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79 CHAPTER

Biological Attack

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Bioterrorism can be broadly defined as the deliberate use of microbial agents or their toxins as weapons. The broad scope and mounting boldness of worldwide terrorism exemplified by the massive attacks on New York City and Washington, DC, on September 11, 2001, coupled with the apparent willingness of terrorist organizations to acquire and deploy biological weapons, constitute ample evidence that the specter of bioterrorism will continue to pose a 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 biological 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 79-1). 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 biological attack is statistically low, it is not zero. Because the negative consequences of an attack are potentially catastrophic, an understanding of biological threat agents and a cogent biodefense strategy are important components of disaster medicine.

HISTORICAL PERSPECTIVE

Biological weapons have been used against both military and civilian targets throughout history, perhaps as early as 600 BC.[1] In the fourteenth century, Tatars attempted to use epidemic disease against the defenders of Kaffa, by catapulting plague-infected corpses into the city. British forces gave Native Americans blankets from a smallpox hospital in an attempt to affect the balance of power in the Ohio River Valley in the eighteenth century.[2] 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 biological 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 a notorious Japanese biological weapons facility.[3]

The United States maintained an active program for the development and testing of offensive biological weapons from the early 1940s until 1969, when the program was terminated by executive order of then President Nixon. Current efforts continue as countermeasures against biological 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 biological weapons, and assigning enforcement responsibility to the United Nations.[2] Unfortunately, the BWC has not been effective in its stated goals; multiple signatories have violated the terms and spirit of the agreement. The accidental release of aerosolized anthrax spores from a biological weapons plant in the Soviet Union in 1979, with at least 68 human deaths from inhalational anthrax reported downwind, was proven years later to have occurred in the context of offensive weapons production.

Events within the past 30 years have established bioterrorism as a credible and ubiquitous threat: for example, the 1984 incident in The Dalles, Oregon, involving the intentional contamination of restaurant salad bars with *Salmonella*, by a religious cult attempting to influence a local election.[4] Public fears were additionally heightened by the international events following the Japanese Aum Shinrikyo cult's sarin attack in Tokyo in 1995, especially after investigations revealed that the group had been experimenting with aerosolized anthrax release from rooftops for several months prior. More recently, UN weapons-inspector findings of significant quantities of weaponized biological compounds in Iraq during the Gulf War and the subsequent aftermath has served as sentinel warnings of a shift in terrorism trends. This trend culminated with the October 2001 anthrax attacks in the United States, which elevated bioterrorism to the forefront of international dialogue and heightened public concerns regarding systemic health care preparation against the threat of biological attacks.

CURRENT PRACTICE

Threat Assessment

Biological 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 metropolitan 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] Biological weapons possess unique properties among WMDs. By definition, biological 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 biological 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 possibility of a biological attack provokes fear and anxiety—"terror"—disproportionate to that seen with other threats, given their often invisible nature.

TABLE 79-1 U.S. Mortality Risk Analysis*

Heart disease	1 in 397
Cancer	1 in 511
Stroke	1 in 1699
Alzheimer's	1 in 5752
Motor vehicle accident	1 in 6745
Homicide	1 in 15,440
Drowning	1 in 64,031
Fire	1 in 82,977
Bicycle accident	1 in 376,165
Lightning strike	1 in 4,478,159
Bioterrorism (anthrax)	1 in 56,424,800

*U.S. Population divided by the number of annual deaths for 2000.
Source: Harvard Center for Risk Analysis, http://www.hcra.harvard.edu ©2004.

