

Rostrum

Bioterrorism: Relevance to allergy and immunology in clinical practice

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It has become clear in recent months that the threat of bioterrorism is very real. All physicians need to be aware of the presenting signs and symptoms of the most likely agents. Allergists and immunologists care for a unique population of patients with several alterations of their immune system that might change the expected course of illnesses from biologic terror agents. In this review, we discuss specific bioterrorism agents, focusing on their presentation, pathogenesis, and immunology. In addition, we describe how these illnesses might differ in the population of patients followed by allergists and immunologists. (*J Allergy Clin Immunol* 2002;109:214-28.)

Key words: Bioterrorism, biowarfare, immunosuppressed, anthrax, smallpox, plague, tularemia, botulism, hemorrhagic fever viruses, immunodeficiency, atopic dermatitis

Given the recent outbreak of anthrax cases in the United States, all medical practitioners need to develop an awareness of the presentation and treatment of the most likely agents of bioterrorism. As allergists and clinical immunologists, we care for patients who frequently present with signs and symptoms that might be easily confused with the initial presentation of diseases caused by biowarfare. In addition, we frequently follow patients who have various immunodeficiency diseases or are on immunosuppressive therapies; such individuals might have atypical or fulminant disease if exposed to infectious agents.

Allergists and immunologists should be aware of the clinical presentation of individuals exposed to bioterrorist agents to identify and assist in management of these patients. In this regard, it is important to realize that information regarding bioterrorism comes from *in vitro*, animal, and poorly controlled human studies. Scientific experience with real-world bioterrorism, fortunately, is largely lacking, and scientific conclusions have thus far

Abbreviations used

AD:	Atopic dermatitis
CDC:	Centers for Disease Control
EF:	Edema factor
ET:	Edema toxin
HF:	Hemorrhagic fever
LF:	Lethal factor
LT:	Lethal toxin
LVS:	Live vaccine strain
PA:	Protective antigen
PMA:	Phorbol myristate acetate
VIG:	Vaccinia immune globulin

been drawn from small-scale experiences. It is therefore likely that real-world experiences with bioterrorism might be very different from our current expectations.

BIOTERROR AGENTS

There are certain characteristics necessary for an effective biological warfare agent. Such agents should be highly reliable in terms of their action, should be able to be targeted, and should be deliverable and easily producible at little expense in comparison with other weapons of mass destruction. Once prepared, the agents should have a long shelf life, have aerosol durability, and have a high degree of lethality.¹

Although there are many possible agents that might be used for bioterrorism (Table I), this article focuses on those most likely to be used: anthrax, small pox, plague, tularemia, hemorrhagic fever (HF) viruses, and botulism. These agents meet all or most of the aforementioned criteria and have been reported to be in various stages of global development for biological warfare purposes.¹

The release of a biologic agent would initially occur without warning and would probably present itself as a few isolated cases resulting in unexplained deaths. Patients might have been suspected of having common illnesses but would not have responded to therapy or would have had a course of illness more severe than expected. Other clues to an intentionally released pathogen include the occurrence of diseases in age groups different from those in which they are normally seen, unusual seasonal outbreaks, and vector-transmitted diseases in areas not endemic to the vectors.¹

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TABLE I. Australia Group List of biological agents

Viruses	
Chikungunya virus	<i>Rickettsiae</i>
Congo-Crimean hemorrhagic fever virus	<i>Coxiella burnetii</i>
Dengue fever virus	<i>Bartonella quintana</i>
Eastern equine encephalitis virus	<i>Rickettsia quintana</i>
Ebola virus	<i>Rickettsia prowasecki</i>
Hantaan virus	<i>Rickettsia rickettsii</i>
Junin virus	
Lassa fever virus	Bacteria
Lymphocytic choriomeningitis virus	<i>Bacillus anthracis</i>
Machupo virus	<i>Brucella abortus</i>
Marburg virus	<i>Brucella melitensis</i>
Monkey pox virus	<i>Brucella suds</i>
Rift Valley fever virus	<i>Chlamydia psittaci</i>
Tick-borne encephalitis virus (Russian Spring-Summer encephalitis virus)	<i>Clostridium botulinum</i>
Variola virus	<i>Francisella tularensis</i>
Venezuelan equine encephalitis virus	<i>Burkholderia mallei</i> (<i>Pseudomonas mallei</i>)
Western equine encephalitis virus	<i>Burkholderia pseudomallei</i> (<i>Pseudomonas pseudomallei</i>)
White pox	<i>Salmonella typhi</i>
Yellow fever virus	<i>Shigella dysenteriae</i>
Japanese encephalitis virus	<i>Vibrio cholerae</i>
	<i>Yersinia pestis</i>
Toxins	
Botulinum toxins	
<i>Clostridium perfringens</i> toxins	
Conotoxin	
Ricin	
Saxitoxin	
Shiga toxin	
<i>Staphylococcus aureus</i> toxins	
Tetradotoxin	
Verotoxin	
Microcystin (cyanoginosis)	
WARNING LIST	
Viruses	
Kyasanur Forest virus	Bacteria
Louping ill virus	<i>Clostridium perfringens</i>
Murray Valley encephalitis virus	<i>Clostridium tetani</i>
Omsk hemorrhagic fever virus	Enterohemorrhagic <i>Escherichia coli</i> , serotype 0157 and other verotoxin-producing serotypes
Oropouche virus	<i>Legionella pneumophila</i>
Powassan virus	<i>Yersinia pseudotuberculosis</i>
Rocio virus	
St Louis encephalitis virus	
Toxins	
Abrin	
Cholera toxin	
Tetanus toxin	
Trichothecene mycotoxins	

From the Australia Group List of Biological Agents for Export Control Group List 18 August 1998.

Once suspicious illnesses have been identified, local health authorities and the Centers for Disease Control (CDC) in Atlanta should be notified to coordinate isolation, treatment, and containment efforts. As has been seen in the recent anthrax outbreaks, recommendations and criteria for treatment evolve as more information is known.

Anthrax

We begin by addressing anthrax, an agent now in use by bioterrorists in the United States. In human beings, 3 types of anthrax infection occur: inhalational, cutaneous, and gastrointestinal.

