differential Diagnoses and Clinical Clues for Category A Agents of Bioterrorism**			
Syndrome	**Clinical Presentation**	**Differential Diagnosis**	**Bioterrorism-Associated Disease**	**Disease-Specific Clues**
Influenza-like illness	Nonspecific respiratory symptoms: malaise, myalgias, nausea, emesis, dyspnea, cough with or without chest discomfort, without coryza or rhinorrhea, leading to abrupt onset of respiratory distress, with or without shock, mental status changes, with chest radiograph abnormalities (wide mediastinum or infiltrates or pleural effusions)	Influenza, community-acquired bacterial pneumonia, viral pneumonia, *Legionella*, Q fever, psittacosis, *Mycoplasma*, *Pneumocystis* pneumonia, tularemia, dissecting aortic aneurysm, bacterial mediastinitis, SVC syndrome, Nipah virus	Inhalational anthrax	Abdominal pain, headache, mental status abnormalities, hypoxemia Mediastinal adenopathy: ~90% (Figure 75-2) Hemorrhagic pleural effusions: ≈70% Meningoencephalitis: possibly ≈50% Blood cultures positive in untreated patients
Skin lesion(s)	Pruritic, painless papule on exposed areas leading to vesicle(s), ulcer, then edematous black eschar, with or without massive local edema and regional adenopathy and fever, evolving over 3–7 days	Recluse spider bite, staphylococcal lesion, atypical Lyme disease, orf, glanders, tularemia, plague, rat-bite fever, ecthyma gangrenosum, rickettsialpox, cutaneous diphtheria	Cutaneous anthrax	Painless; spider bite is a painful lesion Nonpitting local edema (Figure 75-1) If untreated, may become systemic Blood cultures, skin biopsy positive
Fulminant pneumonia	Abrupt onset, rapidly progressive respiratory illness with cough, fever, rigors, headache, sore throat, myalgias, dyspnea, pleuritic chest pain, GI symptoms, lung consolidation, with or without hemoptysis, shock; variable progression to respiratory failure	Severe community-acquired bacterial or viral pneumonia, inhalational anthrax, pulmonary infarct or hemorrhage, influenza, *Mycoplasma* pneumonia, *Legionella*, Q fever, SARS, tuberculosis, melioidosis	Pneumonic plague Pulmonary tularemia	Lobar or multilobar involvement, with or without buboes Hemoptysis is common with characteristic sputum Gram stain Cough generally nonproductive Pulse–temperature dissociation in 40%
Sepsis with bleeding diathesis and capillary leak	Sepsis syndrome, GI symptoms, mucosal hemorrhage, altered vascular permeability, DIC, purpura, acral gangrene, hepatitis, hypotension, with or without CNS findings, multiorgan system failure	Meningococcemia; toxic shock syndromes; leptospirosis; typhoid fever; borreliosis; typhoidal tularemia; overwhelming postsplenectomy sepsis; Rocky Mountain spotted fever; hemolytic uremic syndrome; TTP; SLE; hemorrhagic smallpox	Septicemic plague Viral hemorrhagic fever	DIC occurs in minority of aerosol exposures Cutaneous findings as late sequelae, with or without buboes High-grade bacteremia Maculopapular rash in Ebola, Marburg Variable presenting signs depending on specific VHF type
Febrile prodrome with generalized exanthem	Fever, malaise, prostration, headache, myalgias and enanthema followed by development of synchronous, progressive, centrifugal papular/vesicular/pustular rash with or without hemorrhagic component, with systemic toxicity	Varicella, drug eruption, Stevens–Johnson syndrome, measles, secondary syphilis, erythema multiforme, disseminated herpes zoster or simplex, meningococcemia, monkeypox, insect bites	Smallpox	Palms and soles involved Lesions are firm and almost nodular Secondary bacterial infection common Hemorrhagic variant in pregnant and immunocompromised
Progressive weakness	Acute onset of afebrile, symmetric, descending flaccid paralysis, dilated pupils, diplopia or blurred vision, dysphagia, dysarthria, ptosis, dry mucous membranes, clear sensorium, no sensory changes	Myasthenia gravis, brain stem CVA, polio, Guillain–Barré syndrome variant, tick paralysis, chemical intoxication	Botulism	Few GI symptoms in aerosol attacks Low-dose inhalation exposure – delayed Dx Anticholinergic effects

CVA, cerebrovascular accident; DIC, disseminated intravascular coagulation; GI, gastrointestinal; SLE, systemic lupus erythematosus; SVC syndrome, superior vena cava syndrome; TTP, thrombotic thrombocytopenic purpura; VHF, viral hemorrhagic fever.

Clinical incubation periods, transmission characteristics and infection control procedures for agents of bioterrorism are provided in Table 75-2. Syndromic differential diagnoses for select, common clinical presentations are detailed in Table 75-3.

