

Combating high-priority biological agents: What to do with drug-allergic patients and those for whom vaccination is contraindicated?

Rebecca S. Gruchalla, MD, PhD,^a and James Jones, MD^b *Dallas, Tex, and Denver, Colo*

The threat of bioterrorism continues to be a very real one. Regularly, there are news stories on bioterrorism-related topics: What biologic weapons will our enemies likely use to attack the United States? How prepared is our country to successfully counter such attacks? Although these critical questions are being addressed by the leaders of our country, allergists-immunologists, too, will have to grapple with difficult questions during these uncertain and frightening times. We care for a special group of patients with various allergic and immunologic disorders. Some of our patients have immunodeficiency disorders that might preclude them from receiving life-saving vaccines. Our patients with drug allergies are fearful that should they become infected with a biologic agent, they will not be able to receive appropriate treatment. In this article we focus on the various vaccine-related and antibiotic-related adverse effects that the allergist-immunologist might see during treatment of infections caused by Category A agents. Where possible, potential management approaches are outlined. (*J Allergy Clin Immunol* 2003;112:675-82.)

Key words: Bioterrorism, Category A biologic agents, anthrax, smallpox, botulism, plague, vaccine-related adverse reactions, antibiotic allergy

In light of the current events in the world, physicians must be prepared to diagnose illnesses caused by biologic warfare agents and to treat patients with such illnesses. Although allergists-immunologists will not be the primary treating physicians in most of these cases, their services most certainly will be required. Some of the affected patients will have antibiotic allergies that will preclude them from receiving appropriate antibiotic therapy. Others will have underlying illnesses or conditions that will preclude them from receiving life-saving vaccines. For both of these groups of individuals, the allergist-immunologist will play a critical role in their medical management by providing recommendations and by guiding treatment.

Abbreviations used

AD: Atopic dermatitis
CDC: Centers for Disease Control and Prevention
EV: Eczema vaccinatum
GV: Generalized vaccinia
PV: Progressive vaccinia
VIG: Vaccinia immune globulin

OVERVIEW OF POTENTIAL BIOLOGIC TERRORISM AGENTS

In 1999, there was a congressional initiative to enhance the nation's capabilities to respond to acts of biologic terrorism, and the Centers for Disease Control and Prevention (CDC) was put in charge of this massive public health endeavor. The military and the Working Group on Civilian Biodefense, using an expert panel consensus-based approach, assessed various biologic agents for their effectiveness on the battlefield and as high-effect agents against civilian populations.¹⁻⁵ Subsequently, in June 1999, a CDC Strategic Planning Workgroup met to review and make recommendations regarding the threat potential of various biologic agents to civilian populations.⁶ Agents were placed into one of 3 priority categories for initial public health preparedness efforts: A, B, or C (Table I). Agents in Category A (1) can be easily disseminated or transmitted from person to person, (2) result in high mortality rates and have the potential for major public health effect, (3) might cause public panic and social disruption, and (4) require special action for public health preparedness. Although those in Category B also have some potential for widespread dissemination with resultant illness, they generally cause less morbidity and mortality and therefore would have lower medical and public health effects. Agents in Category C are not thought to present a high bioterrorism risk to public health at the current time.⁶

In the February 2002 issue of the *Journal of Allergy and Clinical Immunology*, Fritz et al⁷ discussed the clinical features associated with infection with the 5 Category A agents: *Variola major* (smallpox), *Bacillus anthracis* (anthrax), *Yersinia pestis* (plague), *Clostridium botulinum* (botulism), *Francisella tularensis* (tularemia), and filviruses and arenaviruses (viral hemorrhagic fevers). In this article we focus on potential adverse reactions that might occur both during antibiotic treatment and with vaccine administration.

From ^aUniversity of Texas Southwestern Medical Center and ^bNational Jewish Medical and Research Center, Denver.

Received for publication July 22, 2003; revised July 28, 2003; accepted for publication August 1, 2003.

Reprint requests: Rebecca S. Gruchalla, MD, PhD, 5323 Harry Hines Ste Q5 302, Dallas, TX 75390.