TABLE 79-2 Agents of Concern for Use in Bioterrorism

MICROBE OR TOXIN	DISEASE
Highest Priority (Category A)	
Bacillus anthracis	Anthrax
Variola virus	Smallpox
Yersinia pestis	Plague
Clostridium botulinum	Botulism
Francisella tularensis	Tularemia
Filoviruses	Ebola hemorrhagic fevers and Marburg disease
Arenaviruses	Lassa fever and South American hemorrhagic fevers
Bunyaviruses	Rift Valley fever and Congo-Crimean hemorrhagic fevers
Moderately High Priority (Category B)	
Coxiella burnetti	Q fever
Brucella spp.	Brucellosis
Burkholderia mallei	Glanders
Alphaviruses	Viral encephalitis
Ricin	Ricin intoxication
Staphylococcus aures	Staphylococcal toxin illness enterotoxin B
Salmonella spp.	Food- and water-borne gastroenteritis
Shigella dysenteriae	Bacillary dysentery (shigellosis)
Escherichia coli	Gastroenteritis, 0157:H7-induced HUS
Vibrio cholerae	Cholera diarrhea
Cryptosporidium parvum	Cryptosporidiosis
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 and smallpox-Ebola)	

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The goals 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 but instead disrupting daily life. The anthrax attacks in the United States in 2001 evoked significant 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 has been inadequate to deal with the emergency needs, resulting in reform and additional planning after the event.

To be used in large-scale bioterrorism, biological 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, revelations have suggested that some agents may be available on the worldwide black market and in other illicit settings, thus obviating the need for the extensive production process.[6] Although traditionally thought to require an efficient delivery mode, recent events, including the 2001 United States anthrax attacks, demonstrated 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 biological weapon: availability or ease of large-scale production, ease of dissemination (usually by the aerosol route), stability of the product in storage, 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) has prioritized biological-agent threats based on the aforementioned characteristics, and this has influenced current preparation strategies (Table 79-2).[7] Category A agents, considered the highest priority, are associated with high mortality and the greatest potential for major effects 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 thus have proven feasibility. Category C agents include emerging threats and pathogens that may be available for development and weaponization.

Another factor that must be addressed in assessing future bioterrorism risk is the historical record of experimentation with specific pathogens, informed by 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.[2,7,8] Information from these sources, combined with the burgeoning fields of molecular biology and genomics, demonstrates that future risk scenarios will likely have to contend with genetically altered and "designer" pathogens intended to bypass current known medical countermeasures or defenses. To this end, a miscellaneous grouping of potential threat agents is added to the extant CDC categories in Table 79-2. The most cautious approach to assessing risk requires public health officials to remain open to additional and novel possibilities in the setting of a suspected bioterrorism event.

BIOTERRORISM RECOGNITION

Bioterrorist attacks are often insidious. Absent of advance warning or specific intelligence information, clinical illness will likely manifest before the circumstances of a release event are known. For this reason, health care providers are likely to be the first responders and reporting agents of 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 health care 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. Early recognition and rapid deployment of specific therapy remains the most effective way to minimize the deleterious effects of bioterrorism on both exposed individuals and public health.

Unfortunately, early recognition is hampered for multiple reasons. As previously discussed, it is likely that the circumstances of any event will only be known in retrospect. Therefore responders may be unable to discern the extent of exposure immediately. Also, terrorists have a nearly unlimited number of targets in most open democratic societies, and it is unrealistic to expect any governing body without detailed intelligence of an impending attack to secure an entire population at all times. Certain sites, such as government institutions, historic landmarks, or large public gatherings, may be predictable targets; however, other facilities may fall victim to bioterrorism. In fact, government data support that businesses and other economic concerns were the main targets of global terrorism during the period from 1996 to 2002.[9] Metropolitan areas are traditionally considered especially vulnerable given the dense populations and already existing public gathering areas such as subways and office buildings. Because of the expansion of suburbs and the commuter lifestyle, as well as the clinical latency period between exposure and symptoms, 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. Finally, current modes of transportation ensure that there will be affected persons thousands of miles away, at both national and international locations, related to a single common exposure. This adds layers of complexity to an already complicated management strategy and illustrates the critical importance of surveillance and real-time communication in the response to suspected bioterrorism.