ANTHRAX

Anthrax results from infection with *Bacillus anthracis*, a gram-positive, spore-forming, rod-shaped organism that exists in its host as a vegetative bacillus and in the environment as a spore. Details of the microbiology and pathogenesis of anthrax are found in Chapter 134. In nature anthrax is a zoonotic disease of herbivores that is prevalent in many geographic regions; sporadic human disease results from environmental or occupational contact with endospore-contaminated animal products.[14] Anthrax is uncommon in higher-income countries. In low- and middle-income countries (LMIC) the cutaneous form of anthrax is the most common presentation; gastrointestinal and inhalational forms are exceedingly rare in naturally acquired disease. Recently, a novel, soft-tissue form of infection was described in injection drug users in Europe.[15] Cutaneous anthrax is rarely seen in current-day industrialized countries due to importation restrictions. The last known case of naturally occurring inhalational anthrax in the USA occurred in 1976.[16]

The 2001 anthrax attacks in the USA were on a relatively small scale, and nearly 40% of the confirmed cases were of the cutaneous variety.[17]

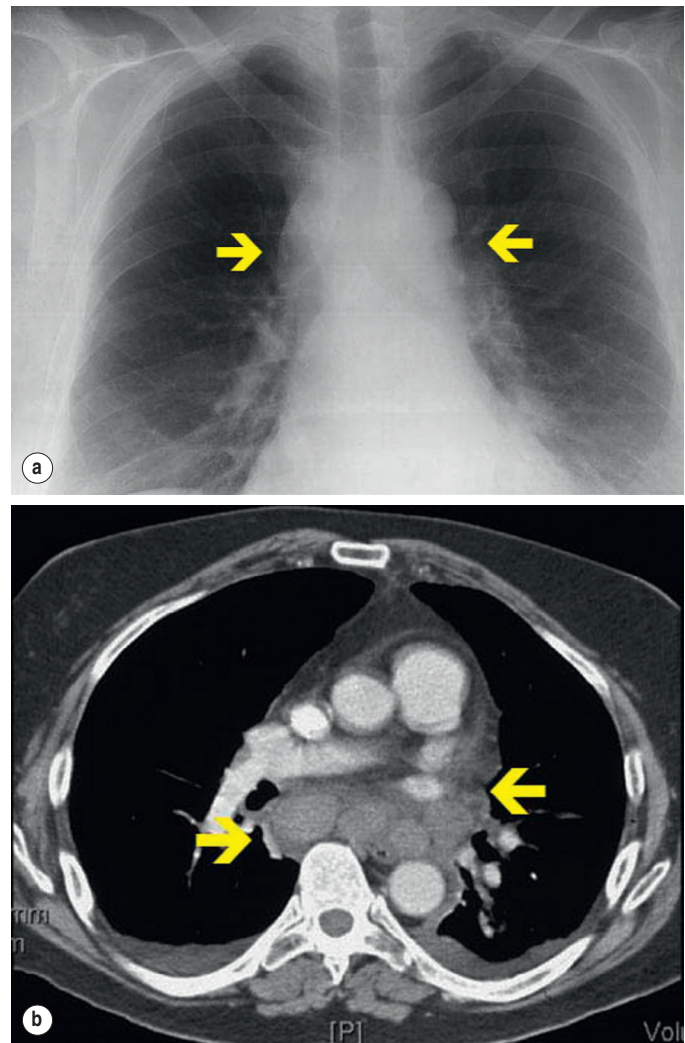**Figure 75-1** Lesion of cutaneous anthrax. (©Diepgen T.L., Yihune G., et al. *Dermatology Online Atlas* (http://www.dermis.net). Reprinted with permission.)


Figure 75-2 (a) Chest X-ray, inhalational anthrax, United States, 2001 demonstrating mediastinal widening (arrows). (b) Chest CT scan demonstrating mediastinal widening (arrows) and bilateral pleural effusions. (From Jernigan J., Stephens D.S., Ashford D.A., et al.: Bioterrorism-related inhalational anthrax: The first 10 cases reported in the United States. Emerg Infect Dis 2001; 7:933-944.)

The serious events following the outbreak were related to inhalational disease. Therefore, planning for larger-scale events with aerosolized anthrax is warranted.