© 2003 American Academy of Allergy, Asthma and Immunology

0091-6749/2003 \$30.00 + 0

doi:10.1067/mai.2003.1777

TABLE I. Biologic diseases

Category A
Anthrax
Botulism
Plague
Smallpox
Tularemia
Viral hemorrhagic fevers
Category B
Brucellosis
Epsilon toxin of <i>Clostridium perfringens</i>
Food safety threats (eg, <i>Salmonella</i> species, <i>Escherichia coli</i> 0157:H7, <i>Shigella</i>)
Glanders
Melioidosis
Psittacosis
Q fever
Ricin toxin
Staphylococcal enterotoxin B
Typhus fever
Viral encephalitis
Water safety threats (eg, <i>Vibrio cholerae</i> , <i>Cryptosporidium parvum</i>)
Category C
Emerging infectious disease threats, such as Nipah virus and hantavirus

ANTHRAX

In September 2001, *B anthracis* spores were distributed to several places in the United States through the US Postal Service. Twenty-two cases, either confirmed or suspected, resulted, and almost half (5/11) of the individuals with inhalation anthrax died. As a result of these attacks, the 1999 consensus statement that outlined the medical and public health management efforts to be used in the event of an attack were updated.⁴ Currently, although there are no US Food and Drug Administration–approved strategies for treatment of anthrax, this updated document contains consensus recommendations regarding vaccine and antibiotic use in the face of an aerosolized *B anthracis* bioterrorism attack that are based on a very small series of cases in human subjects, limited studies in experimental animals, and the possibility of treating large numbers of casualties.⁶

Vaccination and vaccine-related adverse reactions

A licensed vaccine, Anthrax Vaccine Absorbed, has been available in the US since 1970.⁸ It consists of a sterile filtrate of a culture of an attenuated strain of *B anthracis*. The apparent dominant protein in this preparation is protective antigen, one of 3 components of the toxin. The other components are known as “lethal factor” and “edema factor.” All of the components are encoded by the plasmid pXO1. The original alum-precipitated preparation tested for the prevention of animal-transmit-

ted infection was shown to be effective in prevention of both the cutaneous and the inhaled forms of infection. The administration regimen is 0, 2, and 4 weeks and 5, 12, and 18 months, with yearly boosters. There are no efficacy data, however, for the current aluminum hydroxide–precipitated preparation.

Information regarding the safety of the vaccine was gathered from active monitoring of 16,000 doses in 7000 individuals. Mild local reactions (<3 cm) occurred in 3% to 20% of all doses, and moderate local reactions (>3–<12 cm) occurred in 1% to 3% of all doses.⁹ Severe local reactions (>12 cm) occurred in less than 1% of individuals. Systemic reactions consisting of fever, chills, nausea, and general body aches were reported in only 4 (0.06%) individuals.

Subsequent studies in various peacetime military¹⁰ and laboratory⁹ populations have generally confirmed this range of adverse effects. The more in-depth studies have shown that local reactions in general are more common in women and that there is a decrease in severity with repeated administration.¹¹ The vaccine, however, does not adversely affect pregnancy and birth outcomes.¹² Credible reports of severe reactions include anaphylaxis and large local reactions, including circumferential arm swelling. Reports to the Vaccine Adverse Events Reporting System of systemic reactions have been infrequent, either as a result of poor reporting or the existence of few reactions.¹⁰ Using the Vaccine Adverse Events Reporting System database, a separate study identified several types of joint complaints after immunization, with the greatest being arthralgias (130 per million vaccinations) and the least being joint disease (12 per million).¹³ Unusual systemic reactions, such as hypersensitivity pneumonitis, have also been reported with vaccine administration, but these have not been well substantiated.¹⁴

When individuals who had served during the first Gulf War were questioned several years later about reactions that occurred after immunization with the anthrax vaccine and other vaccines, 3.6% of the men and 10.6% of the women reported severe reactions, and 31.6% and 40.2%, respectively, described mild reactions to vaccines in general.¹⁵ Of all the individuals who received the anthrax vaccine, 46.4% recalled mild reactions, and 7.8% remembered severe reactions. The fact that higher rates were seen in these individuals compared with those that were obtained during active monitoring supports the need for both short-term and long-term follow-up studies in a variety of settings.

Antibiotic therapy

The course of symptomatic inhalation anthrax is rapid, and therefore it is critical that antibiotic therapy is initiated early for those with known disease and for those in high-risk groups who have fever or other evidence of systemic disease, even though a microbiologic diagnosis might not have yet been made. Unfortunately, there have been no controlled trials for the treatment of inhalational anthrax in human subjects nor have the antibiotic regi-

mens recommended for the empiric treatment of sepsis been studied for disease contracted through the inhaled route. Thus because of the limited clinical experience with this disease and the lack of controlled trials in human subjects, recommendations for therapy are based on studies in nonhuman primates, as well as additional animal and in vitro data.

