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chapter 63

Biologic Attack

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Bioterrorism can be broadly defined as the deliberate use of microbial agents or their toxins as weapons against noncombatants outside the setting of armed conflict. The broad scope and mounting boldness of worldwide terrorism, exemplified by the massive attacks on New York City and Washington, DC, on Sept. 11, 2001, coupled with the apparent willingness of terrorist organizations to acquire and deploy biologic weapons, constitute ample evidence that the specter of bioterrorism will pose a persistent global threat.

As in other aspects of daily life, and the practice of medicine in particular, the concept of "risk" is germane to considerations regarding an attack using biologic agents. ***Risk,*** broadly defined as the probability that exposure to a hazard will lead to a negative consequence, can be accurately calculated for a variety of conditions of public health importance (Table 63-1). However, the quantification of risk as it pertains to bioterrorism is imprecise because accurate assessment of exposure depends on the whims of terrorists, by nature an unpredictable variable. Although the probability of exposure to a biologic attack is statistically low, it is not zero; and because the negative consequences are potentially catastrophic, an understanding of biologic threat agents and a cogent biodefense strategy are important components of disaster medicine.

TABLE 63-1 U.S. MORTALITY RISK ANALYSIS*

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HISTORICAL PERSPECTIVE

Biologic weapons have been used against both military and civilian targets throughout history. In the fourteenth century, Tatars attempted to use epidemic disease against the defenders of Kaffa by catapulting plague-infected corpses into the city.[1] British forces gave Native Americans blankets from a smallpox hospital in an attempt to affect the balance of power in the eighteenth century Ohio River Valley.[1] In addition to their well-described use of chemical weapons, Axis forces purportedly infected livestock with anthrax and glanders to weaken Allied supply initiatives during World War I. Perhaps the most egregious example of biologic warfare involved the Japanese program in occupied Manchuria from 1932 to 1945. Based on survivor accounts and confessions of Japanese participants, thousands of prisoners were murdered in experiments using a variety of virulent pathogens at Unit 731, the code name for the biologic weapons facility there.[2]

The United States maintained an active program for the development and testing of offensive biologic weapons from the early 1940s until 1969, when the program was terminated by executive order of then President Nixon, although efforts continue with regard to countermeasures against biologic weapons. The Convention on the Prohibition of the Development, Production, and Stockpiling of Biological and Toxin Weapons and on Their Destruction (BWC) was ratified in 1972, formally banning the development or use of biologic weapons and assigning responsibility for enforcement to the United Nations.[1] Unfortunately, the BWC has not been effective in its stated goals; multiple signatories, including the former Soviet Union and Iraq, have violated the terms and spirit of the agreement. The accidental release of aerosolized anthrax spores from a biologic weapons plant in the Soviet Union in 1979, with at least 68 human deaths from inhalational anthrax reported downwind, was proved years later to have occurred in the context of Soviet offensive weapons production.

Recent events have established bioterrorism as a credible and ubiquitous threat. 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 Shinri Kyo, the Japanese cult that released sarin nerve agent in the Tokyo subway system in 1995 had unsuccessfully experimented on multiple occasions with spraying anthrax from downtown rooftops before their successful chemical attack; and the findings of the UN weapons inspectors of massive quantities of weaponized biologic weapons in Iraq during the Gulf War and its aftermath[4] served as sentinel warnings of a shift in terrorism trends. The anthrax attacks in the United States in October and November 2001, following the catastrophic events of Sept. 11, elevated bioterrorism to the fore of the international dialogue.

CURRENT PRACTICE

Threat Assessment

Biologic agents are considered weapons of mass destruction (WMDs) because, as with certain conventional, chemical, and nuclear weapons, their use may result in large-scale morbidity and mortality. A World Health Organization (WHO) model based on the hypothetical effects of the intentional release of 50 kg of aerosolized anthrax spores upwind from a population center of 500,000 (analogous to that of Providence, RI) estimated that the agent would disseminate in excess of 20 km downwind and that nearly 200,000 people would be killed or injured by the event.[5] Biologic weapons possess unique properties among WMDs. By definition, biologic agents are associated with a clinical latency period of days to weeks, in most cases, during which time early detection is quite difficult with currently available technology. Yet, early detection is critical because specific antimicrobial therapy and vaccines are available for the treatment and prevention of illness caused by certain biologic weapons; casualties from other forms of WMDs can generally only be treated by decontamination (with antidotes available for only some types), trauma mitigation, and supportive care. Additionally, the specter of a biologic attack provokes fear and anxiety—"terror"—disproportionate to that seen with other threats.