The differential diagnoses of cutaneous and inhalational anthrax are described in Table 75-3. The lesion of cutaneous anthrax may be similar in appearance to other lesions, including cutaneous forms of other agents of bioterrorism; however, it may be distinguished by epidemiologic as well as certain clinical features. Anthrax is traditionally a painless lesion, unless secondarily infected, and it is associated with significant local edema (Figure 75-1). The bite of *Loxosceles reclusa*, the brown recluse spider, shares many of the local and systemic features of anthrax but is typically painful from the outset and lacks significant edema.[18] Cutaneous anthrax may be associated with systemic disease and its attendant mortality in up to 20% of cases if untreated; with appropriate therapy, mortality is <1%.[16]

Once the inhaled endospores reach the alveoli, they are phagocytosed by macrophages and transported to regional lymph nodes, where they germinate into vegetative bacteria and, subsequently, disseminate hematogenously.[14] The bacteria generate potent exotoxins, lethal toxin and edema toxin, which lead to hemorrhagic mediastinitis, systemic illness and death. Spores may remain latent for extended periods of time in the host, up to 100 days in some experimental animal models,[17] resulting in prolonged clinical incubation periods following exposure to endospores. Cases of inhalational anthrax occurred up to 43 days after exposure in the Sverdlovsk experience, although the average incubation period is 2–10 days, perhaps influenced by inoculum.[15]

Although the clinical experience derived from the 2001 USA attacks had much in common with the clinical manifestations of inhalational anthrax noted in the Sverdlovsk cases, some novel findings emerged. Of 11 confirmed cases of inhalational anthrax, 5 (45%) died. Although this contrasts with a case fatality rate of greater than 85% reported from Sverdlovsk, the reliability of reported data from the latter outbreak is questionable[17] and, perhaps more importantly, patients in the 2001 outbreak were more likely to receive appropriate treatment at an earlier stage.

Patients with inhalational anthrax almost uniformly seek medical attention an average of 3.3 days after symptom onset with fevers, chills, malaise, myalgias, nonproductive cough, chest discomfort, dyspnea, nausea or vomiting, tachycardia, peripheral neutrophilia and liver enzyme elevations.[11,19] Many of these findings are nondiagnostic and overlap considerably with those of influenza or other common viral respiratory tract infections. Data suggest that discrimination between inhalational anthrax and benign, influenza-like illnesses may be possible on the basis of initial symptoms: shortness of breath, nausea, and vomiting are significantly more common in anthrax, while rhinorrhea is uncommonly seen in anthrax but noted in the majority of community-acquired viral respiratory infections.[20]

Other common clinical manifestations of inhalational anthrax include abdominal pain, headache, mental status abnormalities and hypoxemia. Abnormalities on chest radiography appear to be universally present, although these may only be identified retrospectively in some cases. Pleural effusions are the most common abnormality; infiltrates, consolidation and/or mediastinal adenopathy/widening are noted in the majority of cases (Figure 75-2a). Mediastinal adenopathy appears to be an early indicator of disease; CT scan is more sensitive than chest radiographs for this finding (Figure 75-2b). In the 2001 outbreak, more than 80% of cases were noted to have mediastinal widening with or without pleural effusions or infiltrates.

The clinical manifestations generally evolve to a fulminant septic picture with progressive respiratory failure. *B. anthracis* is routinely isolated in blood cultures if obtained prior to the initiation of antimicrobials (Figure 75-3). Pleural fluid is typically hemorrhagic; the bacteria can either be isolated in culture or documented by antigen-specific immunohistochemical stains of this material (Figure 75-4) in most patients.[11] The average time from hospitalization until death was 3 days (range 1–5 days). Autopsy typically reveals hemorrhagic mediastinal lymphadenitis and disseminated metastatic infection. Pathology data
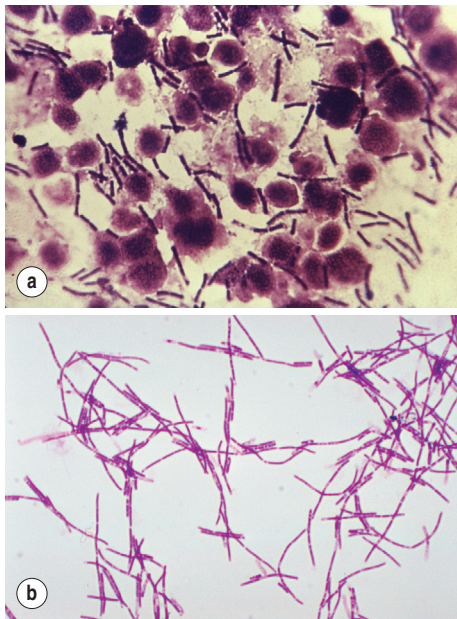
Figure 75-3   *Bacillus anthracis.* (a) *Bacillus anthracis* appearing as Gram-positive bacilli. (b) The typical 'jointed bamboo-rod' appearance of the organism from blood cultures. *(Courtesy of CDC and Dr William A. Clark.)*
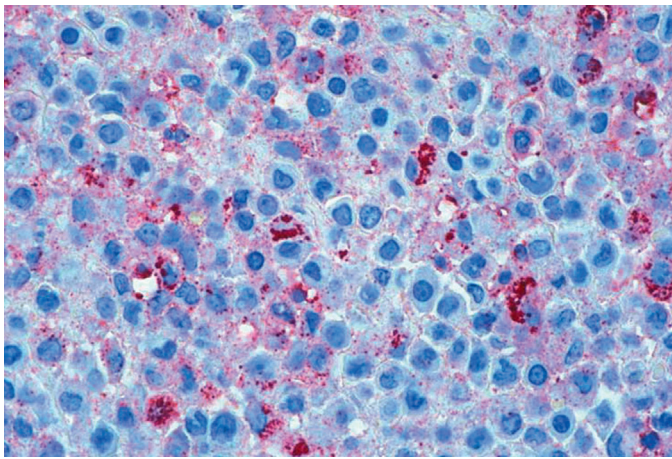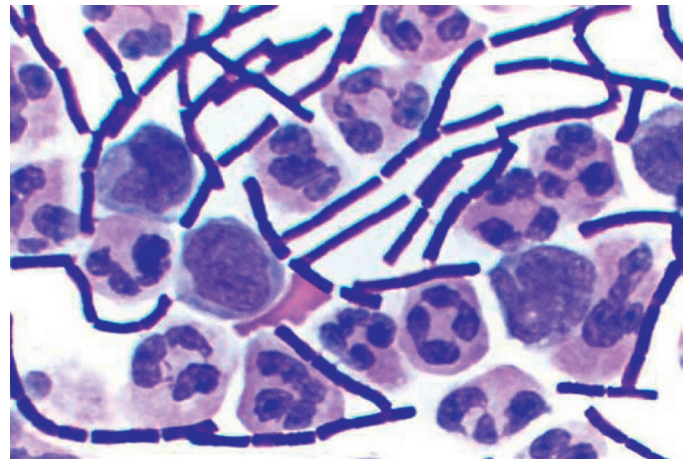