After the 2001 anthrax attacks, the CDC¹⁶ provided guidelines suggesting the use of 2 or 3 antibiotics in combination on the basis of susceptibility testing with epidemic strains in individuals with inhalational anthrax. Even though there were little data, it was found that persons were more likely to survive if they were treated with 2 or more intravenous antibiotics with activity against *B anthracis*.¹⁷ Moreover, the use of more than one antibiotic would become critical if a resistant strain of *B anthracis* was developed for use in a future bioterrorist attack.

Currently, the treatment of inhalation anthrax is intravenous ciprofloxacin or doxycycline until microbial susceptibility results are known. In addition to one or the other of these 2 agents, therapy with 1 or 2 additional antimicrobial agents should be initiated as well. Recommended agents, each of which has demonstrated in vitro activity against *B anthracis*, include rifampin, vancomycin, penicillin, ampicillin, chloramphenicol, imipenem, clindamycin, and clarithromycin. Because in vitro activity against the organism has not been demonstrated with trimethoprim-sulfamethoxazole and numerous cephalosporins, neither sulfonamides nor cephalosporins should be used for treatment. Therapy should be continued for at least 60 days after exposure, with oral therapy replacing intravenous therapy if the patient is stable enough to take oral medications.

For children younger than 16 to 18 years of age, fluoroquinolones typically are contraindicated because of a link to the development of arthropathy. However, this risk must be weighed against the even greater risk that an anthrax outbreak might be caused by an engineered antibiotic-resistant strain. Because of the possibility of the latter, the Working Group on Civilian Biodefense recommends ciprofloxacin be used as one component of combination therapy for children with inhalational anthrax.⁴ Doxycycline, too, although contraindicated in children less than 9 years of age, should be used in children if antibiotic susceptibility testing, insufficient drug supplies, or adverse reactions preclude the use of ciprofloxacin.⁴

For cutaneous anthrax, penicillin has been the drug of choice. However, because *B anthracis* has an inducible β -lactamase, as well as a constitutive cephalosporinase, it is now recommended that oral ciprofloxacin or doxycycline be used as first-line therapy of cutaneous anthrax until antibiotic sensitivities are known. If there is a contraindication to fluoroquinolone or doxycycline use, such as pregnancy, lactation, or young age, amoxicillin is a suitable alternative.⁴ Even though a 7- to 10-day treatment course is sufficient to treat cutaneous disease, therapy should continue for 60 days after exposure in the setting of a bioterrorist attack because of the high probability of concomitant inhalation exposure.

Antibiotic-related adverse reactions

After the 2001 anthrax crisis, agencies of the US Public Health Service planned and implemented a rapid response to the crisis.¹⁸ As a part of this response, prophylactic antibiotics were distributed to individuals thought to be at risk for anthrax exposure. A clinic run by US Public Health Service personnel treated most of these people, and to assist them, an anthrax health and medication worksheet that included medication allergy information was developed. The drug allergy information was extremely useful to the dispensing pharmacist. If a positive response regarding drug allergies was indicated on the worksheet, the pharmacist obtained further, more detailed information about the previous drug reaction. If the reaction was to the drug of choice for anthrax treatment or to a related drug and it appeared to be a true allergic drug reaction, an alternative agent was prescribed. If, however, the reaction was due to drug intolerance and not an allergy, the pharmacist decided whether an alternative agent was required.

When evaluating drug-induced reactions, it is important to first determine the known common side effects of the particular agent. Oftentimes, side effects are tolerable and are not a contraindication to drug readministration. The most common side effects associated with quinolone therapy are nausea, vomiting, and diarrhea. Central nervous system effects, such as headache, dizziness, tiredness, or sleeplessness, might occur as well, but they are typically mild. More severe neurotoxic side effects, such as psychotic reactions, hallucinations, depression, and seizures, although reported, are very rare.¹⁹ In addition to the above effects, prescribing physicians must also be aware of the cardiotoxic, phototoxic, and chondrotoxic effects of these drugs, as well as their ability to induce tendinitis.¹⁹

Other quinolone-induced reactions have been reported as well. It is well known that quinolones can cause generalized pruritus and flushing.²⁰ Because some of these reactions have occurred after the first dose and because drug-specific IgE antibodies have not been identified, it is thought that they might be anaphylactoid in nature because of direct mast cell activation.²¹ Other reactions that have been described include hypersensitivity vasculitis, Schonlein-Henoch purpura, and serum sickness-like disease. Although an immune mechanism might underlie some or all of these reactions, they are so rare that little data exist regarding their immunopathology.