The aims of bioterrorism are those of terrorism in general: morbidity and mortality among civilian populations, disruption of the societal fabric, and exhaustion or diversion of resources. A successful outcome, from a terrorist standpoint, may be achieved without furthering all of these aims. The anthrax attacks in the United States in 2001 evoked fear and anxiety and diverted resources from other critical public health activities despite the limited number of casualties. In many cases, the surge capacity of our public health system was inadequate to deal with the emergency needs.

To be used in large-scale bioterrorism, biologic agents must undergo complex processes of production, cultivation, chemical modification, and weaponization. For these reasons, state sponsorship or direct support from governments or organizations with significant resources, contacts, and infrastructure would predictably be required in large-scale events. However, recent revelations have suggested that some agents may be available on the worldwide black market and in other illicit settings,[6] thus obviating the need for the production process. Although an efficient mode of delivery has traditionally been felt to be necessary, the anthrax attacks in the United States 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 selection of a pathogen as a biologic weapon: availability or ease of large-scale production; ease of dissemination, usually by the aerosol route; stability of the product in storage, as a weapon, and in the environment (biologic entities differ in their physical properties); cost; and clinical virulence. The last of these refers to the reliability with which the pathogen causes high mortality, morbidity, or social disruption. The Centers for Disease Control and Prevention (CDC) have prioritized biologic agent threats based on the aforementioned characteristics,[7] and this has influenced current preparedness strategies (Table 63-2). Category A agents, considered the highest priority, are associated with high mortality and the greatest potential for major impact on the public health. Category B agents are considered "incapacitating" because of their potential for moderate morbidity but relatively low mortality. Most of the category A and B agents have been experimentally weaponized in the past and are thus of proven feasibility. Category C agents include emerging threats and pathogens that may be available for development.

Another factor that must be addressed in assessing future bioterrorism risk is the historical track record of experimentation with specific pathogens, an area that has been informed from the corroborated claims of various high-level Soviet defectors and data released from the former offensive weapons programs of the United States and United Kingdom.[1,6,8] It is apparent from these sources, combined with the burgeoning fields of molecular biology and genomics, that future risk scenarios may have to contend with genetically altered and "designer" pathogens. To this end, a miscellaneous grouping of potential threat agents is added to the extant CDC categories in Table 63-2. The most cautious approach to assessing risk may be to remain open to additional, novel possibilities.

Bioterrorism Recognition

By definition bioterrorism is insidious; absent advance warning or specific intelligence information, clinical illness will be manifest before the circumstances of a release event are known. For this reason, healthcare providers are likely to be the first responders to this form of terrorism. This is in contrast to the more familiar scenarios in which police, firefighters, paramedics, and other emergency services personnel are deployed to the scene of an attack with conventional weaponry or a natural disaster. Physicians and other healthcare workers must therefore maintain a high index of suspicion of bioterrorism and recognize suggestive epidemiologic clues and clinical features to enhance early recognition and guide initial management of casualties. This remains

TABLE 63-2 AGENTS OF CONCERN FOR USE IN BIOTERRORISM

HIGHEST PRIORITY (CATEGORY A)	
Microbe or toxin	Disease
Bacillus anthracis	Anthrax
Variola virus	Smallpox
Yersinia pestis	Plague
Clostridium botulinum	Botulism
Fracisella tularensis	Tularemia
Filoviruses	Ebola hemorrhagic fevers, Marburg disease
Arenaviruses	Lassa fever, South American hemorrhagic fevers
Bunyaviruses	Rift Valley fever, Congo-Crimean hemorrhagic fevers
MODERATELY HIGH PRIORITY (CATEGORY B)	
Coxiella burnetti	Q fever
Brucella spp.	Brucellosis
Burkholderia mallei	Glanders
Alphaviruses	Viral encephalitides
Ricin	Ricin intoxication
Staphylococcus aures enterotoxin B	Staphylococcal toxin illness
Salmonella spp., *Shigella dysenteriae, Escherichia coli* 0157:H7, *Vibrio cholerae, Cryptosporidium parvum*	Food- and water-borne gastroenteritis
CATEGORY C	
Hantavirus	Viral hemorrhagic fevers
Flaviviruses	Yellow fever
Mycobacterium tuberculosis	Multidrug resistant tuberculosis
MISCELLANEOUS	
Genetically engineered vaccine-and/or antimicrobial-resistant category A or B agents	
HIV-1	
Adenoviruses	
Influenza	
Rotaviruses	
Hybrid pathogens (e.g., smallpox-plague, smallpox-ebola)	