Figure 75-4   Pleural fluid cell block immunohistochemical stain demonstrating *Bacillus anthracis* antigen (red) within a mononuclear inflammatory cell infiltrate. *(From Jernigan J., Stephens D.S., Ashford D.A., et al.: Bioterrorism-related inhalational anthrax: The first 10 cases reported in the United States.* Emerg Infect Dis *2001; 7:933-944.)*

Figure 75-5   Cerebrospinal fluid Gram stain from anthrax index case, United States, 2001, demonstrating numerous gram-positive rods and neutrophils. *(From Jernigan J., Stephens D.S., Ashford D.A., et al.: Bioterrorism-related inhalational anthrax: The first 10 cases reported in the United States.* Emerg Infect Dis *2001; 7:933-944.)*

from the Sverdlovsk outbreak confirm meningeal involvement, typically hemorrhagic meningitis, in 50%;[21] meningoencephalitis was the presenting diagnosis (Figure 75-5) in the index case in the USA from 2001.[22]

The diagnosis of inhalational anthrax consists of a compatible clinical presentation in the context of a known exposure, a possible exposure, or epidemiologic factors suggesting bioterrorism, e.g. clustered cases of a rapidly progressive, systemic illness. The diagnosis should also be considered in a single individual with a consistent or suggestive clinical illness in the absence of another etiology. Table 75-3 delineates a detailed differential diagnosis of anthrax.

The early recognition and treatment of inhalational anthrax appear to be associated with a survival advantage;[11] in the USA experience, patients who received appropriate antimicrobials within 4.7 days of symptom onset had a mortality rate of 40% as compared with a mortality rate of 75% for those treated after that period.[23] Therefore, prompt, empiric antimicrobial therapy should be initiated if infection is clinically suspected. Combination parenteral therapy is appropriate in the ill individual for a number of reasons:[11]

- to cover the possibility of antimicrobial resistance;
- to target specific bacterial virulence properties, e.g. the theoretical effect of clindamycin on toxin production;
- to optimize adequate drug penetration into the central nervous system; and
- to favorably impact survival.