Further hindering the early recognition of bioterrorism is that initial symptoms of a biological weapon may be nonspecific and 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 viral or flu-like illness. If allowed to progress beyond the early stages, many of these illnesses deteriorate quite rapidly, and treatment may be significantly more difficult. Most of the diseases caused by agents of bioterrorism are rarely, if ever, seen in modern first-world clinical practice. Physicians are likely to be inexperienced with their clinical presentation and be less aware of alarming symptomatic constellations. 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 signs and symptoms—especially if regionally unusual or otherwise characteristic of bioterrorism agents—is suggestive of an intentional exposure 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. 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 rapid activation of public health, emergency management, and law enforcement infrastructures.

THREAT AGENTS

This section provides a broad overview of the biological 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] These agents can possess rapid person-to-person transmission or the potential for rapid dissemination if weaponized, with high-mortality potential, small infective doses, and significant environmental stability.[12,13] Data concerning clinical incubation periods, transmission characteristics, and infection-control procedures for agents of bioterrorism are provided in Table 79-3. Syndromic differential diagnoses for select clinical presentations are detailed in Table 79-4.

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 124. 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] The cutaneous form of anthrax is the most common presentation; gastrointestinal and inhalational forms are exceedingly rare in naturally acquired disease. An additional form, injectional anthrax, represents a potentially lethal, deep soft-tissue infection that has been well described in injection heroin users in several western European countries.[14a] 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 because of importation restrictions. The last-known fatal case of naturally occurring inhalational anthrax in the United States occurred in 1976, when an individual was exposed to imported wool from Pakistan.[15] Case reports of naturally occurring anthrax do occur within the United States, although they are rare.[16] It has been previously hypothesized that large-scale bioterrorism with anthrax would involve aerosolized endospores with resultant inhalational disease, but the 2001 attacks in the United States illustrate the difficulties in predicting modes and outcomes in bioterrorism. These attacks were on a relatively small scale, and nearly 40% of the confirmed cases were of the cutaneous variety.[17] The serious morbidity and mortality of anthrax is instead related to inhalational disease, as was the case in the Sverdlovsk outbreak in 1979. As a result, planning for larger-scale events with aerosolized agent is warranted given the high-mortality cost of an exposure to this more weaponized form of anthrax.

The clinical presentations and differential diagnoses of cutaneous and inhalational anthrax are described in Table 79-4. The skin lesion

TABLE 79-3 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 h	No	Standard
Primary pneumonic	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

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*Based on limited data from human outbreaks; experimental animal data support clinical latency periods of up to 100 days.

TABLE 79-4 Presentations and Differential Diagnoses of Bioterrorism Agents

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

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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 is 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.[18] Cutaneous anthrax is associated with systemic disease, and it carries an associated mortality in up to 20% of untreated cases, although with appropriate antimicrobial therapy mortality is less than 1%.[14]

Once the inhaled endospores reach the terminal alveoli of the lungs—generally requiring particle sizes of 1 to 5 μm—they are phagocytosed by macrophages and transported to regional lymph nodes. Here the endospores germinate into vegetative bacteria and subsequently disseminate hematogenously.[13] Spores may remain latent for extended periods in the host, up to 100 days in experimental animal exposures.[15] This translates to prolonged clinical incubation periods after respiratory exposure to endospores. Cases of inhalational anthrax occurred up to 43 days after exposure in the Sverdlovsk accident, although the average incubation period is thought to be 2 to 10 days, perhaps influenced by exposure dose.[13,15]

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, data that are more detailed are available from the recent U.S. experience. There were 11 confirmed persons with inhalational anthrax, 5 (45%) of whom died. This contrasts with a case-fatality rate of greater than 85% reported from Sverdlovsk with an estimated 100 deaths. The reliability of reported data from this outbreak is questionable, given Soviet documentation, but a majority of victims were located downwind of the ill-fated weapons plant.[15,18] Patients almost on average present 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.[11,19,20] Many of these findings are nondiagnostic, and they overlap considerably with those of influenza and other common viral respiratory tract infections. Recently compiled data suggest 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, an important clinical distinction.[21] 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, although radiographs may demonstrate patchy infiltrates, consolidation, and/or mediastinal adenopathy. The latter is thought to be an early indicator of disease, but computed tomography appears to provide greater sensitivity compared with chest radiographs for this finding.