(Artenstein AW, Bioterrorism and Biodefense. In: Cohen J, Powderly WG, eds. Infectious Diseases, second edition. Mosby: London, 2003:99-107) Used with permission.

the most effective way to minimize the deleterious effects of bioterrorism on individual patients and on the public health.

Early recognition is hampered for multiple reasons. As discussed above, it is likely that the circumstances of any event will only be known in retrospect, therefore it may prove problematic to immediately discern the extent of exposure. Terrorists have an unlimited number of targets in most open, democratic societies; it is unrealistic to expect that without detailed intelligence data, all of these can be secured at all times. Certain sites such as government institutions, historic landmarks, or large events may be predictable targets, but there are other, less predictable possibilities. In fact, government data support businesses and other economic concerns as the main targets of global terrorism during the period from 1996 to 2002.[9] Metropolitan areas are considered vulnerable, but owing to the expansion of suburbs, commuters, and the clinical latency period between exposure and symptoms inherent with biologic agents, casualties of bioterrorism are likely to present for medical attention in diverse locations and at varying times after a common exposure. An event in New York City on a Wednesday morning may result in clinically ill persons presenting over the ensuing weekend to a variety of emergency departments within a 60-mile radius. Additionally, modern modes of transportation ensure that there will be affected persons thousands of miles away at both national and international locations related to a common exposure. This adds layers of complexity to an already complicated setting and illustrates the critical importance of surveillance and real-time communication in this setting.

Further hindering the early recognition of bioterrorism is that initial symptoms may be nondiagnostic. In the absence of a known exposure, many symptomatic persons may not seek medical attention early, or if they do, they may be misdiagnosed as having a flu-like illness. Once beyond the early stages, many of these illnesses progress quite rapidly and treatment may be less successful. Most of the diseases caused by agents of bioterrorism are rarely, if ever, seen in clinical practice; physicians are therefore likely to be inexperienced with their clinical presentation. Additionally, these agents by definition will have been manipulated in a laboratory and may not present with the classic clinical features of naturally occurring infection. This was dramatically illustrated by some of the inhalational anthrax cases in the United States in October 2001.[10]

Early recognition of bioterrorism is facilitated by the recognition of epidemiologic and clinical clues. Clustering of patients with common symptoms and signs, especially if these are unusual or characteristic of bioterrorism agents, is suggestive and should prompt expeditious notification of local public health authorities. This approach will also lead to the recognition of outbreaks of naturally occurring disease or emerging pathogens. The recognition of a single case of a rare or nonendemic infection, in the absence of a travel history or other potential natural exposure, should raise the suspicion of bioterrorism and should prompt notification of public health authorities. Finally, unusual patterns of disease such as concurrent illness in human and animal populations should raise suspicions of bioterrorism or another form of emerging infection. An effective response to bioterrorism requires coordination of the medical system at all levels, from the community physician to the tertiary care center, with public health, emergency management, and law enforcement infrastructures.

Threat Agents

This section provides a broad overview of the biologic threat agents thought to be of major current concern—largely, the CDC category A agents. Extensive coverage of specific pathogens can be found in related chapters in

this text and in other sources.[11] Data concerning clinical incubation periods, transmission characteristics, and infection control procedures for agents of bioterrorism are provided in Table 63-3. Syndromic differential diagnoses for select clinical presentations are detailed in Table 63-4.