In order to optimize the outcome in inhalational anthrax, novel therapies, such as toxin inhibitors or receptor antagonists, are in development with effective antimicrobial agents, optimal hemodynamic and ventilatory support, and pleural fluid drainage.[23,24] A variety of such strategies, guided by the pathogenesis of the organism and its disease-producing toxins, has shown promise in animal studies and will likely be components of effective therapeutic regimens in the future.[25,26]

Detailed therapeutic and postexposure prophylaxis recommendations for adults, children and special groups have been recently reviewed elsewhere.[17,24,27] Anthrax vaccine adsorbed (AVA), the current product in use for select indications, is effective in preventing cutaneous anthrax in human clinical trials and in preventing inhalational disease after aerosol challenge in nonhuman primates.[28] The vaccine has generally been found to be safe but requires multiple initial doses over 18 months with the need for frequent boosting. Second-generation anthrax vaccines employing recombinant protective antigen are in clinical trials and several experimental products containing spore and capsule antigens are in development. A fully humanized monoclonal antibody, raxibacumab, has been approved for the treatment and prevention of inhalational anthrax.[26]

SMALLPOX

The last known naturally acquired case of smallpox occurred in Somalia in 1977; in 1980, as the culmination of a 12-year, intensive campaign by the WHO, smallpox became the first and only disease to be eradicated as a scourge of humans.[29] However, because of concerns that variola virus stocks may have either been removed from or sequestered outside of their WHO-designated repositories, smallpox is considered to be a potential agent of bioterrorism.

Smallpox could be a devastatingly effective weapon as its re-introduction into human populations would be a global public health catastrophe. It is stable in aerosol form with a low infective dose; case fatality rates approach 30%; secondary attack rates among unvaccinated close contacts are 37–88% and are amplified, especially in healthcare settings; and much of the world's population is susceptible. Routine civilian vaccination was terminated more than two decades

ago and vaccine-induced immunity may wane over time to some extent in vaccinees.[30] Although a second-generation smallpox vaccine has been approved for use, it is currently not routinely recommended. There are no known antiviral therapies of proven clinical effectiveness against this pathogen.

Following an average incubation period of 10–12 days (range 7–19 days), patients experience the acute onset of a 2- to 3-day prostrating prodrome consisting of fever, rigors, malaise, vomiting, headache and backache. They subsequently develop a centrifugally distributed eruption that initially involves the face and extremities and then generalizes as it evolves through macular, papular, vesicular, and pustular stages in synchronous (i.e. lesions progress concurrently and have similar appearances diffusely) fashion over approximately 8 days, with umbilication in the latter stages (Figure 75-6). An oropharyngeal enanthem typically precedes the exanthem by 1 or 2 days; this is indicative of high titer viral replication in the upper respiratory tract and correlates with high infectivity. The rash generally remains denser peripherally and typically involves the palms and soles in its early stages, a potentially useful clue in narrowing the differential diagnosis (Figure 75-7). The umbilicated pustules begin crusting during the second week of the eruption. Separation of scabs is usually complete by the end of the third week, but the course of the systemic illness may be attenuated and the appearance of the exanthem milder in those with partial, pre-existing immunity or more progressive and virulent in those with immunodeficient states.

The differential diagnosis of smallpox (see Table 75-3) may be aided by a number of features: synchronous lesions, umbilicated appearance in the pustular stage, early involvement of palms and soles, and the centrifugal distribution of the eruption. Historically, varicella and drug reactions posed the most frequent diagnostic dilemmas,[30] along with monkeypox in Africa and importation of monkeypox along with animal reservoirs from Africa.[31] Although the diagnosis of smallpox is suggested by clinical features, definitive diagnosis requires analysis of blood and lesional contents or scrapings from crusts by electron microscopy, viral antigen immunohistochemistry, polymerase chain reaction, and viral isolation. Because processing and evaluation of specimens from a suspected case of smallpox requires high-level biocontainment facilities, collaboration with public health authorities is necessary.

Smallpox is transmitted from person-to-person by respiratory droplet nuclei and, less commonly, by contact with lesions or contaminated fomites. Airborne transmission by fine-particle aerosols has been documented[32] and should be assumed as a potential mode of spread in a bioterrorism event. The virus is communicable from the onset of the enanthem, generally one or two days prior to the rash, until all of the scabs have separated; however, the highest transmission risk occurs

Figure 75-6 Smallpox. (a) Third day of rash in smallpox. Additional lesions continue to appear and some of the papules are becoming obviously vesicular. (b) Fifth day of rash in smallpox. Almost all the papules have now become vesicular or pustular, the truly 'vesicular' stage usually being very brief. Some of the lesions on the upper arm show early umbilication. (c) Eighth day of rash in smallpox. This case is now clearly classified as discrete ordinary-type smallpox. In the confluent subtype of ordinary-type smallpox the lesions would have been confluent on the face and forearms: in the semiconfluent subtype they would have been confluent on the face but not on the forearms. (d) Twentieth day of rash in smallpox. The scabs have separated except on the palms of the hands and the soles of the feet, leaving depigmented areas. (From Fenner F., Henderson D.A., Arita I., Jezek Z., et al.: Smallpox and its eradication, Geneva, World Health Organization, 1988.)