The clinical manifestations of inhalational anthrax generally evolve to a fulminant presentation with progressive respiratory failure and shock. *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.[11] 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.[22]

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 clinical illness consistent with anthrax exposure in the absence of another etiology. The early recognition and prompt treatment of inhalational anthrax is likely associated with a survival advantage.[11] Therefore the emergency physician should promptly initiate empiric antimicrobial therapy 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.[11] Drainage of pleural effusions is indicated to reduce toxin burden. Detailed therapeutic and post-exposure prophylaxis recommendations have been recently reviewed elsewhere.[22a] A monoclonal antibody targeted at the protective antigen component of anthrax toxin, raxibacumab, is available for the adjunctive treatment of systemic anthrax.[14a] In the future, it is likely that novel therapies such as toxin inhibitors or cell-specific receptor antagonists will be available to treat anthrax post exposure.[23] Detailed therapeutic and postexposure prophylaxis recommendations for adults, children, and special groups have been recently reviewed elsewhere.[15] With regard to postexposure prophylaxis, the Anthrax Vaccine Adsorbed is effective for prevention of cutaneous anthrax in human clinical trials, as well as preventing inhalational disease after aerosol challenge in nonhuman primates.[21] Current studies are investigating the efficacy of this vaccine when paired with antibiotics in the postexposure period. For preexposure prophylaxis, the vaccine is generally very safe, but it requires five doses over 18 months, with the need for annual boosting for ongoing preventative immunity.[24] Preexposure use of the vaccine is currently limited to individuals at high risk for anthrax exposure, such as military personnel and specific laboratory workers. Although not currently available, additional research into second-generation anthrax vaccines is aimed to generate a more easily distributed means of mass prophylaxis following an anthrax exposure.[25]

Smallpox

The last-known naturally acquired case of smallpox occurred in Somalia in 1977. In one of the greatest triumphs of modern medicine, smallpox was officially certified as having been eradicated in 1980, the culmination of a 12-year intensive campaign undertaken by the WHO.[26] 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 a potential and certainly dangerous agent of bioterrorism. Multiple features make smallpox an attractive biological weapon and ensure that any reintroduction into human populations would be a global public health catastrophe: it is stable in aerosol form, has a low infective dose, is associated with up to a 30% case-fatality rate, and has a large vulnerable target population because civilian vaccination was terminated in 1972. Smallpox is also especially dangerous because secondary attack rates among unvaccinated close contacts are estimated at 37% to 88% and are only further amplified by the lack of vaccine-induced immunity and a lack of naturally circulating virus to induce low-level booster exposures.[27] Because of the successful eradication, preexposure vaccination is currently limited to specific military and laboratory professionals. 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), patients will develop a 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. Enanthem in the oropharynx typically precedes the exanthem by 24 to 48 hours. 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 79-4. Historically, varicella and drug reactions have posed the greatest diagnostic dilemmas; this would likely be further complicated by the absence of this clinical disease and therefore experience in its diagnosis for the past 40 years.[21]

Smallpox is transmitted person to person by respiratory droplet nuclei and (although less commonly) by contact with lesions or contaminated fomites. Airborne transmission by fine-particle aerosols has also been documented under certain conditions.[21] The virus is communicable from the onset of the enanthem until all of the scabs have separated, although patients are thought to be most contagious during the first week of the rash because of high titers of replicating virus in the oropharynx. Household members, other face-to-face contacts, and health care workers have traditionally been at highest risk for secondary transmission, given their proximity to infected individuals during the highly infectious period. As a result, patients with signs and symptoms concerning for smallpox should be placed in negative-pressure rooms with contact and airborne precautions to minimize this risk. Those not requiring hospital-level care should remain isolated at home to avoid infecting others in public places.