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 102. 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.[12] The cutaneous form of anthrax is the most common presentation; gastrointestinal and inhalational forms are exceedingly rare in naturally acquired disease. Cutaneous anthrax occurred regularly in the first half of the twentieth century in association with contaminated hides and wools used in the garment industry, but it is uncommonly seen in current-day industrialized countries due to importation restrictions. The last known case of naturally occurring inhalational anthrax in the United States occurred in 1976.[13]

It had been previously hypothesized that large-scale bioterrorism with anthrax would involve aerosolized endospores with resultant inhalational disease, but the recent attacks in the United States illustrate the difficulties in predicting modes and outcomes in bioterrorism: the attacks were on a relatively small scale, and nearly 40% of the confirmed cases were of the cutaneous variety.[14] The serious morbidity and mortality, however, were related to inhalational disease, as was the case in the Sverdlovsk outbreak in 1979. Therefore, planning for larger-scale events with aerosolized agent seems warranted.

The clinical presentations and differential diagnoses of cutaneous and inhalational anthrax are described in Table 63-4. 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 associated with significant local edema. 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 such significant edema.[15] Cutaneous anthrax is associated with systemic disease and its attendant mortality in up to 20% of untreated cases, although with appropriate antimicrobial therapy mortality is less than 1%.[13]

Once the inhaled endospores reach the terminal alveoli of the lungs, generally requiring particle sizes of 1 to 5 fm, they are phagocytosed by macrophages and transported to regional lymph nodes, where they germinate into vegetative bacteria and, subsequently, disseminate hematogenously.[12] Spores may remain latent for extended periods of time in the host, up to 100 days in experimental animal exposures.[14] This has translated into prolonged clinical incubation periods after 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 to 10 days, perhaps influenced by exposure dose.[12,14]

Before the U.S. anthrax attacks in October 2001, most of the clinical data concerning inhalational anthrax derived from Sverdlovsk, the largest outbreak recorded. Although there is much overlap between the clinical manifestations noted previously and those observed during the recent outbreak, more detailed data are available from the recent U.S. experience. There were 11 confirmed persons with inhalational anthrax, 5 (45%) of whom died. Although this contrasts with a case-fatality rate of greater than 85% reported from Sverdlovsk, the reliability of reported data from this outbreak is questionable.[14] Patients almost uniformly present 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.[10,16] Many of these findings are nondiagnostic and overlap considerably with those of influenza and other common viral respiratory tract infections. Recently compiled data suggest

TABLE 63-3 INFECTION CONTROL ISSUES FOR SELECTED AGENTS OF BIOTERRORISM

DISEASE	INCUBATION PERIOD (DAYS)	PERSON-TO-PERSON TRANSMISSION	INFECTION CONTROL PRACTICES
Inhalational anthrax	2–43*	No	Standard
Botulism	12–72 hours	No	Standard
Primary pneumonic plague	1–6	Yes	Droplet
Smallpox	7–17	Yes	Contact and airborne
Tularemia	1–14	No	Standard
Viral hemorrhagic fevers	2–21	Yes	Contact and airborne
Viral encephalitides	2–14	No	Standard
Q fever	2–14	No	Standard
Brucellosis	5–60	No	Standard
Glanders	10–14	No	Standard

*Based on limited data from human outbreaks; experimental animal data support clinical latency periods of up to 100 days (Artenstein AW Bioterrorism and Biodefense. In: Cohen J, Powderly WG, eds. Infectious Diseases, second edition. Mosby: London, 2003:99-107). Used with permission.