Figure 75-7   (a) Typical centrifugal distribution of the rash in smallpox. (b) Patient with smallpox, Kosovo, Yugoslavia epidemic, March and April 1972. The scabs will eventually fall off leaving marks on the skin that will become pitted scars. The infection is transmissible until all scabs have fallen off. *((a) Courtesy of CDC and Dr Paul B. Dean; (b) Courtesy of CDC and Dr William Foege.)*

during the first week of the rash due to high titers of replicating virus in the oropharynx. Household members, other face-to-face contacts, and healthcare workers have traditionally been at highest risk for secondary transmission; the latter group is of greatest concern with regards to amplification of infection, especially among medically vulnerable populations. Thus, hospitalized cases of suspected smallpox must immediately be placed in negative-pressure rooms with contact and airborne precautions. Those not requiring hospital-level care should remain isolated at home in order to avoid infecting others.

The suspicion of a single smallpox case should prompt immediate notification of local public health authorities and the hospital epidemiologist. Containment of the disease is predicated on the 'ring vaccination' strategy, which was successfully deployed in the WHO global eradication campaign and which mandates the identification and immunization of all directly exposed persons or those at high risk of exposure, including close contacts, healthcare workers, and laboratory personnel. Vaccination of infected individuals, if deployed within 4 days of infection during the early incubation period, can significantly attenuate or prevent disease and may favorably impact secondary transmission.[30] Because the disease does not exist in nature, the occurrence of even a single case of smallpox would be tantamount to bioterrorism and would warrant an epidemiologic investigation to ascertain the perimeter of the initial release, so that ring vaccination can be accomplished.[33]

BOTULISM

Botulism is an acute neurologic disease resulting from intoxication with *Clostridium botulinum* that occurs sporadically and in focal outbreaks throughout the world. Generally, the illness is associated with wound contamination by the bacterial form or ingestion of preformed, food-borne toxin. A detailed discussion of botulism is found in Chapter 22. Aerosol forms of the toxin, a rare mode of acquisition in nature,

have been weaponized for use in bioterrorism although their actual use has never been documented.[4] Botulinum toxin is considered to be the most toxic molecule known; it is lethal to humans in minute quantities and acts by blocking the release of the neurotransmitter acetylcholine from presynaptic vesicles, thereby inhibiting muscle contraction.[34]

Botulism presents with the clinical features of an acute, afebrile, symmetric, descending, flaccid paralysis without mental status or sensory changes. The disease manifests initially in the bulbar musculature; fatigue, dizziness, dysphagia, dysarthria, diplopia, dry mouth, dyspnea, ptosis, ophthalmoparesis, tongue weakness and facial muscle paresis are early findings seen in more than 75% of cases. Progressive muscular involvement leads to respiratory failure in untreated cases. The clinical presentations of food-borne and inhalational botulism are indistinguishable in experimental animals.[34]

The diagnosis of botulism is based largely on epidemiologic and clinical features and the exclusion of other possible differential diagnoses (see Table 75-3); there is no commercial assay currently available to confirm intoxication. While sporadic or clustered cases occur regularly, albeit infrequently in higher-income countries, it must be recognized that any single case of botulism could be the result of bioterrorism or could herald a larger-scale event. Certainly, large numbers of epidemiologically unrelated, geographically dispersed or multifocal cases should raise the specter of an intentional release of the agent, either in food/water supplies or as an aerosol.

The mortality from food-borne botulism has declined from 60% to 6% over the last four decades, probably as a result of improvements in intensive and supportive care. Because the need for mechanical ventilation may be prolonged in these patients, the finite resource of ventilators would be rapidly overwhelmed in the event of a large-scale bioterrorism event using botulism toxin, even though these devices are part of the Strategic National Stockpile in the USA for such incidents. New developments in ventilator technology may mitigate some of the predicted shortfalls. Treatment with an equine antitoxin is available in limited supply from the CDC and may ameliorate disease if given early.

PLAGUE

Plague, a systemic disease caused by the gram-negative pathogen *Yersinia pestis*, presents in a variety of clinical forms in nature as detailed in Chapter 126. Plague is endemic in parts of South East Asia, Africa and the western USA. While naturally acquired disease results from a variety of exposure modes, bioterrorism carried out using aerosolized preparations of the agent would likely result in cases of primary pneumonic plague occurring outside of endemic areas. However, as was the case with the anthrax attacks in the USA in 2001, unexpected forms of the disease, such as bubonic and septicemic plague, might also occur in an event.