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. This strategy mandates the identification and immunization of all directly exposed persons, including close contacts, health care 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.[21] Because the occurrence of even a single case of smallpox would be tantamount to bioterrorism, an immediate epidemiologic investigation is necessary to establish a biological perimeter and trace initially exposed individuals for ring vaccination purposes.

Botulism

Botulism is an acute neurologic disease caused by *Clostridium botulinum*, which occurs both sporadically and in focal outbreaks throughout the world related to wound contamination by the bacterium or the ingestion of the foodborne toxin. A detailed discussion of botulism is found in Chapter 154. Aerosolized forms of the toxin are fortunately a rare mode of acquisition in nature, but they have been weaponized for use in bioterrorism.[5] Botulinum toxin is considered the most toxic molecule known; it is lethal to humans in very minute quantities. It is estimated that a single gram of concentrated *Clostridium botulinum* neurotoxin could kill up to 1 million otherwise healthy individuals.[29] The toxin functions by blocking the release of the neurotransmitter acetylcholine from presynaptic vesicles, thereby inhibiting muscle contraction.[30]

Botulism presents as an acute, afebrile, symmetric, descending, and 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, ophthalmoplegia, 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.[24] Fortunately, outside of the toxin itself being utilized for bioterrorism, botulism is not spread directly from person to person. Typically, these patients will recover with supportive care in weeks to months.

The diagnosis of botulism is largely based on epidemiologic and clinical features and the exclusion of other possibilities (Table 79-4). 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 sources, water supplies, or as an aerosol.

The mortality from foodborne botulism has declined from 60% to 6% over the last four decades, likely because 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. There is no currently available vaccine.

Plague

Plague, a disease responsible for multiple epidemics throughout human history, is caused by the gram-negative pathogen *Yersinia pestis*. This pathogen is found in a variety of forms in the natural world. It is extensively covered in Chapter 125. 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. Additional forms of the disease, such as bubonic and septicemic plague, are also concerning from a bioterrorism perspective.

Primary pneumonic plague classically presents as an acute, febrile, pneumonic illness with prominent respiratory and systemic symptoms. Patients will often endorse gastrointestinal symptoms and purulent sputum production, with variable levels of reported hemoptysis.[31] Chest x-rays will typically show patchy, bilateral, multilobar infiltrates or consolidations. Unlike other forms of community-acquired pneumonia, 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 for these symptoms including rapidly progressive pneumonia is very broad as noted in Table 79-4. Plague is suggested by the characteristic small gram-negative coccobacillary forms found in stained sputum specimens with the bipolar uptake ("safety pin") of Giemsa or Wright stain.[32] Culture confirmation is necessary to establish the diagnosis; the microbiology laboratory should be notified in advance if plague is suspected because special techniques and precautions must be employed. Of note, initial Gram staining of samples can often be negative despite positive culture in *Y. pestis* detection. Serologic testing is also possible if the aforementioned studies are persistently negative.

Treatment recommendations for plague have been reviewed elsewhere.[26] Pneumonic plague can be transmitted from person to person by respiratory droplet nuclei, thus placing close contacts, other patients, and health care workers at risk for secondary infection. Prompt recognition and treatment of this disease, appropriate deployment of postexposure prophylaxis, and early institution of droplet precautions

will help to interrupt secondary transmission. Both live and attenuated plague vaccines exist; however, these are not currently approved for commercial use in the United States. High-risk populations, including laboratory and military personnel, may receive a formaldehyde-killed version of the vaccine as prophylaxis in certain situations.[13] Fortunately, new recombinant vaccines are currently in development, although some parts of the world continue to use live versions of the vaccine.[33]