The clinical presentation of **inhalational anthrax** is

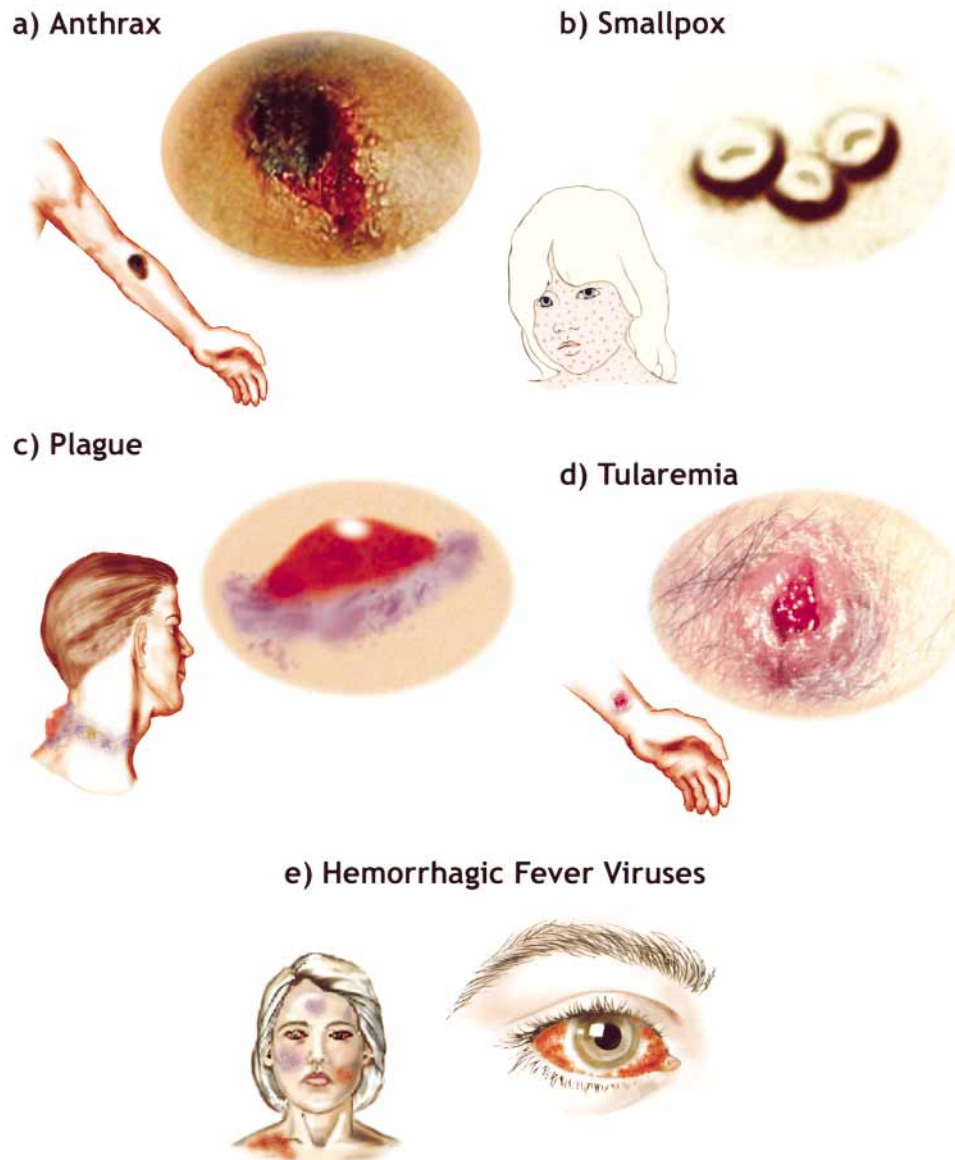


FIG 1. Most prominent cutaneous manifestations of 5 biological warfare agents. **A**, Anthrax. Note the ulcerated lesion with characteristic black-colored eschar and extensive local edema. **B**, Smallpox. Note the characteristic round, tense, and deeply embedded pustules. **C**, Plague. Note the cervical bubo caused by lymph node infection and the cervical purpura, which probably gave rise to the title line of the children's nursery rhyme "Ring around the rosie." **D**, Tularemia. Note the presence of a characteristic heaped-up ulcer of cutaneous tularemia. **E**, HF viruses. Note the characteristic petechiae and purpura. Each of these agents might exploit portals of entry caused by skin abrasions seen in patients with atopic dermatitis.

characterized as a 2-stage illness; however, the relevant data have been obtained in studies from other primates. Patients first develop a spectrum of nonspecific symptoms, including fever, dyspnea, cough, headache, vomiting, chills, weakness, abdominal pain, and chest pain, which last from hours to a few days.² In the second stage, patients develop sudden fever, dyspnea, diaphoresis, and shock. Up to 50% of patients develop hemorrhagic meningitis with meningismus, delirium, and obtundation.² In this second

stage of illness, cyanosis and hypotension progress rapidly and death can occur within hours. In fatal cases, the interval between onset of symptoms and death averages 3 days, and development of the disease can occur even after a latency period as long as 58 days.²

Cutaneous anthrax occurs after deposition of the organism into skin through an abrasion or laceration. There are no data to suggest a prolonged latency period in cutaneous anthrax, and it is suggested that it can be

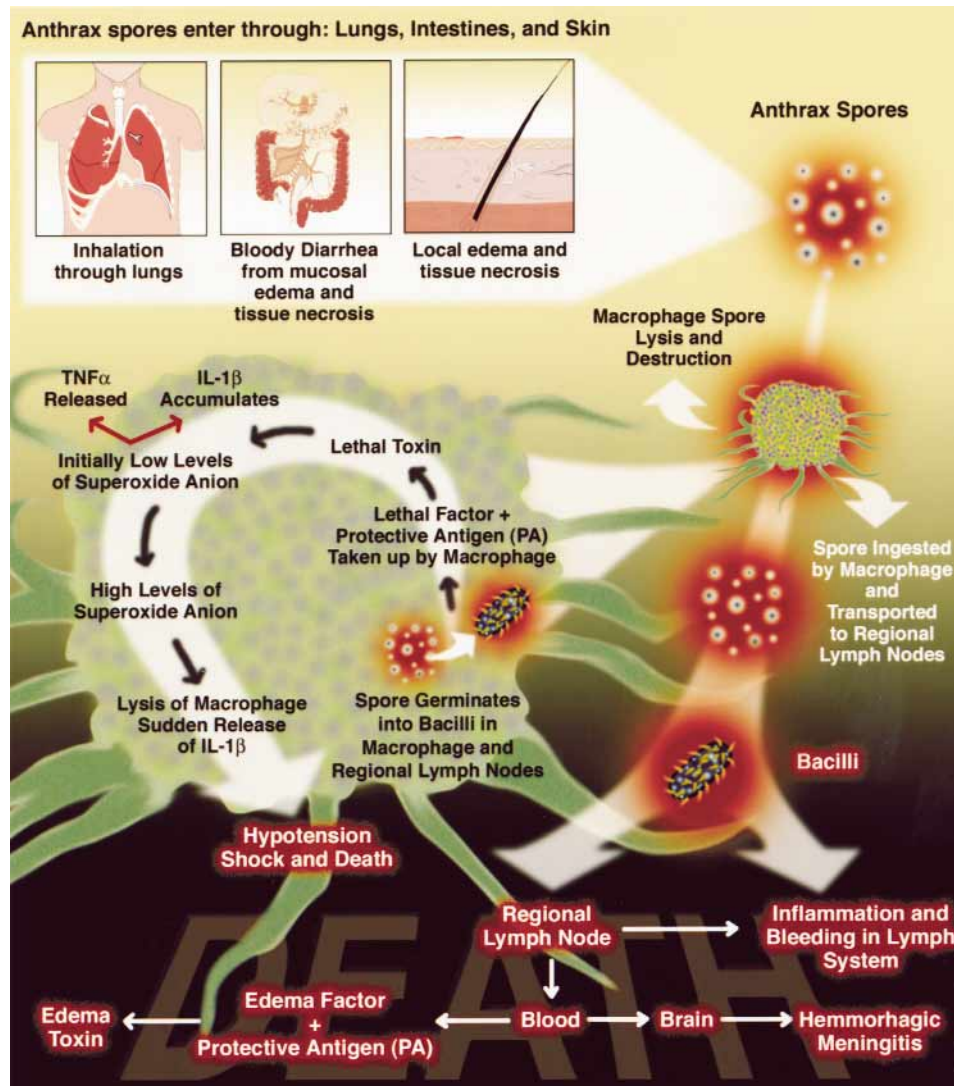


FIG 2. Anthrax pathogenesis. Anthrax spores enter through the lungs, intestines, and skin and are taken up by macrophages that facilitate transport to regional lymph nodes. There the spores germinate into bacilli that produce LT. LT acts exclusively in macrophages to increase superoxide anion production. Initially, the low levels of superoxide anion lead to TNF- α release and IL-1 β accumulation in macrophages. As the superoxide levels rise, there is sudden lysis of macrophages and release of IL-1 β , leading to shock and death. The bacilli also produce ET, causing tissue edema. ET also inhibits phagocytosis and oxidative burst and, through increased IL-6 production, downregulates the host immune response.⁴⁻⁷

induced by as few as 100 spores. In the 1979 accidental release of anthrax in Sverdlovsk, in what was formerly the Soviet Union, cutaneous cases occurred only as late as 12 days after the original aerosol release.³ A patient with cutaneous anthrax initially presents with a pruritic macule or papule that enlarges into a round ulcer by the second day.² Subsequently, 1- to 3-mm vesicles that discharge clear or serosanguineous fluid might appear. This is followed by the development of a painless, depressed, black-colored eschar with extensive local edema.² The eschar dries, loosens, and falls off in the next 1 to 2 weeks, most often leaving no permanent scar² (Fig 1). Lymphangitis

and painful lymphadenopathy can occur with associated systemic symptoms.² Without antibiotic therapy, the mortality rate has been reported to be as high as 20%; with antibiotics, death due to cutaneous anthrax is rare.³

Gastrointestinal anthrax occurs after deposition and germination of spores in the upper or lower gastrointestinal tract. Symptoms correlate with the location of anthrax lesions and might be associated with regional lymphadenopathy, edema, vomiting, bloody diarrhea, and sepsis.²

Toxins produced by anthrax bacilli are generally considered to be the most important factor contributing to dis-

ease symptoms (Fig 2). The 2 major toxins, edema toxin (ET) and lethal toxin (LT), have 2 subunits, the protective antigen (PA) molecule being common to both of them.