Primary pneumonic plague classically presents as an acute, febrile, pneumonic illness with prominent respiratory and systemic symptoms; gastrointestinal symptoms, purulent sputum production or hemoptysis occur variably.[35] Chest roentgenogram typically shows patchy, bilateral, multilobar infiltrates or consolidations (Figure 75-8). Untreated or inappropriately treated patients progress rapidly to develop respiratory failure, vascular collapse, purpuric skin lesions, necrotic digits and death. The differential diagnosis involves other etiologies of rapidly progressive pneumonia and includes clinical syndromes caused by a number of other agents of bioterrorism (see Table 75-3). The diagnosis may be suggested by observing the characteristic small, gram-negative, coccobacillary forms in sputum specimens with bipolar or 'safety pin' pattern uptake of Giemsa or Wright stain (Figure 75-9).[36] Culture confirmation is necessary to confirm the diagnosis; the microbiology laboratory should be notified in advance if plague is suspected, as special techniques and precautions must be employed to prevent inadvertent transmission to laboratory personnel.

Treatment recommendations for plague have been reviewed elsewhere.[27,36] Pneumonic plague can be transmitted from person-to-person by respiratory droplet nuclei, thus placing close contacts, such as patients and healthcare workers in the healthcare setting at risk. Domestic cats may participate in maintaining a transmission chain
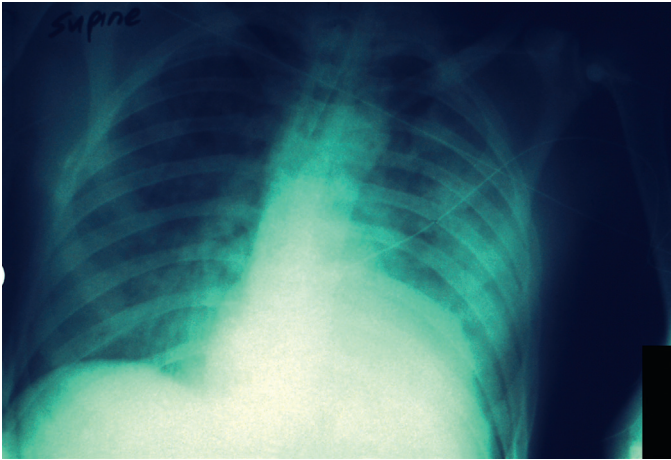
Figure 75-8 Chest X-ray, pneumonic plague, demonstrating multilobar infiltrates. *(Courtesy of CDC and Dr Jack Poland.)*
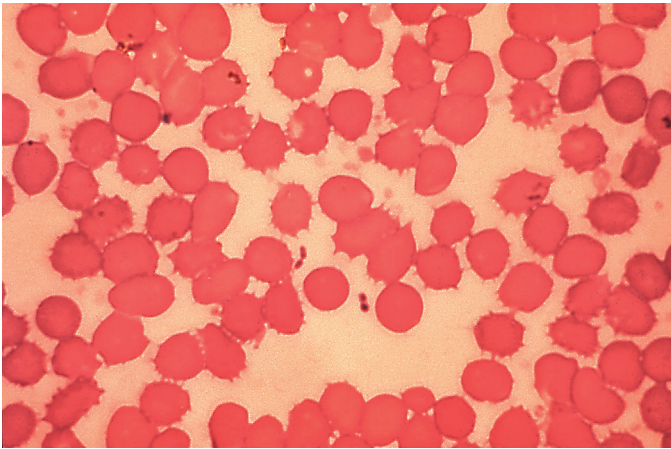
Figure 75-9 Peripheral blood smear demonstrating bipolar uptake of stain, the so-called 'safety pin' appearance of *Yersinia pestis*. *(Courtesy of CDC and Dr Jack Poland.)*

during a bioterrorism event.[11] Prompt recognition and treatment of cases, appropriate deployment of postexposure prophylaxis, and early institution of droplet precautions for infected individuals will interrupt secondary transmission of plague.

TULAREMIA

The causative agent of tularemia, *Francisella tularensis*, is another small gram-negative coccobacillus that would be predicted to cause a primary pneumonic illness if delivered as an aerosol in a bioterrorism event. Once again, however, vigilance is necessary as naturally occurring disease can be acquired by a variety of routes and present in many clinical forms; an intentional release of bacteria may also result in more than one form of tularemia. Pulmonic tularemia presents with the abrupt onset of a febrile systemic illness with prominent upper respiratory symptoms, pleuritic chest pain, and the variable development of pneumonia, hilar adenopathy, and progression to respiratory failure and death in approximately 30% of inappropriately treated patients.[37] The diagnosis is generally established on clinical features, based on the differential diagnosis (see Table 75-3) and microbiologic data. Laboratory personnel should be notified in advance if tularemia is suspected, as the organism can be very infectious when manipulated in laboratory conditions. This agent is discussed in depth in Chapter 127.

VIRAL HEMORRHAGIC FEVERS

Pathogenic members of four distinct families of RNA viruses are potential agents of viral hemorrhagic fevers (VHF): the agents of Ebola, Marburg, Lassa fever, Rift Valley fever and Crimean-Congo hemorrhagic fever. These syndromes are discussed in detail in Chapter 132. VHF cause clinical syndromes with many common features: fever, malaise, headache, myalgias, prostration, mucosal hemorrhage and other signs of increased vascular permeability, leading to shock and multiorgan system failure in advanced cases.[38] Additionally, specific VHF pathogens are associated with distinct target organ effects.