TABLE 63-4 PRESENTATIONS AND DIFFERENTIAL DIAGNOSES OF BIOTERRORISM AGENTS

CLINICAL PRESENTATION	DISEASE	DIFFERENTIAL DIAGNOSIS
Non-specific flu-like symptoms with nausea, emesis, 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, infiltrates, pleural effusions)	Inhalational anthrax	Bacterial mediastinitis, tularemia, Q fever, psittacosis, Legionnaires' disease, influenza, *Pneumocystis carinii* pneumonia, viral pneumonia, ruptured aortic aneurysm, superior vena cava syndrome, histoplasmosis, coccidioidomycosis, sarcoidosis
Pruritic, painless papule, leading to vesicle(s), leading to ulcer, leading to edematous black eschar with or without massive local edema and regional adenopathy and fever, evolving over 3-7 days	Cutaneous anthrax	Recluse spider bite, plague, staphylococcal lesion, atypical Lyme disease, orf, glanders, tularemia, rat-bite fever, ecthyma gangrenosum, rickettsialpox, atypical mycobacteria, diptheria
Rapidly progressive respiratory illness with cough, fever, rigors, dyspnea, chest pain, hemoptysis, possible gastrointestinal symptoms, lung consolidation with or without shock	Primary pneumonic plague	Severe community-acquired bacterial or viral pneumonia, inhalational anthrax, inhalational tularemia, pulmonary infarct, pulmonary hemorrhage
Sepsis, disseminated intravascular coagulation, purpura, acral gangrene	Septicemic plague	Meningococcemia; Gram-negative, streptococcal, pneumococcal or staphylococcal bacteremia with shock; overwhelming postsplenectomy sepsis; acute leukemia; Rocky Mountain spotted fever; hemorrhagic smallpox; hemorrhagic varicella (in immunocompromised patients)
Fever, malaise, prostration, headache, myalgias followed by development of synchronous, progressive papular leading to vesicular and then pustular rash on face, mucous membranes (extremities more than the trunk); the rash may become generalized, with a hemorrhagic component and system toxicity	Smallpox	Varicella, drug eruption, Stevens-Johnson syndrome, measles, secondary syphilis, erythema multiforme, severe acne, meningococcemia, monkeypox, generalized vaccinia, insect bites, Coxsackie virus infection, vaccine reaction
Non-specific flu-like illness with pleuropneumonitis; bronchiolitis with or without hilar lymphadenopathy; variable progression to respiratory failure	Inhalational tularemia	Inhalational anthrax, pneumonic plague, influenza, mycoplasma pneumonia, Legionnaire's disease, Q fever, bacterial pneumonia
Acute onset of afebrile, symmetric, descending flaccid paralysis that begins in bulbar muscles; dilated pupils; diplopia or blurred vision; dysphagia; dysarthria; ptosis; dry mucous membranes leading to airway obstruction with respiratory muscle paralysis; clear sensorium and absence of sensory changes	Botulism	Myasthenia gravis, brain stem cerebrovascular accident, polio, Guillain-Barre syndrome variant, tick paralysis, chemical intoxication
Acute-onset fevers, malaise, prostration, myalgias, headache, gastrointestinal symptoms, mucosal hemorrhage, altered vascular permeability, disseminated intravascular coagulation, hypotension leading to shock with or without hepatitis and neurologic findings	Viral hemorrhagic fever	Malaria, meningococcemia, leptospirosis, rickettsial infection, typhoid fever, borrelioses, fulminant hepatitis, hemorrhagic smallpox, acute leukemia, thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, systemic lupus erythematosus

(Artenstein AW, Bioterrorism and Biodefense. In: Cohen J, Powderly WG, eds. Infectious Diseases, second edition. Mosby: London, 2003:99-107) Used with permission.

that shortness of breath, nausea, and vomiting are significantly more common in anthrax, whereas rhinorrhea is uncommonly seen in anthrax but noted in the majority of viral respiratory infections.[17]

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. The latter is thought to be an early indicator of disease, but computed tomography appears to provide greater sensitivity than chest radiographs for this finding.

The clinical manifestations of inhalational anthrax generally evolve to a fulminant septic picture with progressive respiratory failure. *B. anthracis* is routinely isolated in blood cultures if obtained before the initiation of antimicrobials. Pleural fluid is typically hemorrhagic; the bacteria can either be isolated in culture or documented by antigen-specific immunohistochemical stains of this material in the majority of patients.[10] In the five fatalities in the U.S. series, the average time from hospitalization until death was 3 days (range, 1 to 5 days), which is consistent with other reports of the clinical virulence of this infection. Autopsy data typically reveal hemorrhagic mediastinal lymphadenitis and disseminated, metastatic infection. Pathology data from the Sverdlovsk outbreak confirm meningeal involvement, typically hemorrhagic meningitis, in 50% of disseminated cases.[18]