In ET, edema factor (EF) is an adenylate cyclase whose activity is dependent on the presence of the eukaryotic cytoplasmic cofactor calmodulin.⁴ EF therefore converts host ATP to cyclic adenosine monophosphate, which is believed to cause the edema associated with anthrax.⁴ ET is also believed to downregulate the body's cell-mediated response to infection. Treatment of neutrophils with ET inhibits both phagocytosis and the oxidative burst abilities of these cells.⁵ Cultured monocytes treated with ET display inhibited TNF- α expression in response to lipopolysaccharide.⁶

The other toxin, LT, causes hypotension, shock, and death in laboratory animals. This effect, which closely mimics the symptoms seen in the disseminated forms of anthrax infection, is felt to be mediated by IL-1 β (Fig 2).⁵ Unlike EF, lethal factor (LF) has been shown to be active only in macrophages, killing them in 1 to 2 hours.⁵ Cultured macrophages treated with lytic concentrations of LT were shown to release large amounts of superoxide anion beginning at approximately 1 hour, which correlated with the onset of macrophage cytolysis.⁷ The levels of superoxide anion were noted to be 2 to 3 times as high as those seen with macrophages stimulated with the oxidative burst stimulator phorbol myristate acetate (PMA).⁷ Because PMA alone did not induce cell death, it is possible that the greater reactive oxide intermediate burden imposed by LT overloads the macrophage's capacity to protect itself from its own dangerous metabolites. In addition, sublytic concentrations of LF induced macrophages to express IL-1 β by an amplification factor of nearly 1:100,000 per LF molecule.⁵ The presence of antioxidants significantly inhibits LT-induced TNF- α and IL-1 β expression in cultured monocytes.⁷ Cells treated with mouse anti-IL-1 β sera or an IL-1 β receptor antagonist are protected from LT challenge as well.⁵ Understanding the pathogenesis of LT suggests that patients with defects in superoxide production or taking drugs that inhibit superoxide anion might be relatively protected from LT effects. In fact, in vitro studies lend support to this possibility. A study using cultured blood monocyte-derived macrophages from a patient with autosomal recessive chronic granulomatous disease has shown these macrophages to be resistant to LT, in contrast to normal human monocyte controls.⁷

Anthrax infection can be suspected by its clinical syndrome, and the diagnosis can be confirmed by identification of large gram-positive bacilli on unspun blood smear or by blood culture with identification of *Bacillus* species. Anthrax can also be identified by ELISA or PCR testing at national reference laboratories.² A chest radiograph most often shows a widened mediastinum consistent with lymphadenopathy. Patients who have immunodeficiency disorders or are taking steroids might be more difficult to diagnose because of suppression of early symptoms or decreased lymphadenopathy. It is not known whether these individuals—or people with asth-

ma, for that matter—are more susceptible to the inhalation form of the disease.

Severe cases of anthrax might result in complications such as electrolyte disturbances, respiratory depression, shock, respiratory alkalosis, and terminal acidosis requiring intensive care therapy.² Most naturally occurring anthrax strains are sensitive to penicillin and doxycycline, which are approved by the US Food and Drug Administration for this indication. Other antibiotics effective against *Bacillus anthracis* in vitro include chloramphenicol, erythromycin, clindamycin, extended-spectrum penicillins, macrolides, aminoglycosides, vancomycin, cefazolin, and other first-generation cephalosporins.⁸ Animal models suggest that ciprofloxacin has excellent efficacy, protecting against inhalation anthrax if taken after exposure to aerosolized particles but before symptoms develop.⁸ It would be expected that other fluoroquinolones would also be effective. Antibiotic therapy must be tailored to known sensitivities of isolated organisms. Because early treatment with antibiotics might prevent an immune response to anthrax, it is recommended that antibiotic therapy be continued for 60 days to prevent latent spores from causing disease. For post-exposure prophylaxis, it is recommended that patients also complete a 60-day course of antibiotics, though the exact efficacy of this treatment in the absence of concomitant vaccine administration is unclear. For pediatric patients, ciprofloxacin is recommended initially because of concerns of anthrax caused by an engineered antibiotic-resistant strain.² However, once susceptibility is known, penicillin should be immediately substituted.² Pregnant women can receive fluoroquinolones in the usual adult dosages.² If susceptibility testing allows, intravenous penicillin in the usual adult dosages should be substituted for fluoroquinolones. As a third alternative, intravenous doxycycline can be used for therapy and post-exposure prophylaxis if antibiotic susceptibility testing, exhaustion of drug supplies, or allergic sensitivity precludes the use of penicillin and ciprofloxacin. The antibiotic treatment or post-exposure prophylaxis for anthrax among those who are immunosuppressed has not been studied in human or animal models. It is therefore recommended that such patients receive the same antibiotics that would be administered to immunocompetent patients as initial therapy.

Pre-exposure prophylaxis is available in the form of an anthrax vaccine, which is currently not available in the United States (Table II). The vaccine is based on a cell-free filtrate of a nonencapsulated, attenuated strain of *B anthracis* and does not contain whole or live bacteria. The vaccine is aluminum hydroxide-adsorbed and predominately targets the PA molecule⁹; it also contains 0.0025% benzethonium chloride (and 0.0037% formaldehyde for stabilization).⁹ Local reactions are most common, including tenderness, erythema, induration, and subcutaneous nodule formation. Systemic reactions (fever, chills, body aches, nausea) occur rarely (in less than 0.06% of those vaccinated).¹⁰ Although these reactions are brief, lasting from 1 to 3 days, from 1.9% to 7.9% of vaccine recipients have reported limitations in their work function after

TABLE II. Bioterrorist agent vaccines

Name	Vaccine type	Preservatives/ adjuvants	Side effects	Contraindications	Schedule	Availability
Anthrax	Cell-free filtrate of a nonencapsulated, attenuated strain of <i>B anthracis</i> contains PA, LF, and EF, adsorbed to aluminum hydroxide	Benzathonium chloride, formaldehyde	Local: tenderness, induration, erythema, subcutaneous nodule	Anaphylactic reaction to prior dose of vaccine	0, 2, 4 wk with booster doses at 6, 12, 18 mo and then yearly	USAMRID Special Immunization Program, Fort Detrick, Md
Smallpox	Live vaccinia virus obtained from NYCBOH strain raised from calf lymph	Polymyxin B sulfate, streptomycin sulfate, chlortetracycline, neomycin	Scar formation at inoculation site, fever, secondary spread of rash	Anaphylaxis to vaccine components, eczema, immunodeficiency Relative contraindications: pregnancy	Once by scarification with boosters every 10 y	15 million doses stored at National Pharmaceutical stockpile to be released in the event of an outbreak or attack
Tularemia	Live-attenuated vaccine derived from the avirulent LVS Biovac-Palaeartica type B	No preservatives	Scar formation at inoculation site, fever, secondary spread of rash	Anaphylaxis to prior dose of vaccine, immunodeficiency	Once by scarification	Investigational new drug available from US Army Regional Research & Material Command, Fort Detrick, Md
Botulism	Toxoid protective against serotypes A through E	Alum, thimerosal, formaldehyde	Local: tenderness, induration	Anaphylaxis to prior dose of vaccine, sensitivity to alum, formaldehyde, and thimerosal	0, 2, 12 wk with annual boosters	USAMRID Special Immunization Program, Fort Detrick, Md
Plague	Formalin-killed whole-cell	Phenol	Local: erythema, tenderness 11% Systemic: headache, malaise 4%. Rarely: sterile abscess, necrotic lesions, anaphylaxis	Anaphylaxis to prior dose of vaccine	1 mL at 0, 0.2 mL at 1-3 mo, 0.2 mL at 5-6 mo, 0.2 mL boosters every 6 mo $\times$ 3, then every 1-2 y	Not currently available in the United States
Yellow fever	Live attenuated 17D strain	Egg protein, gelatin	Fatal vaccine associated encephalitis in patients aged <4 mo	Immunodeficiency, egg allergy, gelatin allergy, age <4 mo Relative contraindications: pregnancy	Single dose, then booster at 10 y	Aventis-Pasteur, Swiftwater, Pa