In the event of a bioterrorism attack with *B anthracis*, physicians are going to have to determine how to best treat infected and exposed individuals who have had previous quinolone-induced reactions. For those individuals who previously experienced mild side effects or mild drug eruptions not thought to be IgE mediated, drug readministration is not contraindicated. However, for those who had severe side effects or other severe drug-induced reactions, alternative agents should be selected. For those who previously experienced anaphylactoid reactions, a desensitization protocol might be attempted. Intravenous protocols have been described in case reports, and one of these is shown in Table II.²²

TABLE II. Desensitization protocol for ciprofloxacin

Ciprofloxacin concentration (mg/mL)	Volume given (mL)	Absolute amount (mg)	Cumulative total dose (mg)
0.1	0.1	0.01	0.01
0.1	0.2	0.02	0.03
0.1	0.4	0.04	0.07
0.1	0.8	0.03	0.15
1	0.16	0.16	0.31
1	0.32	0.32	0.63
1	0.64	0.64	1.27
2	0.6	1.2	2.47
2	1.2	2.4	4.87
2	2.4	4.8	9.67
2	5	10	19.67
2	10	20	39.67
2	20	40	79.67
2	40	80	159.67
2	120	240	399.67

Drug volumes of less than 1 mL were mixed with normal saline solution to a final volume of 3 mL and then slowly infused. The other doses were administered over 10 minutes, except the last dose, which was administered with an infusion pump over 20 minutes. Used with permission from Gea-Banacloche J and Metcalfe D.²²

Common and dose-dependent side effects of doxycycline, the other first-line therapeutic agent for anthrax, include nausea, vomiting, epigastric burning, and vaginal candidiasis. Severe adverse drug reactions are uncommonly seen. Although another tetracycline, minocycline, has been reported to cause rare serious adverse reactions, including the hypersensitivity syndrome, serum sickness-like reactions, and drug-induced lupus, these reactions are even more rarely seen with doxycycline. A recent retrospective review of records from a Drug Safety Clinic, reports from the Adverse Drug Reaction Monitoring Division of the Health Protection Branch in Ottawa, Ontario, and the literature, found only a single reported case of hypersensitivity syndrome with doxycycline, 2 cases of serum sickness-like syndrome, and no reports of drug-induced lupus.²³ Erythema multiforme has been reported on 2 occasions^{24,25} and Stevens-Johnson syndrome once.²⁶ Urticarial reactions, although not described in the literature, were seen in some of the clinic patients evaluated by Shapiro et al²³ at the Drug Safety Clinic.

Patients who previously experienced serious doxycycline-induced reactions like those described above should avoid doxycycline, as well as all antibiotics in the tetracycline class. For those patients who previously experienced urticarial reactions, drug desensitization might be attempted. Currently, there are no reports in the literature describing drug desensitization to doxycycline. Despite this, a protocol on the basis of the one used for penicillin desensitization²⁷ might be attempted.²⁸ If the previous doxycycline reaction was not severe and it was not consistent with an IgE-mediated process, drug readministration can occur through a graded challenge.²⁸

SMALLPOX

Smallpox represents a very serious biologic threat because of its case fatality rate of 30% or greater among unvaccinated persons and because there is no specific therapy for this disease. Although smallpox has long been feared as the most devastating of all infectious diseases, its potential for devastation is greater now than ever before. Routine vaccination in the United States ceased in 1972, and because our population currently is so widely mobile, the spread of disease would be rapid and widespread if an outbreak were to occur now.²⁹

The only treatment for smallpox is pre-exposure preventative vaccination. Once infected, the only thing that can be offered is supportive therapy plus antibiotics for treatment of secondary bacterial infections. There are currently no antiviral agents that have been proved effective for the treatment of smallpox.

Vaccination and vaccine-related adverse reactions

The immunizing agent in the smallpox vaccine licensed in the United States is the Wyeth strain of vaccinia virus. It is an attenuated strain that historically originated as the New York City Board of Health strain and is administered by scarification of the skin.³⁰ This route allows generation of an effective immune response, and the development of a visible pustule and the subsequent healed scar allow identification of a take.

Adverse responses have been detailed by Fritz et al⁷ and Engler et al³¹ in these pages and, more recently, by Cono et al.³² Local reactions include contact hypersensitivity to covering bandages and bacterial infections. Non-specific skin reactions, those that do not contain virus, are usually mediated by the host's response to the vaccine and include varying types of erythematous eruptions and urticaria. More complex nonspecific reactions include erythema multiforme (Fig 1) and Stevens-Johnson syndrome.