Tularemia

Francisella tularensis, the causative agent of tularemia, is another small gram-negative coccobacillus with potential to cause a primary pneumonic presentation if delivered as an aerosol agent of bioterrorism. This bacterium is commonly found in smaller mammals, most classically hares and rabbits. Humans serve as an accidental host; typically, natural infections occur via insect bites, consuming infected animal products, or direct contact with infected domesticated animals.[34] The causative bacteria can be transmitted between humans by close contact via mucous membrane contact, cutaneous inoculation, and inhalation if patients are exposed to aerosolized forms of the bacteria.[14]

Pulmonary tularemia presents with the abrupt onset of a febrile, systemic illness with prominent upper-respiratory symptoms of a highly variable nature. Patients may exhibit inconsistent development of pneumonia, hilar adenopathy, hemoptysis, pulse-temperature dissociation, malaise, and progression toward respiratory failure and death in excess of 30% of those who do not receive appropriate therapy.[35] The diagnosis is generally based on clinical features after other agents are ruled out, but again it requires a high level of clinical suspicion. Confirmatory serology using various immunologic assays is currently available.[13] 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 126. Moreover, treatment typically consists of antibiotic therapy with streptomycin or gentamicin, with an estimated overall mortality after treatment of only 1%.[13] A live attenuated vaccine against tularemia exists; however, it is not currently available for human use in the United States.[36] Tularemia remains a significant concern, given the lack of current vaccine, especially when coupled with the high infectivity and mortality of pulmonary tularemia.

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 with circulatory dysregulation. Unfortunately, they are all capable of leading to shock and multiorgan system failure in advanced cases.[37] Specific agents are also associated with specific target organ effects, although each has a propensity to damage vascular endothelium. These pathogens, discussed in detail in Chapters 142 to 145, include Ebola, Marburg, Lassa fever, Rift Valley fever, and Congo-Crimean hemorrhagic fever.

Hemorrhagic fever viruses have been viewed as being emerging infections because of their sporadic occurrence in focal outbreaks throughout the world; the ongoing epidemic of Ebola hemorrhagic fever in West Africa has resulted in more than 25,000 cases and 10,000 deaths since 2014.[36a] Often in novel outbreak situations, these severe effects of these viruses on humankind are thought to be the results of human intrusion into a viral ecologic niche. They are concerning potential weapons of bioterrorism because they are highly infectious in aerosol form, are transmissible in health care settings, cause high morbidity and mortality, and are purported to have been successfully weaponized.[9] Blood and other bodily fluids from infected patients are extremely infectious, and person-to-person airborne transmission may occur, as well. As a result, strict contact and airborne precautions should be instituted if viral hemorrhagic fevers are implicated in a terrorism event.[28]

The diagnosis of viral hemorrhagic fevers is complicated, especially in a potential bioterrorist attack, which would lack a known exposure, or following recent travel to Africa. Microbiology studies and immunological testing are difficult to perform routinely, and often require evaluation by CDC laboratories.[38] Treatment is largely supportive, and it 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. For a majority of these diseases, the treatment is largely supportive therapy. Nonetheless, ribavirin should be initiated empirically in patients presenting with a syndrome consistent with viral hemorrhagic fever until the exact etiology is confirmed. Even though there are vaccines available for similar diseases, such as yellow fever and Argentine hemorrhagic fever, there are no current options for preexposure vaccination for viral hemorrhagic fevers. This paired with the highly infectious nature and significant mortality rates make this category of viruses worrisome potential agents of bioterrorism.

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.[14,26,27] 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 immunization because certain vaccines, such as smallpox, pose higher risk to these special groups than to others. This will affect mass vaccination strategies and will likely warrant case-by-case decisions.

Of note, the prevalence of antivaccine sentiments has implications with regard to global biosecurity. A decline in herd immunity against a vaccine-preventable communicable disease could leave even a medically prepared society vulnerable to a terrorist-introduced agent previously well controlled with prophylactic vaccinations. This will be yet another special population to consider in the event of a mass casualty bioterrorist attack.