References: 1, 9, 10, 12-14, 18, 22, 24, 26, and 28.

USAMRID, US Army Medical Research Institute of Infectious diseases; NYCBOH, New York City Board of Health.

receiving doses of the vaccine.⁹ Currently, the vaccine is given at 0, 2, and 4 weeks, with booster doses at 6, 12, 18 months and every 12 months thereafter. Data pertaining to the licensed vaccine show 83% seroconversion after 2 weeks and 91% seroconversion after the second dose. After completion of full vaccination, 95% of subjects show a 4-fold rise in anti-PA antibody titer.⁹ It is unknown, however, how well the anti-PA IgG titer predicts protection against disease.¹¹ In vivo studies in macaque monkeys have shown the vaccine to be protective against inhalation anthrax when a limited number of spores are used; this protection lasts as long as 2 years after vaccination.² A study in human beings showed

92.5% efficacy after an outbreak of inhalation anthrax.¹² Studies have not investigated the efficacy of the vaccine in children or in those older than 65 years.

Concerns about chronic or systemic illness related to vaccine administration have not been validated by long-term (25-year) follow-up studies.^{13,14} The vaccine is currently contraindicated in patients with allergies to components of the vaccine and in those who have experienced an anaphylactic reaction to a prior dose of vaccine. A history of anthrax illness is also a contraindication to vaccination, inasmuch as these patients might have a higher likelihood of having severe adverse events related to administration.² At this time, the anthrax vac-

Day 0	Virus contacts respiratory and/or oropharyngeal mucosa or broken skin—Migration to regional lymph nodes and multiplication
Day 4	Asymptomatic Viremia Multiplication in: Spleen, Lymph Nodes, Bone Marrow
Day 8	Secondary Viremia is characterized by fever and toxemia Death may be due to Toxemia and immune complexes Virus localizes to dermal blood vessels/oropharyngeal mucosal vessels with local spread
Days 12-14	Fever/Malaise/Headache/Backache Maculopapular rash on face/forearms
Days 13-16	Rash becomes widespread and Vesiculopustular
Days 21-25	Rash crusts over

FIG 3. Smallpox infection cycle.^{15,18}

cine is recommended only for those who work with anthrax cultures, those routinely exposed to imported animal products, and those in the military. Because anthrax has not been shown to be transmitted person to person, contacts of those infected do not require vaccination or treatment unless they have been directly exposed to the aerosolized anthrax.² In the light of recent events, the current vaccine policy might need to be reassessed to include people who work as emergency first-responders. Efforts to produce the vaccine in an acceptable manner for licensing in the United States must be redoubled.

Smallpox

Smallpox, caused by the variola virus, is another agent with biological warfare potential. Before the eradication of smallpox in the mid 1970s, smallpox vaccination was required in the United States. Since 1972, the vaccine has not been given routinely, leaving a large proportion of the population susceptible. Patients receiving only 1 dose of vaccine probably do not have immunity, and studies with natural disease suggest that immunity in those vaccinated more than once might not last longer than 30 years.¹⁵ A former deputy director of the Soviet Union's civilian bioweapons program reported that the Soviet Union had successfully produced large quantities of smallpox virus to be delivered by means of bombs as recently as the 1980s.¹⁶ There are increasing concerns that existing expertise and equipment might fall into non-Russian hands, now that financial support for laboratories in Russia has declined in recent years.

The orthopox virus family consists of viruses with a double-stranded DNA genome.¹⁷ After inoculation, the virus is taken up by pinocytosis; it then uncoats and starts to replicate in cytoplasmic inclusions. As infection progresses, the viral particles are manufactured and prepared for release. Unique to the orthopox virus is its second envelope. As the virus is released, the outer membrane is shed, exposing antigens not expressed in the intracellular form of the virus.¹⁸ As with other viral infections, cellular and humoral response is necessary for the host defense. Although not much is known about the immune response to smallpox, information has been obtained about its immunology from experience with the vaccinia virus. After vaccination, CD4⁺ cytotoxic T lymphocytes specific for the virus are identified.¹⁹ The antibody response has specificity for viral envelope proteins.¹⁹

Smallpox spreads from person to person primarily by respiratory droplets or by direct contact.¹⁵ Contaminated clothing or bed linens can also spread the variola virus. It is theorized that a smallpox attack might be most successful during winter and early spring, because the duration and survival of aerosolized small pox is inversely proportional to both temperature and humidity.²⁰

Infected individuals present after a 12- to 14-day incubation period with high fever, malaise, prostration, headache, and backache. Severe abdominal pain and delirium are sometimes present. A maculopapular rash then appears on the oropharyngeal mucosa, face, and forearms, with spread to the trunk and legs. Within 1 to 2 days, the rash becomes vesicular and then pustular. The

pustules are characteristically round, tense, and deeply embedded in the dermis; crusts begin to form on or about the eighth or ninth day of rash (Figs 1 and 3). Patients are most infectious from onset of rash through the first 7 to 10 days and until lesions have fully crusted over and separated.¹⁵ The smallpox rash is different from that of varicella; in smallpox, the rash appears in synchronous clusters, whereas varicella occurs in different stages of evolution at the same time. Death usually occurs during the second week of illness, most likely from the toxemia associated with circulating immune complexes and soluble variola antigens.¹⁵

Death rates from smallpox **variola major** infections in Asia resulted in case-fatality rates of 30% or higher among the unvaccinated.¹⁵ A less virulent form of the disease, **variola minor**, results in fatality rates of 1% or less.¹⁵ Although at least 90% of smallpox cases are variola major or variola minor, 2 other forms of smallpox exist that are difficult to recognize. **Hemorrhagic** cases of smallpox are uniformly fatal and have a shorter incubation period. The prodromal stage is similar but has rapid progression to dusky erythema, progressive petechiae, and hemorrhage into the skin and mucous membranes. Death usually occurs by the fifth or sixth day after onset of rash. In the frequently fatal **malignant** form of smallpox, the abrupt onset and prostrating constitutional symptoms are similar. The confluent lesions develop slowly but remain soft, flat, and velvety to the touch.¹⁵ Skin desquamation might follow. If the patient survives, the lesions gradually disappear without forming scabs.¹⁵

Diagnosis of smallpox is facilitated by collecting specimens from vesicular or pustular fluid, which often requires opening lesions with the blunt edge of a scalpel, and sending the specimens to a reference laboratory.¹⁵ Laboratories might use electron microscopic examination of specimens to identify smallpox, but definitive diagnosis is by culture of virus, PCR, and restriction fragment length polymorphism.¹⁵