Of particular importance to the allergist-immunologist are patients receiving immunosuppressive therapy or those with primary or secondary disease-associated altered immune responses. A primary illness of key importance is atopic dermatitis (AD). Patients with AD can have eczema vaccinatum (EV), a vaccinia infection that is usually acquired by inadvertent inoculation of the affected skin (Fig 2). Immunization of individuals with AD or acquisition of infection through contact with immunized persons or infected persons whose disease is quiescent might also lead to EV.³³ Before routine vaccination was halted in 1972, the fatality rate for this complication was less than 1% to 6%. This topic was reviewed in detail by Engler et al³¹ in September 2002.

Attempts to identify the underlying immune defects that predispose patients with AD to have EV have concentrated on altered innate and adaptive cell-mediated immune processes. Recently, both decreased levels and function of innate antimicrobial peptides in the skin have been shown to potentially affect illness in AD.³⁴



FIG 1. Vaccinia erythema multiforme in a patient who received the smallpox vaccine. Source: Vincent A. Fulginiti, MD. Copyright © Logical Images, Inc.

EV is differentiated from progressive vaccinia (PV), a condition that occurs in individuals with altered humoral and cellular immune responses. It is recognized as a non-healing primary vaccination site with painless progression of central necrosis. Because PV occurs in markedly immunodeficient individuals, it is often difficult to treat.

Generalized vaccinia (GV) is due to hematogenous spread of the virus with development of a maculopapular or vesicular skin eruption 6 to 9 days after vaccination. The course in immunocompetent individuals is usually self-limited. Interestingly, Lane et al,³⁵ in 1969, reported that of 143 patients with GV, 11 individuals had identifiable underlying diseases, of which 4 persons had allergies. The immune status of the other individuals with GV was not stated, but all persons recovered without major sequelae. Postvaccinial encephalitis is not virus specific and is similar to other postinfectious encephalides.

Although there remains no cure for vaccinia infections, specific antivaccinia therapy is recommended for EV and PV and in seriously ill patients with GV or those with a predisposing condition. It consists of vaccinia immune globulin (VIG), currently available as a 0.01% thiomersol-preserved preparation for intramuscular administration with an investigational new drug classification from the CDC or Department of Defense. Intravenous preparations are being developed.

Universally effective antiviral therapy was not available when smallpox and the associated vaccine-related adverse reactions were clinical problems. Since then, cidofovir, an analog of cytosine, has been shown to have *in vitro* and *in vivo* effectiveness against other orthopox viruses. It is available for treatment of smallpox with an investigational new drug classification provided by the CDC.

ADVERSE REACTIONS TO VIG

In general, reactions to VIG are like those to other immune globulin preparations.³² The probable mechanisms include specific antibody-mediated responses or nonspecific immune complex-triggered, complement-mediated reactions. Local reactions to intramuscular injections are pain, swelling, and tenderness lasting hours or a few days. Systemic reactions are due to activation of mediators of inflammation, and they might occur after either intravenous or intramuscular administration. Anaphylaxis (and its consequences) and the aseptic meningitis syndrome are the most serious reactions that have been seen. A less common but real problem is transmission of known or unknown infectious agents by the plasma-derived end product, although preparation processes usually inactivate viruses. Prevention of this problem is best controlled by rigorous scrutiny of plasma



FIG 2. EV in a patient with AD who received the smallpox vaccine: vaccinia generalized. Source: Henry Kempe, MD. Copyright © Logical Images, Inc.

donors. Contraindications to the use of VIG are a sensitivity to the preservatives in the vaccine, active vaccinia keratitis, or IgA deficiency in persons who have previously received blood products. There are no known adverse effects specific to VIG if used in pregnancy.

BOTULISM

Botulinum toxin, the most poisonous substance known, poses a great biologic threat because of its potency and lethality. In addition, it is easy to produce, transport, and misuse. The toxin's potency resides in its enzymatic ability to block acetylcholine release at the neuromuscular junction. A single gram, if evenly dispersed and inhaled, would kill more than 1 million people.³

Antitoxin therapy

The therapy for botulism consists of passive immunization with equine antitoxin and supportive care. Antitoxin therapy should be administered early because delayed administration will not reverse any existent paralysis.³⁶ Its administration should not be delayed for microbiologic testing. Currently, botulinum antitoxin is available from the CDC through state and local health departments. The licensed material contains neutralizing antibodies against the 3 most common toxin types (A, B, and E) that cause human botulism. The current recommended dose is a single 10-mL vial per patient diluted