The diagnosis of inhalational anthrax should be entertained in the setting of a consistent 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 illness). The diagnosis should also be considered in a single individual with a consistent or suggestive clinical illness in the absence of another etiology. The early recognition and treatment of inhalational anthrax is likely to be associ-

ated with a survival advantage.[10] Therefore, prompt empiric antimicrobial therapy should be initiated if infection is clinically suspected. Combination parenteral therapy is appropriate in the ill person for a number of reasons: to cover the possibility of antimicrobial resistance; to target specific bacterial functions (e.g., the theoretical effect of clindamycin on toxin production); to ensure adequate drug penetration into the central nervous system; and perhaps to favorably affect survival.[10] In the future, it is likely that novel therapies such as toxin inhibitors or receptor antagonists will be available to treat anthrax.[19] Detailed therapeutic and postexposure prophylaxis recommendations for adults, children, and special groups have been recently reviewed elsewhere.[14] Anthrax vaccine adsorbed has been proved to be effective in preventing cutaneous anthrax in human clinical trials and in preventing inhalational disease after aerosol challenge in nonhuman primates.[20] The vaccine has generally been found to be safe but requires six doses over 18 months with the need for frequent boosting. Its availability is currently limited although it is hoped that second-generation anthrax vaccines, currently in clinical trials, will prove effective.

Smallpox

The last known naturally acquired case of smallpox occurred in Somalia in 1977; the disease was officially certified as having been eradicated in 1980, the culmination of a 12-year intensive campaign undertaken by the WHO.[21] However, because of concerns that variola virus stocks may have either been removed from or sequestered outside of their officially designated repositories, smallpox is considered to be a potential agent of bioterrorism. Multiple features make smallpox an attractive biologic weapon and ensure that its reintroduction into human populations would be a global public health catastrophe: it is stable in aerosol form with a low infective dose; case fatality rates are historically high, approaching 30%; secondary attack rates among unvaccinated close contacts are 37% to 88% and are amplified; and much of the world's population is susceptible, as routine civilian vaccination was terminated more than two decades ago, vaccine-induced immunity wanes over time, and there is no virus circulating in the environment to provide low-level booster exposures.[22] Additionally, vaccine supplies are currently limited, although this problem has begun to be addressed, and there are currently no antiviral therapies of proven effectiveness against this pathogen.

After an incubation period of 7 to 17 days (average, 10 to 12 days), the patient experiences the acute onset of a prostrating prodrome of fever, rigors, headache, and backache that may last 2 to 3 days. This is followed by a centrifugally distributed eruption that generalizes as it evolves through macular, papular, vesicular, and pustular stages in synchronous fashion over approximately 8 days, with umbilication in the latter stages. Enanthema in the oropharynx typically precedes the exanthem by a day or two. The rash typically involves the palms and soles early in the course of the disease. The pustules begin crusting during the second week of the eruption; separation of scabs is usually complete by the end of the third week. The differential diagnosis of smallpox is delineated in Table 63-4. Historically, varicella and drug reactions have posed the most diagnostic dilemmas.[22]

Smallpox is transmitted person to person by respiratory droplet nuclei and, less commonly, by contact with lesions or contaminated fomites. Airborne transmission by fine-particle aerosols has, under certain conditions, been documented.[22] The virus is communicable from the onset of the enanthema until all of the scabs have separated, although patients are thought to be most contagious 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. Thus, hospitalized cases are placed in negative-pressure rooms with contact and airborne precautions to minimize this risk, and those not requiring hospital-level care should remain isolated at home 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 smallpox is predicated on the "ring vaccination" strategy, which was successfully deployed in the WHO global eradication campaign and mandates the identification and immunization of all directly exposed persons, including close contacts, healthcare workers, and laboratory personnel. Vaccination, if deployed within 4 days of infection during the early incubation period, can significantly attenuate or prevent disease and may favorably affect secondary transmission.[22] Because the occurrence of even a single case of smallpox would be tantamount to bioterrorism, an epidemiologic investigation would be necessary to ascertain the perimeter of the initial release, so that tracing of initially exposed persons can be accomplished.