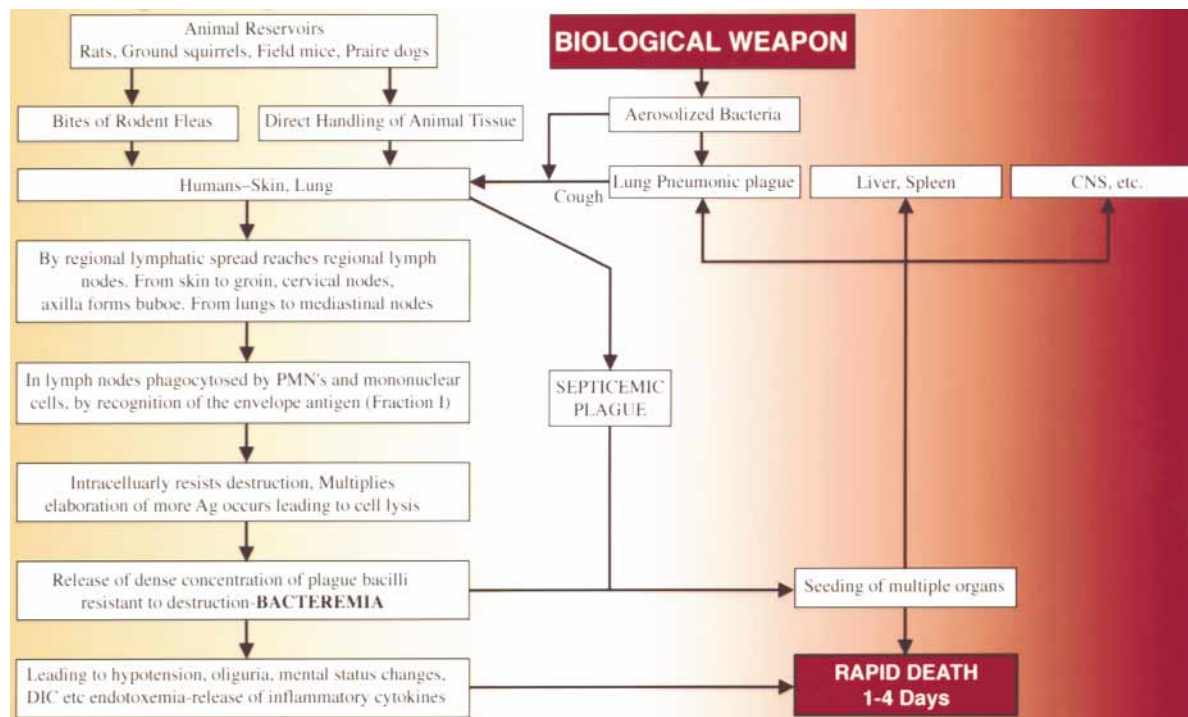
Treatment of smallpox is by vaccination. The smallpox vaccine is a less virulent strain of vaccinia virus obtained from the New York City Board of Health.²¹ Because vaccinia and variola are from the same viral family, there is cross-reactive immunity. This was initially discovered with Jenner's early observation that cowpox afforded immunity from smallpox.¹⁸ Vaccine-derived antibody is protective during the mucosal and viremic phase of the illness. Those who have been infected by smallpox and not protected by vaccine rely on cell-mediated immunity to contain the infection. The importance of cellular immunity in this illness was seen in patients vaccinated for smallpox. Patients with impaired cellular immunity from eczema might develop widespread lesions from the weaker vaccinia virus.¹⁸ A case report from 1987 described a military recruit with undiagnosed and subclinical HIV who developed widespread vaccinia after receiving multiple vaccines, including smallpox vaccine.²² Although not much is known about smallpox in immunocompromised populations, from vaccination experience it can be extrapolated that this

population would have widespread and rapidly progressive smallpox. In addition, vaccination would be relatively contraindicated in this population. If administered within 4 days of exposure, it has been shown to offer some protection against acquiring infection and significant protection against a fatal outcome.²³

For individuals who are immunocompromised or for whom vaccination is otherwise contraindicated, vaccinia immune globulin (VIG) should be provided. If VIG is not available, a judgment will have to be made regarding the relative risks of acquiring the disease in contrast with the risks associated with vaccination. Vaccination has been successfully and safely administered to persons of all ages, from birth onward.²⁴ However, there are certain groups for whom elective vaccination has not been recommended because of complications such as postvaccinal encephalitis, vaccinia gangrenosa, eczema vaccinatum, and generalized vaccinia.²⁴ Five groups of people are ordinarily considered at special risk of smallpox vaccine complications: (1) individuals with eczema or other significant exfoliative skin conditions; (2) patients undergoing chemotherapy or radiation therapy for malignancy; (3) patients with HIV infection; (4) individuals with hereditary immune deficiency disorders; and (5) pregnant women.²⁴ More than 95% of those vaccinated have protective antibody after a single dose. It is not known, however, how low the antibody level can be and still be protective.²¹ The most common minor side effect with vaccination is fever; 70% of those who receive the vaccine have a temperature higher than 38.5°C at 4 to 14 days after vaccination (Table II).²¹ At the time of this writing, the United States has anywhere from 7 to 15 million doses of vaccine available.¹⁵

Other aspects of treatment are more limited than vaccination. Recent studies on tissue culture, mice, and a small number of monkeys have suggested the possibility that cidofovir, a nucleoside analog DNA polymerase inhibitor, might prove useful in preventing smallpox infection if administered within 1 or 2 days after exposure.¹⁵ There is no evidence that cidofovir is more effective than vaccination in this early period.¹⁵ Other than vaccination, cidofovir, supportive care, and antibiotics for occasional secondary bacterial infections, there is little that can be offered to patients with smallpox infection.¹⁵ As soon as the diagnosis of smallpox is made, any individual in whom smallpox is suspected should be isolated immediately and all contacts should be vaccinated. This includes all health care workers involved, as well as any face-to-face contacts. In the event of a limited outbreak with few cases, patients should be admitted to the hospital and confined to rooms that are under negative pressure and equipped with high-efficiency particulate air filtration.¹⁵ In larger outbreaks, home isolation and care should be the objectives for most patients.¹⁵ Patients who die of smallpox should be cremated whenever possible, and mortuary workers should be vaccinated.¹⁵

It is clear from recent events that the threat of bioterrorism is very real, and it is imperative to increase supplies of vaccine to protect a highly susceptible popula-

FIG 4. Plague pathogenesis.^{25,26}

tion. However, because of the complications with the vaccine, its use should be restricted and might be particularly a problem for several types of patients followed by allergists.

Plague

The third potential biological weapon to discuss is plague, caused by *Yersinia pestis*. After World War II, the biological weapons programs of the United States and the Soviet Union developed techniques to aerosolize plague directly.¹ A report published by Russian scientists cited quinolone-resistant *Y. pestis*.²⁵ There have also been assertions that Russian scientists have engineered multidrug-resistant strains of *Y. pestis*.²⁵ Intentional dissemination of plague would most probably occur via an aerosol of *Y. pestis*, a mechanism that has been shown to produce disease in nonhuman primates.²⁵

A primary pneumonic plague would occur 1 to 6 days after inhalation. Patients would present with fever, cough, and dyspnea, sometimes with the production of bloody, watery, or (less commonly) purulent sputum.²⁵ Prominent gastrointestinal symptoms, including nausea, vomiting, abdominal pain, and diarrhea, might be present (Fig 4). The time from respiratory exposure to death in human beings is reported to have been between 2 to 6 days in epidemics during the preantibiotic era.²⁵

In primates, as few as 1 to 10 *Y. pestis* organisms are sufficient to cause an infection by the oral, intravenous, and subcutaneous routes. For the respiratory route, 100 to

20,000 organisms are felt to be required.²⁶ When introduced into the mammalian host, plague is susceptible to phagocytosis and killing by neutrophils. Some bacteria grow and proliferate within macrophages by acquiring virulence factors that make them resistant to phagocytosis. Environmental signals in the human host, such as an elevated temperature in comparison with the ambient temperature, contact with eukaryotic cells, and low pH, are thought to induce the synthesis and activity of a multitude of virulence factors.²⁶ The virulence factors include antiphagocytic fraction 1 capsule, pH6 antigen, antiphagocytic *Yersinia* outer proteins (Yops) H and E, V antigen, Yop M, and plasminogen activator.²⁶ After acquiring these virulence factors, the bacteria are resistant to phagocytosis and will proliferate unimpeded extracellularly. Dissemination from the bubo is thought to be related to the action of plasminogen activator and Yop M.²⁶ The endotoxin of *Y. Pestis* contributes to the development of septic shock as well as to the resistance of the organism.²⁶ Coagulase activity of the plasminogen activator causes the acral cyanosis and necrosis.²⁶ Primary pneumonic plague is more rapidly fatal than secondary plague because the inhaled droplets already contain phagocytosis-resistant bacilli.