1:10 in 0.9% saline and administered by means of slow infusion. A single vial provides between 5500 and 8500 IU of each type-specific antitoxin.³

Antitoxin-related adverse reactions

There is little published information about the safety of botulinum antitoxins. During the time period from 1967 to 1977, when the recommended dose was greater than that given today, approximately 9% of recipients of the antitoxin experienced urticaria, serum sickness reactions, or other hypersensitivity-like reactions, whereas 2% experienced anaphylaxis.³⁷ Typically, patients are skin tested before drug administration to determine the presence of equine-specific IgE antibodies. For those individuals who demonstrate positive wheal-and-flare skin test responses, desensitization might be attempted.³ Because there is no treatment for serum sickness reactions and because this reaction is more common in patients who receive more than 40 mL of antitoxin, it is recommended that the lowest effective treatment dose be administered.³⁷ Impurities in the commercial preparations might also lead to adverse reactions.

A potential problem with using botulinum toxins for treatment of neurologic diseases and hyperhidrosis and for cosmetic purposes is the development of antibodies to these preparations or their byproducts (eg, botulinum toxoid).³⁸ These previously existing antibodies could potentially interfere with antitoxin efficacy.

PLAGUE

Another critical biologic agent is *Y pestis*, the causative agent of plague. Because of its widespread availability around the world, its capacity to be mass produced and disseminated, and the high fatality rate associated with pneumonic plague, this organism is of great concern as a potential biologic weapon.² The proposed release by means of aerosolization would induce pneumonic plague, a form that is more rare than the bubonic form of the disease. Up to 1999, a formaldehyde-killed whole bacilli vaccine was available in the United States. This vaccine was not effective in the prevention of pneumonic plague, and because it is no longer available, antibiotic therapy is the only treatment option.

Antibiotic therapy and antibiotic-related adverse reactions

Data regarding antibiotic treatment of plague in human subjects is sparse. In light of limited data, the Working Group on Civilian Biodefense has proposed recommendations on the basis of the best available evidence. The preferred treatment of plague infection historically has been streptomycin. If administered early, mortality rates are greatly reduced. Currently, however, because streptomycin is infrequently used in the United States, there are only modest supplies of this drug. Gentamicin, although not US Food and Drug Administration-approved for the treatment of plague, has been used successfully,³⁹ and because of this, it can be used as a suitable alternative antibiotic.² Other antibiotics recommended for treatment include doxycycline, ciprofloxacin, and chloramphenicol.²

Reactions to doxycycline and ciprofloxacin have been previously discussed. The most severe adverse reactions to gentamicin are nephrotoxicity and ototoxicity, and the most severe adverse reaction to chloramphenicol is aplastic anemia.

Vaccines and vaccine-related adverse reactions

The discontinued US vaccine is a model of old-time "vaccinology." An organism was grown in culture and inactivated by adding formaldehyde to render the bacteria incapable of replicating. The concentration of bacteria was determined from murine studies, the desired concentration being the one that yielded a protective level against infection by means of injection. Other components of the vaccine included formalin, phenol as a preservative, and culture medium ingredients (beef heart extract, yeast extract, agar, and soy and casein peptides and peptones).⁴⁰

Vaccine-induced adverse reactions have been documented. Reisman⁴⁰ described urticaria in 22 persons in the armed forces out of an unknown number immunized at Ft Sam Houston, Texas, during the late 1960s over an 18-month period when smallpox vaccinations were routinely given, but outcome data were not collected. The study was based on the clinical experience of military allergists who had observed urticarial reactions after vaccinations that appeared to occur more frequently than the

10% rate expected at the time. Although no incidence was determined, only a small proportion of the reactions were consistent with an immediate hypersensitivity mechanism. The results of a more formal prospective study published in 1974 demonstrated that the type of vaccine, the dose, and the schedule affected reaction rates and severity.⁴¹ A companion article reiterated the need for human clinical trials in vaccine development.⁴²

The military vaccine used at the time of these studies was based on potential exposure of troops in southeast Asia and of laboratory workers in the United States. It was an apparent improvement, in terms of side effects, over other vaccines in use in that part of the world. Even though a killed whole-cell vaccine is still produced (Commonwealth Serum Laboratories) for use by travelers, laboratory workers, and veterinarians, no formal efficacy studies in human subjects have been performed. The fact that this type of vaccine effectively prevented bubonic plague in US troops in Vietnam while the local unimmunized population was not protected was an important observation. With plague being a very real bioterrorist agent and with the risk of pneumonic disease being great, efforts are ongoing to develop new, more effective vaccines.