Hemorrhagic fever viruses represent emerging infections in nature due to their sporadic occurrence in focal outbreaks throughout the world when their ecological niches are disrupted by expanding human populations. These viruses are also potential weapons of bioterrorism for a number of reasons:
- some are highly infectious in aerosol form;
- they are transmissible in healthcare settings;
- they cause high morbidity and mortality; and
- they are purported to have been successfully weaponized.

Blood and other body fluids from infected patients are infectious. Hence, person-to-person airborne transmission may occur and strict contact and airborne precautions should be instituted in these cases.[38] Transmission in healthcare settings is a well-described risk with these agents. Treatment is largely supportive and includes the early use of vasopressors as needed. Ribavirin is effective against some forms of VHF but not those caused by Ebola and Marburg viruses. Nonetheless, this drug should be initiated empirically in patients presenting with a consistent clinical syndrome until an alternate etiology is confirmed.

Associated Issues and Sequelae of Bioterrorism

SURVEILLANCE

Surveillance is perhaps the most critical element in the early recognition and identification of bioterrorism events. For the individual clinician, surveillance is analogous to clinical vigilance. In the broader context of communities and larger populations, it involves a public health system and infrastructure designed to detect perturbations in the baseline occurrence of either symptoms, as is the case with syndromic surveillance systems, or diseases, as is the case with a standard public health system of reporting. Syndromic surveillance systems, such as monitoring prescription drug sales from retail pharmacies, have been used to successfully track influenza activity and that of other emerging infectious diseases and have been proposed as surrogate indicators of early disease activity.[39]

QUARANTINE

Quarantine, the physical separation and geographic restriction of groups of uninfected individuals potentially exposed to a communicable illness, has been variably considered to be a management strategy following bioterrorism. The potential effectiveness, feasibility, legality and consequences of quarantine were reviewed following the USA anthrax attacks.[40] The logistics of this approach are complex and impractical and it can be associated with adverse consequences such as increased risk of disease transmission among a quarantined group or public unrest. It seems clear that there are only limited scenarios in which the potential public health benefits of the imposition of quarantine may outweigh the potential problems it engenders; these scenarios involve highly transmissible, lethal agents. In most situations a disease-specific containment strategy, based on transmission epidemiology and disease prevention tenets, is preferable.

MANAGEMENT OF SPECIAL PATIENT POPULATIONS

The approach to the management of diseases of bioterrorism must include provisions for children, pregnant women and immunocompromised individuals. Specific recommendations for treatment and prophylaxis of these special patient groups for selected bioterrorism agents have been reviewed elsewhere.[16,27,36,37] The approach requires an assessment of the risk of using certain drugs or products in select populations versus the potential risk of the infection in question,

accounting for the extent of exposure and agent involved. Live virus vaccines, such as smallpox, pose higher risk to these special groups than to others. This consideration will impact mass vaccination decisions and, like most other aspects of medicine, will require an assessment of risk versus benefit.

PSYCHOSOCIAL MORBIDITY

An often overlooked but vitally important issue is that of psychosocial morbidity related to bioterrorism. Acute anxiety reactions and exacerbations of chronic psychiatric illness during the stress of the event, or post-traumatic stress disorder (PTSD) in its aftermath may affect clinical victims of bioterrorism as well as healthcare workers and other first responders. Nearly half of the emergency department visits during the Gulf War missile attacks in Israel in 1991 were related to acute psychological illness or exacerbations of underlying behavioral problems.[41] Data from recent acts of terrorism in the USA suggest that PTSD and/or depression may develop in more than 35% of those impacted by the events.[42,43] Although close proximity to an event and personal loss appear to be directly correlated with PTSD and depression, respectively, those indirectly involved also experience substantial morbidity.[43] The long-term psychosocial impact of these events and of the persistent threat of terrorism in general remains to be determined.

Conclusion

The response to bioterrorism is unique among WMD because it necessitates management strategies common to all disasters as well as the application of basic infectious diseases principles: surveillance, infection control, antimicrobial therapy and prophylaxis, and vaccine prevention. For these reasons, physicians (and specifically infectious diseases specialists) are likely first responders to bioterrorism and must keep their diagnostic and clinical skills current and remain clinically vigilant to potential threat agents. Because we clinicians are expected to be reliable sources of information for our patients, colleagues and public health authorities, we must guard against the inexorable 'bioterrorism fatigue' that may otherwise result from a persistent state of heightened readiness without an actual event taking place.[5]

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