Plague should be suspected if several individuals present with severe pneumonia and sepsis. Chest radiographic findings are variable, but bilateral infiltrates or consolidations are common.²⁵ Laboratory studies might reveal leukocytosis, coagulation abnormalities, aminotransferase elevations, azotemia, and other evidence of

multiorgan failure. There are no widely available rapid diagnostic tests for plague. Enzyme immunoassay, immunostaining, and PCR are available only in some state health departments, at the CDC, and in military laboratories.²⁵ Gram staining of sputum or blood might reveal gram-negative bacilli or coccobacilli. A Wright, Giemsa, or Wayson stain will often show bipolar staining.²⁵ In the unlikely event that a cervical bubo is present in pneumonic plague, an aspirate can be cultured and similarly stained (Fig 1).²⁵ The bacteria can be cultured from affected sites and usually grow within 48 hours.²⁵

Antibiotics are the therapy for primary pulmonary plague. Early administration might reduce mortality to 5% to 15%.²⁵ On the basis of evidence from in vitro, animal, and uncontrolled human data, aminoglycosides are recommended as first-line parenteral antibiotic therapy. In a mass casualty setting, in which aminoglycosides administration might not be available, doxycycline is the second choice.²⁵ Infected patients also need supportive care for complications such as sepsis, acute respiratory distress, disseminated intravascular coagulation, shock, and multiorgan system failure. In a community experiencing a pneumonic plague epidemic, every individual developing a temperature of $\geq 38.5^{\circ}\text{C}$ or a new cough should empirically begin parenteral antibiotic treatment. Oral antibiotics can be used if parenteral antibiotics are unavailable. All asymptomatic individuals having close contact with someone with untreated pneumonic plague should receive post-exposure antibiotic prophylaxis for 7 days and close observation for symptoms.²⁵ In large pneumonic plague epidemics, transmission was prevented in close contacts by the wearing of masks.²⁵ Therefore people living or working in close contact with patients with confirmed pneumonic plague who have had less than 48 hours of antimicrobial treatment should follow respiratory droplet precautions. These forms of protection might not be adequate for asthmatic or immune-deficient individuals, and pneumonic plague could be life-threatening in these individuals even if they are appropriately treated.

A formalin-killed whole-cell plague vaccine is not currently available in the United States because of production problems (Table II).²⁶ In the past, it was indicated for military personnel working in plague-endemic areas, laboratory personnel working with *Y pestis*, and people residing in enzootic or epidemic plague areas. The vaccine is administered with 1 mL initially, 0.2 mL at 1 to 3 months, and 0.2 mL at 5 to 6 months; boosters of 0.2 mL are then performed at 6-month intervals for 1.5 years. If risk of exposure continues, boosters are to be given every 1 to 2 years. After 3 doses, 92% to 93% of those vaccinated will produce antibody titers.²⁶ The vaccine is protective mainly against bubonic plague and not against pneumonic plague. Local side effects of erythema, tenderness, and induration occur in 11% of those vaccinated; headache, malaise, and myalgias have occurred in 4%. Rarely, sterile abscess, necrotic lesions, and anaphylaxis are seen with vaccination.²⁶ A new recombinant vaccine is being studied that has been

shown to protect animals against inhalational challenge with plague bacilli.²⁶

There is no evidence to suggest that residual plague bacilli pose an environmental threat to the population after the dissolution of the primary aerosol.¹⁵ No spore is formed during the *Y pestis* life cycle, so the organism is very sensitive to the action of sunlight and heating and does not long survive outside the host.²⁵ In natural plague, the mammalian reservoir (rats that harbor fleas) die off first; people in close proximity to these animals then get the disease. Aerosolized plague bacilli is the most plausible method of bioterrorism. In such a scenario, rapid human-to-human spread with fulminant pneumonic disease is seen. If intentional release of plague-ridden fleas occurs, the troops or other exposed human beings get the disease first, and this is followed by death in the animal reservoirs.

Tularemia

Francisella tularensis, the causative agent of tularemia, is another potential biological weapon. The Soviet Union, as recently as the early 1990s, developed weapons-grade strains engineered to be resistant to antibiotics and vaccines.¹⁶ *F tularensis* can infect human beings through the skin, mucous membranes, gastrointestinal tract, and lungs.²⁷ The major target organs are the lymph nodes, lungs, spleen, liver, and kidney.²⁷ It is thought that aerosolized bacteria would be most likely in an attack. After inoculation, *F tularensis* is ingested by and multiplies within macrophages.

In response to infection with *F tularensis*, the host uses cell-mediated immunity as its major protective mechanism. Cell-mediated immunity is primarily accomplished by T cell-independent mechanisms, which appear less than 3 days after infection. Initially, macrophages that have ingested bacteria secrete TNF- α .²⁸ TNF- α stimulates natural killer cells to produce IFN- γ , which in turn feeds back on macrophages and stimulates the cells to kill intracellular bacteria through the production of nitric oxide.²⁸ T cell-dependent mechanisms occur more than 3 days after infection, also as part of cell-mediated immunity. In the T cell-dependent host response, macrophages present bacterial antigen in the context of the MHC II to CD4⁺ T lymphocytes.²⁹ These cells respond by proliferating and secreting TNF- α , IL-2, and IFN- γ , which stimulate the macrophages to kill intracellular bacteria.²⁹

The role of humoral immunity and neutrophils in the host defense against *F tularensis* is unclear. The specific immunoglobulins IgG, IgA, and IgM appear within 1 week of infection, and passive transfer of immune serum protects naive mice against challenge with attenuated vaccine strains.³⁰ This protection, however, is not evident when mice are challenged with virulent wild-type strains.²⁹ Although some of the antibodies produced are opsonic and facilitate phagocytosis by neutrophils, neutrophils are not efficient in killing ingested bacteria.²⁹ Studies using animals depleted of neutrophils suggest that neutrophils are important in resistance to infection with attenuated strains, but the relevance of these find-

ings to virulent wild-type tularemia is unknown.²⁸ In general, the data suggest that the humoral immune response plays a limited role in the host defense against naturally acquired infection.

Patients exposed to inhalational tularemia would present within 2 to 5 days with an abrupt fever (38 to 40°C), headache, rigors, myalgias, arthralgias, and sore throat.²⁷ A pulse-temperature dissociation has been noted in as many as 42% of patients.²⁷ Some patients develop a fulminant pneumonia, whereas others have a more indolent course. Early on, only 25% to 50% of patients have radiologic evidence of pneumonia.²⁷ Any form of tularemia can be complicated by hematogenous spread, resulting in secondary pleuropneumonia, sepsis, and (rarely) meningitis. Before the advent of antibiotics, the overall mortality was as high as 30% to 60%.²⁷ Oropharyngeal tularemia is acquired by drinking contaminated water, by ingesting contaminated food, and sometimes by inhaling contaminated droplets or aerosols.²⁷ Affected persons might develop stomatitis but more commonly develop exudative and possibly ulcerative pharyngotonsillitis.²⁷ Pronounced cervical or retropharyngeal lymphadenopathy can occur.