CONCLUSIONS

Although allergists-immunologists will not be the primary physicians to evaluate patients with illnesses caused by biologic warfare agents, they will be called on to evaluate and manage those who have adverse reactions to the antibiotics and vaccines used for treatment, as well as to determine which chronically ill patients might safely receive life-saving vaccines. It is imperative that we are prepared for these challenges. Allergists-immunologists will be called on to determine who can safely receive the vaccines that are available to the various Category A biologic agents. They also will be called on to manage patients who become infected and who have multiple antibiotic allergies (see Table III for summary of adverse reactions). The current recommendation is that individuals who are receiving immunosuppressive therapy and those who have primary or secondary immunodeficiency diseases should not be vaccinated. Individuals who have AD are in this category as well. Because research is ongoing to determine the mechanisms responsible for the development of EV in this group of patients, it is hoped that we will soon be able to determine who can and who cannot safely receive the smallpox vaccine.

For individuals who have multiple antibiotic allergies and who become infected with a biologic agent, the allergist will have to determine whether the previous drug-induced reactions were true immunologic reactions or nonimmunologic adverse effects. For nonimmunologic and mild reactions, the drug most likely can be cautiously introduced by means of graded challenge. For those that had features suggestive of an immunologic cause, desensitization might be warranted.

Although we have not yet faced an emergency bioterrorism situation, the day might not be far off. Thus aller-

TABLE III. Category A biologic agents: Adverse reactions associated with agents used in prophylaxis and treatment

Anthrax vaccine: Local reactions (mostly mild), fever, chills, nausea, arthralgias, anaphylaxis (rare), hypersensitivity pneumonitis (not well substantiated)
Smallpox vaccine: Local reactions, erythema multiforme, Stevens-Johnson syndrome, EV (in patients with AD), PV (in patients with altered humoral cellular immune responses), GV
VIG: Local reactions (pain, tenderness), systemic reactions caused by activation of mediators of inflammation, anaphylaxis, aseptic meningitis syndrome
Botulinum antitoxin: Urticaria, serum sickness, anaphylaxis
Ciprofloxacin: Nausea, vomiting, diarrhea, central nervous system effects (headache, dizziness, fatigue), neurotoxic side effects (psychotic reactions, hallucinations, depression, seizures), arthropathy (children <16 years of age), tendinitis, generalized pruritus, flushing, anaphylactoid reactions, hypersensitivity vasculitis, Schonlein-Henoch purpura, serum sickness-like disease
Doxycycline: Nausea, vomiting, epigastric burning, urticaria, hypersensitivity syndrome (1 report), serum sickness-like syndrome (2 reports), erythema multiforme (2 reports), Stevens-Johnson syndrome (1 report)
Gentamicin: Nephrotoxicity and ototoxicity (most common)
Chloramphenicol: Aplastic anemia (most severe)

gists-immunologists must be ready. Our primary care colleagues will be calling.