Botulism

Botulism, an acute neurologic disease resulting from intoxication with *Clostridium botulinum*, occurs sporadically and in focal outbreaks throughout the world related to wound contamination by the bacterium or ingestion of foodborne toxin. A detailed discussion of botulism is found in Chapter 132. Aerosol forms of the toxin, a rare mode of acquisition in nature, have been weaponized for use in bioterrorism.[4] Botulinum toxin is considered to be the most toxic molecule known; it is lethal to humans in minute quantities. It blocks the release of the neurotransmitter acetylcholine from presynaptic vesicles, thereby inhibiting muscle contraction.[23]

Botulism presents as an acute, afebrile, symmetric, descending, flaccid paralysis. The disease manifests initially in the bulbar musculature and is unassociated with mental status or sensory changes. 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 leading to respiratory failure ensues. The clinical presentations of foodborne and inhalational botulism are indistinguishable in experimental animals.[23]

The diagnosis of botulism is largely based on epidemiologic and clinical features and the exclusion of other possibilities (see Table 63-4). Clinicians should recognize that any single case of botulism could be the result of bioterrorism or could herald a larger-scale "natural" outbreak. A large number of epidemiologically unrelated, multifocal cases should be clues to an intentional release of the agent, either in food or water supplies or as an aerosol.

The mortality from foodborne botulism has declined from 60% to 6% over the last four decades, probably as a result of improvements in supportive care and mechanical ventilation. Because the need for the latter may be prolonged, limited resources (e.g., mechanical ventilators) would likely be exceeded in the event of a large-scale bioterrorism event. Treatment with an equine antitoxin, available in limited supply from the CDC, may ameliorate disease if given early.

Plague

Plague, the disease caused by the gram-negative pathogen *Yersinia pestis*, presents in a variety of forms in naturally acquired disease and is extensively covered in Chapter 103. Plague is endemic in parts of Southeast Asia, Africa, and the western United States. Aerosolized preparations of the agent, the expected vehicle in bioterrorism, would be predicted to result in cases of primary pneumonic plague outside of endemic areas. As was the case with the anthrax attacks in the United States in 2001, however, additional forms of the disease such as bubonic and septicemic plague might also occur.

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.[24] Chest roentgenogram typically shows patchy, bilateral, multilobar infiltrates or consolidations. In the absence of appropriate treatment there may be rapid progression to respiratory failure, vascular collapse, purpuric skin lesions, necrotic digits, and death. The differential diagnosis, as noted in Table 63-4, is largely that of rapidly progressive pneumonia. The diagnosis may be suggested by the characteristic small gram-negative coccobacillary forms in stained sputum specimens with bipolar uptake ("safety pin") of Giemsa or Wright stain.[25] Culture confirmation is necessary to confirm the diagnosis; the microbiology laboratory should be notified in advance if plague is suspected because special techniques and precautions must be employed.

Treatment recommendations for plague have been reviewed elsewhere.[25] Pneumonic plague can be transmitted from person to person by respiratory droplet nuclei, thus placing close contacts, other patients, and healthcare workers at risk. Prompt recognition and treatment of this disease, appropriate deployment of postexposure prophylaxis, and early institution of droplet precautions will interrupt secondary transmission.

Tularemia

Francisella tularensis, the causative agent of tularemia, is another small gram-negative coccobacillus that would likely cause a primary pneumonic presentation if delivered as an aerosol agent of bioterrorism. Inhalational 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 excess of 30% of those who do not receive appropriate therapy.[26] The diagnosis is generally based on clinical features after other agents are ruled out. Laboratory personnel should be notified in advance if tularemia is suspected because the organism can be very infectious under culture conditions. This agent is discussed in depth in Chapter 104.

Viral Hemorrhagic Fevers

The agents of viral hemorrhagic fevers are members of four distinct families of ribonucleic acid viruses that cause clinical syndromes with overlapping features: fever, malaise, headache, myalgias, prostration, mucosal hemorrhage, and other signs of increased vascular permeability and circulatory dysregulation leading to shock and multiorgan system failure in advanced cases.[27] Specific agents are also associated with specific target organ effects. These pathogens, discussed in detail in Chapters 118 to 121, include the agents of Ebola, Marburg, Lassa fever, Rift Valley fever, and Congo-Crimean hemorrhagic fever.

Hemorrhagic fever viruses have been viewed as emerging infections in nature due to their sporadic occurrence in focal outbreaks throughout the world, and they are thought to be the results of human intrusion into a viral ecologic niche. They are, however, potential weapons of bioterrorism because they are highly infectious in aerosol form, are transmissible in healthcare settings, cause high morbidity and mortality, and are purported to have been successfully weaponized.[8] Blood and other body fluids from infected patients are extremely infectious, and person-to-person airborne transmission may occur; therefore, strict contact and airborne precautions should be instituted in these cases.[27] Treatment is largely supportive and includes the early use of vasopressors as needed. Ribavirin is effective against some forms of viral hemorrhagic fevers but not those caused by Ebola and Marburg viruses. Nonetheless, this drug should be initiated empirically in patients presenting with a syndrome consistent with viral hemorrhagic fever until the etiology is confirmed.