Diagnosis might be made by direct examination of secretions, exudates, or biopsy specimens through use of direct fluorescent antibody or immunohistochemical stains. Growth of *F tularensis* in culture is the definitive means of confirming the diagnosis of tularemia. Antigen detection assays, PCR, enzyme-linked immunoassays, immunoblotting, pulsed-field gel electrophoresis, and other specialized techniques might also be used to identify *F tularensis* and characterize strains.²⁷

In the United States, a live attenuated vaccine (derived from an avirulent strain) called *live vaccine strain* (LVS) has been used to protect laboratory workers from *F tularensis* (Table II). Extensive evaluations have demonstrated that the LVS vaccine protected human volunteers against an aerosol challenge with virulent *F tularensis*; however, the immunity was not complete.³¹ Evidence based on an analysis of laboratory-acquired infections indicates that immunization with the live attenuated LVS vaccine prevents the typhoidal form of tularemia and ameliorates the ulceroglandular form.²⁹ The LVS vaccine is currently available as an investigational new drug from the US Army Medical Research and Materiel Command at Fort Detrick in Frederick, Md.²⁹ Given the short incubation period of tularemia and the incomplete protection afforded by current vaccines, vaccination is not recommended for post-exposure prophylaxis. Treatment of adult, pediatric, and pregnant patients is by intravenous gentamycin.²⁷ Ciprofloxacin has also been shown to be effective.²⁷ Tetracyclines and chloramphenicol are also used, but relapses and primary treatment failures occur at a higher rate than with aminoglycosides. Because it is unknown whether drug-resistant organisms might be used in a bioterrorist event, antimicrobial susceptibility testing of isolates should be conducted quickly and treatments altered according to test results and clinical responses. There is scant experience with the treatment of tularemia in asthmatic or immunocompromised

patients, but they should be treated with the same medications as immunocompetent patients. Post-exposure prophylactic antibiotic treatment of close contacts of tularemia patients is not recommended, because human-to-human transmission of *F tularensis* is not known to occur. Standard universal precautions should be observed.¹ People with direct exposure to powder or liquid aerosols containing *F tularensis* should wash body surfaces and clothing with soap and water.¹

Hemorrhagic fever viruses

The next group of possible biologic warfare agents is discussed collectively. Viral HF is caused by several families of RNA viruses and leads to diseases such as yellow fever, Ebola, and hantavirus. The Japanese terrorist group Aum Shinrikyo, as early as 1992, was collecting Ebola virus in Zaire for weapons development.³² As a group, these viruses are highly contagious; transmission is by various means, including aerosol, contact with bodily fluids, and animal or insect vectors. In general, people with these illnesses present with fever, myalgias, and prostration. Initially, there might be mild hypotension, flushing, and petechiae (Fig 1). Disease progression leads to shock and generalized mucosal hemorrhage and can involve neurologic and cardiovascular compromise. The mortality rate is as high as 90% for Ebola virus.¹ Diagnosis is often suspected on the basis of the clinical presentation with support from laboratory studies. Often, there is thrombocytopenia, leukopenia, proteinuria and/or hematuria, jaundice, and hepatic enzyme elevation. A definitive diagnosis can be made by rapid enzyme immunoassays for Lassa fever, Rift Valley fever, Congo-Crimean fever, and yellow fever.¹ Lassa virus and hantavirus IgM might also be detectable.¹

Treatment primarily is supportive. Aggressive fluid resuscitation and vasopressor use should be tried with the recognition that these illnesses often produce profound capillary leak. Ribavirin started within 4 days of onset of fever might be helpful for Lassa, Rift Valley fever, and Congo-Crimean fever. Argentine HF can be treated with convalescent plasma during the first 8 days of illness. At present, only yellow fever has an approved vaccine.¹ There are investigational vaccines for Rift Valley fever and hantavirus.¹ The yellow fever vaccine, a live attenuated virus, is protective in 95% of recipients (Table II). It is generally accepted that a single dose might give lifelong protection.³³ A significant complication of the vaccine is fatal vaccine-associated encephalitis, which is most common in children under the age of 4 months. The vaccine is contraindicated in those less than 4 months old and should be given with caution in those aged 4 to 9 months.

Because HF viruses are more prevalent, they have been more widely studied and more is known about the immune response. Research had indicated that the host response to Ebola and yellow fever causes marked increases in IFN- γ , INF- α , IL-2, IL-10, and TNF- α .³³ Convalescent serum is not protective against Ebola infection, and Ebola virus appears to downregulate cellular response to interferons.³³ The hemorrhagic viruses cause

their pathologic effects by widespread immune response to the virus and virus particles, which causes a cellular response and apoptosis of affected cells. Prevention of transmission by isolation and prevention of contact with blood, secretions, and excretions is paramount to isolate disease outbreaks. Oral ribavirin might be considered for those at high risk of exposure.¹

Botulism

A final agent for consideration is botulism. The clinical syndrome is caused by 7 related botulinum neurotoxins produced by *Clostridium botulinum* and 2 other clostridia species. The spores of these bacilli are ubiquitous and produce the neurotoxins during anaerobic incubation. The botulinum toxins can be delivered by aerosol or used to contaminate food and water supplies.¹ The toxins have been weaponized by many countries, including Iraq, as well as by cults such as the Aum Shinrikyo group in Japan.³² Botulism toxin is considered one of the most toxic substances known, the LD-50 (lethal dose to kill 50% of exposed animals) being 0.001 µg per kg of body weight.¹ The toxins are proteins that can easily be denatured by sunlight, heat, and chlorine.¹ Seven toxins, designated A through G, have been described (A being the most potent); all work by presynaptic inhibition of release of acetylcholine, causing paralysis by blocking neuromuscular transmission.¹ Unlike other toxin threats, botulism is unique in that it produces the same disease after inhalation, oral ingestion, or injection.³⁴ Moreover, because of the rapidity of death and the small quantity of toxin protein required to kill, the botulinum toxin typically does not induce an immune response.³⁴

Symptoms of cranial nerve palsies and descending flaccid paralysis occur within 12 to 36 hours of exposure.¹ Death can occur by paralysis of respiratory muscles, and this could be a particular problem for asthmatic patients. Anticholinergic symptoms and signs, such as dry mouth, ileus, constipation, urinary retention, and dilated pupils, can be seen. Treatment with atropine might worsen symptoms. Diagnosis is primarily made on clinical grounds, but botulism must be differentiated from nerve agent poisoning. Laboratory testing is not critical to diagnosis; however, ELISA and PCR might be used to identify environmental sources. Treatment is by early antitoxin administration, especially when the symptoms are progressing, though this is more useful in those food-borne cases in which continued gastrointestinal absorption is possible.¹ Three different antitoxin preparations are available, a trivalent (type A, B, E) equine antitoxin, a monovalent type A antiserum, and a heptavalent equine antitoxin. There is a risk of anaphylaxis and serum sickness with the equine antitoxin, as with any other horse serum product.¹ Skin testing before use is recommended, and desensitization is an option for a skin test–positive patient who absolutely needs the antitoxin. Pre-exposure prophylaxis is possible through use of a pentavalent toxoid vaccine available as an Investigational New Drug^{1,34} (Table II). Vaccination includes a primary series at 0, 2, and 12 weeks; this is followed by

TABLE III. Corticosteroid-induced changes to the immune system

Lymphocytopenia
Increased PMNs in circulation
Decreased inflammatory response due to:
1. Inhibited macrophage interleukin production
2. Inhibited arachidonic acid metabolites
3. Decreased acute-phase reactants
4. Diminished endothelial cell adhesion molecule expression
5. Decreased TNF-α production

Reference 35.

annual boosters. Severe local and systemic reactions have been noted with the vaccine. Eighty percent of those vaccinated show protective antibody titers at 14 weeks after the primary series of vaccination.³⁴ After 1 year, the titers are almost absent and a booster dose is recommended.³⁴ Contraindications include sensitivity to alum, formaldehyde, thimerosal, or previous dose of vaccine. The vaccine is recommended only for selected individuals and groups judged at high risk for exposure to botulinum toxin aerosols.¹ All stocks of this vaccine are held by the US Army, and the license for the vaccine is held by the CDC.³⁴ The heptavalent antitoxin used as treatment is not recommended for postexposure prophylaxis, because it has been shown to be effective only in animals; data are unavailable in human beings.¹

GENERAL CONSIDERATIONS

Many of the patients followed by allergists are iatrogenically immune-suppressed by corticosteroids to control their inflammatory conditions. This class of medications has its effects through a glucocorticoid receptor that when bound by steroids is translocated to the nucleus of cells. After translocation, the receptor interacts with specific regulatory DNA sequences to induce gene transcription. Systemic administration of steroids causes several significant changes to the immune system; these might alter the presentation of illness caused by agents that could be used for bioterrorism³⁵ (Table III).