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.[39] 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.[40] In the early period after the 9/11 attacks in New York, PTSD and depression were nearly twice as prevalent as in historical control subjects.[41] 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. Among individuals

working on Capitol Hill following the 2001 anthrax scare, 27% were diagnosed with PTSD, with up to 55% diagnosed with any variety of psychiatric disorder. Moreover, a majority of these patients were not adherent with antibiotics prescribed, perhaps because of a newfound lack of trust in the health care system.[42] Although not always clinically apparent, the psychological effect of a bioterrorism event is certainly a significant and important consideration for ongoing public health management strategies following any biological threat or terrorist attack.

PITFALLS

The response to bioterrorism is unique among WMDs because it necessitates consequence management that is common to all disasters, as well as the application of basic infectious diseases principles. Disease surveillance, diagnosis, infection control, antimicrobial therapy, post-exposure prophylaxis, and mass preventative vaccinations are all important considerations when managing a bioterrorism event. For these reasons, physicians are likely first responders to bioterrorism and will be expected to be reliable sources of information for their patients, colleagues, and public health authorities.[43]

A remaining number of potential pitfalls regarding disasters involving a biological attack must be identified and managed to optimize the public health response. As alluded to above, the clinical latency period between exposure to an agent and the manifestation of signs and symptoms is approximately days to weeks with most of the CDC category A, B, or C agents. Thus, early diagnoses of the first cases are likely to prove problematic and require heightened clinical vigilance, a difficult task considering a majority of these agents are rarely observed in the developed world.[44] Even after initial victims have been diagnosed, communications among hospitals and other health care institutions on a local, regional, national, and international level will be essential to help define the epidemiology and identify possible exposure sources. Given the extent and ease of rapid individual movement within our globalized world, clinical presentations from a point-source biological attack could occur in widely disparate geographic locations. Additionally it is possible that a terrorist attack would be multifocal in any case, with components of WMDs paired with biological weapons for maximum effect. A fundamental and consistent 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 of unknown etiology.[45]

Other potential bioterrorism management pitfalls reside in the arena of diagnostic techniques, treatment, and prevention of disease related to biological agents. Although an active area of research, the development of field-ready and highly predictive rapid screening tests for many agents of bioterrorism has not yet progressed to the point at which such assays are approved by the U.S. Food and Drug Administration and available in a "point-of-care" format. Treatment and prevention issues such as the absence of effective therapies for many forms of viral hemorrhagic fevers, shortages in the availability of multivalent antitoxin for botulism, projected shortages in the availability of mechanical ventilators to manage a large-scale botulism attack, lack of human data regarding the use of antiviral agents in smallpox, and the unfavorable toxicity profiles of some currently available smallpox vaccines remain unresolved but active areas of research. Emerging molecular biology techniques capable of producing genetically altered pathogens with "designer" phenotypes including antimicrobial or vaccine resistance add additional layers of complexity to an already multifaceted problem. As was vividly illustrated in the 2003 severe acute respiratory syndrome epidemic and previously well recognized when smallpox occurred with regularity, transmission of infection of potential bioterrorism agents within hospitals is common and difficult to control.[46,21] Health care workers, our first line of defense against an attack using biological agents, remain at significant occupational risk.

Research in the field of bioterrorism recognition has demonstrated a perceived weakness among clinicians in recognition of category-A infectious agents.[47] As pathogens of bioterrorism are not frequently encountered in daily practice, they often fall low on the differential without clinician knowledge of an insidious local mass casualty event.[48] Clearly, awareness of a recent local event heightens clinical suspicion, but it is imperative for the front-line clinician to recognize, report, and initiate treatment of affected patients. This will only serve to facilitate the initial containment and facilitate rapid disaster-protocol activation. Early recognition and initiation of a prompt, unified response will remain the primary challenge for all health care providers in the current era of bioterrorism.

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