Management of Special Patient Populations

The approach to the management of diseases of bioterrorism must be broadened to include children, pregnant women, and immunocompromised persons. Specific recommendations for treatment and prophylaxis of these special patient groups for selected bioterrorism agents have been recently reviewed.[13,25,26] A general approach requires an assessment of the risk of certain drugs or products in select populations versus the potential risk of the infection in question, accounting for extent of exposure and the agent involved. The issue extends to immu-

nization because certain vaccines, such as smallpox, pose higher risk to these special groups than to others. This will affect mass vaccination strategies.

Psychosocial Morbidity

An often overlooked but vitally important issue in bioterrorism is that of psychosocial sequelae. These may take the form of acute anxiety reactions and exacerbations of chronic psychiatric illness during the stress of the event, or posttraumatic stress disorder (PTSD) in its aftermath. 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 problems.[28] Data from recent acts of terrorism in the United States suggest that PTSD may develop in as many as 35% of those affected by the events.[29] In the early period after the Sept. 11, 2001, attacks in New York, PTSD and depression were nearly twice as prevalent as in historical control subjects.[30] Although close proximity to the events and personal loss were directly correlated with PTSD and depression, respectively, there was a substantial burden of morbidity among those indirectly involved. The psychological impact of these events and of the ongoing international concern over terrorism can be expected to be significant and sustained for society as a whole.

PITFALLS

The response to bioterrorism is unique among weapons of mass destruction because it necessitates the consequence management that is common to all disasters as well as the application of basic infectious diseases principles: disease surveillance, infection control, antimicrobial therapy and prophylaxis, and vaccine prevention. For these reasons, physicians are likely first responders to bioterrorism and are expected to be reliable sources of information for their patients, colleagues, and public health authorities.[31]

There remain a number of potential pitfalls regarding disasters involving a biologic attack that must be identified and managed to optimize the public health. As alluded to above, the clinical latency period between exposure to an agent and the manifestation of signs and symptoms is on the order of days to weeks with most of the CDC category A, B, or C agents, other than with preformed pathogen-derived toxins. For this reason, early diagnoses of the first cases are likely to prove problematic and require heightened clinical vigilance.[32] Even after early victims have been diagnosed, communications among hospitals and other healthcare institutions on a local, regional, national, and international level will be essential to define the epidemiology and possibly to identify exposure sources. Given the extent and ease of rapid movement within our world, clinical presentations from a point-source biologic attack could occur in widely disparate geographic locations. Additionally, it is likely that a terrorist attack would be multifocal in any case. A similar epidemiologic approach using case definitions, case identification, surveillance, and real-time communications is necessary whether the event is a malicious attack, emergent from nature, or unknown.[33]

Other potential pitfalls reside in the arena of diagnostic techniques, treatment, and prevention of disease related to biologic agents. Although an active area of research, the development of field-ready, highly predictive, rapid screening tests for agents of bioterrorism has not, as yet, progressed to the point at which such assays are approved by the U.S. Food and Drug Administration and available for deployment. Treatment and prevention issues, such as the absence of effective treatments for many forms of viral hemorrhagic fevers; shortages in the availability of multivalent anti-toxin for botulism; projected shortages in the availability of mechanical ventilators to manage a large-scale attack using botulism; lack of human data regarding the use of antiviral agents in smallpox; and the unfavorable toxicity profiles of currently available smallpox vaccines remain unresolved but active areas of research. The fact that modern molecular biologic techniques have been used to produce genetically altered pathogens with "designer" phenotypes, such as antimicrobial or vaccine resistance, adds additional layers of complexity to an already complex problem. Finally, as has been vividly illustrated during the recent epidemic of severe acute respiratory syndrome[34] and had been well recognized when epidemic smallpox occurred with regularity,[22] transmission of infection within hospitals is common. Healthcare workers, our first line of defense against an attack using biologic agents, remain at significant occupational risk.

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