In general, there is limited experience with immunosuppressed patients and the expected bioterror agents. However, generalizations from other illnesses may be applied to the different classes of suspected bioterror agents. Inhalational anthrax, which relies on spore migration to the lymph nodes for further germination and toxin production, has a flulike prodrome. This is probably secondary to early activation of the immune system, when the lymph nodes are invaded by germinating spores. Patients on steroids might not experience the prodromal phase and could rapidly progress to and present during the toxic phase of the illness. Because steroids abrogate the cytokine-mediated response to bacterial products such as endotoxin, patients on these medications might have diminished cytokine-mediated systemic inflammatory responses.³⁶ Experiences with viral infec-

tions in patients on corticosteroids suggest that an illness such as smallpox would have a much accelerated course and more widespread skin lesions. There is also increased likelihood of the more severe forms of illness in this population. In addition, these patients would have difficulty tolerating the vaccine and would be expected to have more widespread lesions from vaccination; furthermore, they might not be fully protected by the vaccine. They should be vaccinated cautiously and with concurrent administration of VIG.

Allergists also frequently follow patients with atopic dermatitis (AD), a chronic inflammatory condition of the skin. Patients with this condition might be particularly at risk from bioterrorism because of both the nature of their illness and the nature of its treatment. Frequent scratching might lead to small skin abrasions and multiple portals of entry for cutaneously transmitted anthrax or smallpox. Part of the immune abnormalities inherent in AD is a decreased number and function of CD8⁺ suppressor/cytotoxic T cells. This impairment results in decreased ability to prevent or contain cutaneous viral infections, which are particularly relevant to smallpox. Treatments for AD, including topical steroids, might further impair the host response and leave patients vulnerable to infection through delayed wound healing.

A newer medication, topical tacrolimus, was not available when smallpox was endemic or widely vaccinated against. Tacrolimus exerts its anti-inflammatory effects through several mechanisms. It inhibits release of IL-2, IL-4, IL-5, and TNF- α by binding immunophyllins and interfering with calcineurin-mediated release of these cytokines. It has similar downregulatory effects mediated through steroid receptors as well. From clinical experience, it is expected that these patients might develop widespread herpes virus infections and would probably have similar difficulty if exposed to smallpox. Similarly, the downregulated cellular immunity would alter the response to cutaneous anthrax, leaving patients more susceptible to acquiring the illness, altering their response to the bacterium, and potentially causing more local damage from the toxin than would be seen in immunocompetent patients. Common to patients on topical anti-inflammatory (as well as systemic) medications would be an atypical appearance to any of the skin findings. With an impaired inflammatory response, there would probably be more tissue damage from local toxin effects of the illnesses.

Other inhalational illnesses, such as plague and tularemia, would be expected to have a more rapid progression with fewer prodromal symptoms in immunocompromised patients. Radiographic findings might be unreliable because of impaired localization of inflammatory cells to affected lung tissue. As in other patients taking systemic steroids, the typical host responses would be altered and illnesses more fulminant. This modification to illness presentation requires a high degree of suspicion on the part of the clinician to accomplish an accurate and timely diagnosis, and it is especially important when rapid disease identification and containment is of the essence.

OTHER CONSIDERATIONS

The immediate medical effects of a biologic or chemical attack often give way to psychologic stress at the individual and group levels. Those directly exposed or injured by the biologic agent have long-lasting psychologic effects. After the Japanese subway attack with nerve gas, 29% of the victims had difficulty sleeping and 16% reported signs of depression.³⁷ Other people who might not have been directly exposed to the toxin could suffer from somatic reactions related to the stress of the situation and triggered by innocuous stimuli, including odors.³⁷ Mass hysteria from even the threat of an attack, which is often a goal of terrorists, must be countered by timely information and public health measures. The actions of media outlets are particularly disconcerting in this regard because they tend to sensationalize events, which can be detrimental in preventing panic.

FUTURE RESEARCH

Research efforts aimed at combating future bioterrorist attacks will need to focus not simply on the bioterrorist agents themselves but also on improving medical care and public health in general. It is only through the development of such dual-use technologies that we can hope to provide effective and sustainable bioterrorism prevention and treatment. One area on which attention should be focused is the development of better surveillance systems for infections and communicable disease. Better ways of characterizing infectious outbreaks would be tremendously helpful for maintaining and improving public health as well as for detecting bioterrorism attacks. Such improvement might come from the enhancement of information systems coordinating the acquisition and analysis of epidemiologic reports from primary care physicians, schools, hospitals, clinical laboratories, veterinarians, and air quality monitoring stations.

Another focus of preventive research might be the development of new diagnostic techniques for rapid, accurate identification of specific infectious agents. By providing greater access to diagnostic modalities, we can increase the response time to treatment and containment of infections.

A third potential focus of future research might be the development of more efficient vaccines that could provide broad-spectrum immunity and full protection on the first inoculation (in contrast to the requirement of several immunizations over a period of months). In the absence of new vaccines, new, nonspecific immune stimulants that might protect against an infection with multiple organisms would be valuable. Such therapies could also stimulate immunity to prevent the development of cancer, further illustrating the dual-use approach for countermeasures.

In addition to efforts aimed at the prevention of bioterrorist attacks, new treatments must be optimized to improve the prospects of survival in the event of such attacks. New types of antibiotics and antiviral medica-

tions are particularly necessary, especially those with mechanisms or actions different from those of current drugs. Medical and veterinary practices that reduce the indiscriminate use of antibiotics must be implemented to prevent further development of resistance to antibiotics in the organisms that we encounter every day.

There must also be better management of human health risks from animals. Given that animals serve as potential reservoirs for bioterrorist agents or could themselves be the targets of attacks, antiviral or antibacterial therapies must be used cautiously in animals to prevent the development of resistance to these treatments. In addition, vaccines and genetic modification of crops and livestock should be more widely used to protect livestock and crops on a continual basis.

SUMMARY

Allergists and immunologists are in a unique position to participate in many aspects of the emerging bioterrorism threat. In their day-to-day care of patients, they can serve a surveillance function, watching for index cases. Often, the first cases of illness from a mass exposure to a biologic agent occur in those with compromised immune systems; the patients for whom we care range from those with congenital immune deficiency to those who are iatrogenically immunocompromised. Allergists also have the luxury of frequent interaction with their patients who are on immunotherapy, putting us in an important position to monitor patients for the secondary psychologic effects of terrorism. By virtue of our understanding of the immune system, we are able to work with our colleagues in other specialties in the management of patients directly affected by bioterrorism agents. We should be a resource of objective and up-to-date information regarding the risks, benefits, and side effects of vaccine administration. Finally, we as physicians can encourage our political leadership to focus more attention on primary prevention of bioterrorism. It is through our efforts at improving the public health infrastructure today that we will be better capable of responding to the threats of bioterrorism tomorrow.

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Sources of additional information

- CDC Web site: www.cdc.gov
- CDC telephone contact: 1-800-311-3435
- Training courses in bioterrorism recognition, preven-

tion, and treatment are offered through the following agencies:

1. United States Army Medical Research Institute of Infectious Diseases (USAMRIID). Telephone: 410-436-2230.
2. US Public Health Service Noble Training Center. Telephone: 256-820-9135.