REFERENCES

- US Army. US Army activity in the U.S. biological warfare programs. Washington, DC: US Army; 1977.
- Inglesby T, Dennis D, Henderson D, et al. Plague as a biological weapon—medical and public health management. *JAMA* 2000;283:2281-90.
- Amon S, Schechter R, Inglesby T, et al. Botulinum toxin as a biological weapon—medical and public health management. *JAMA* 2001;285:1059-70.
- Inglesby T, O'Toole T, Henderson D, et al. Anthrax as a biological weapon, 2002—updated recommendations for management. *JAMA* 2002;287:2236-52.
- Dennis D, Inglesby T, Henderson D, et al. Tularemia as a biological weapon—medical and public health management. *JAMA* 2001;285:2763-73.
- Rotz L, Khan A, Lillibridge S, Ostroff S, Hughes J. Public health assessment of potential biological terrorism agents—report summary. *Emerg Infect Dis* 2002;8:225-30.
- Fritz S, Singer A, Revan V, Baker J Jr. Bioterrorism: relevance to allergy and immunology in clinical practice. *J Allergy Clin Immunol* 2002;109:214-28.
- Friedlander A, Welkos S, Ivins B. Anthrax vaccines. *Curr Top Microbiol Immunol* 2002;271:33-60.
- Pittman P, Gibbs P, Cannon T, Friedlander A. Anthrax vaccine: short-term safety experience in humans. *Vaccine* 2002;20:972-8.
- Wasserman G, Grabenstein J, Pittman P, et al. Analysis of adverse events after anthrax immunization in US Army medical personnel. *J Occup Environ Med* 2003;45:222-33.
- Joellenbeck L, Zwanziger L, Durch J, Stroms B. The anthrax vaccine: is it safe? Washington, DC: National Academy Press; 2002. p. 1-32, 56-82.
- Wiessen A, Littell C. Relationship between pregnancy and anthrax vaccination and pregnancy and birth outcomes among US Army women. *JAMA* 2002;287:1556-60.
- Geier D, Geier M. Anthrax vaccination and joint related adverse reactions in light of biological warfare scenarios. *Clin Exp Rheumatol* 2002;20:217-20.
- Timmer S, Amundsen D, Malone J. Hypersensitivity pneumonitis following anthrax vaccination. *Chest* 2001;122:741-5.
- Schumm W, Reppert E, Jurich A, Bollman S, Webb F, Castelo C. Self-reported changes in subjective health and anthrax vaccination as reported by over 900 Persian Gulf War era veterans. *Psychol Rep* 2002;90:639-53.
- CDC. Investigation of bioterrorism-related anthrax and interim guidelines for exposure management and antimicrobial therapy, October 2001. *MMWR Morb Mortal Wkly Rev* 2001;50:909-19.
- Jernigan J, Stephens D, Ashford D, et al. Bioterrorism-related inhalational anthrax: the first 10 cases reported in the United States. *Emerg Infect Dis* 2001;7:933-44.
- Haffer A, Rogers J, Montello M, Frank E, Ostroft C. 2001 anthrax crisis in Washington, DC: clinic for persons exposed to contaminated mail. *Am J Health Syst Pharm* 2002;59:1189-92.
- Stahlmann R. Clinical toxicological aspects of fluoroquinolones. *Toxicol Lett* 2002;127:269-77.
- Assouad M, Willcourt R, Goodman P. Anaphylactoid reactions to ciprofloxacin. *Ann Intern Med* 1995;122:396-7.
- Lantner R. Ciprofloxacin desensitization in a patient with cystic fibrosis. *J Allergy Clin Immunol* 1995;96:1001-2.
- Gea-Banacloche J, Metcalfe D. Ciprofloxacin desensitization. *J Allergy Clin Immunol* 1996;97:1426-7.
- Shapiro L, Knowles S, Shear N. Comparative safety of tetracycline, minocycline, and doxycycline. *Arch Dermatol* 1997;133:1224-30.
- Albengres E, Guillaume J, Chevais M, Riant P, Touraine R, Tillement J. Recurrent erythema multiforme following successive treatments with tetracyclines: apropos of a case. *Therapie* 1983;38:577-9.
- Lewis-Jones M, Evans S, Thompson C. Erythema multiforme occurring in association with lupus erythematosis during therapy with doxycycline. *Clin Exp Dermatol* 1988;13:245-7.
- Curley R, Verbov J. Stevens-Johnson syndrome due to tetracyclines: a case report (doxycycline) and review of the literature. *Clin Exp Dermatol* 1987;12:124-5.
- Sullivan T. Drug allergy. In: Middleton E Jr, Reed CE, Ellis EF, Adkinson NF Jr, Yunginger JW, Busse WW, editor. *Allergy: principles and practice*. St Louis: Mosby; 1993. p. 1726-46.
- Bernstein I, Gruchalla R, Lee R, Nicklas R, Dykewicz M. Disease management of drug hypersensitivity: a practice parameter. *Ann Allergy Asthma Immunol* 1999;83:665-700.
- Henderson D, Inglesby T, Bartlett J, et al. Smallpox as a biological weapon—medical and public health management. *JAMA* 1999;281:2127-37.
- Bray M. Pathogenesis and potential antiviral therapy of complications of smallpox vaccination. *Antiviral Res* 2003;58:101-14.
- Engler R, Kenner J, Leung D. Smallpox vaccination: Risk considerations for patients with atopic dermatitis. *J Allergy Clin Immunol* 2002;110:357-65.
- Cono J, Casey C, Bell D. Smallpox vaccination and adverse reactions: guidance for clinicians. *MMWR* 2003;52(RR-4):1-28.
- Neff J, Lane J, Fulginiti V, Henderson D. Contact vaccinia-Transmission of vaccinia from smallpox vaccination. *JAMA* 2002;288:1901-5.
- Ong P, Ohtake T, Brandt C, et al. Endogenous antimicrobial peptides and skin infections in atopic dermatitis. *N Engl J Med* 2002;347:1151-60.
- Lane J, Ruben F, Neff J, Millar J. Complications of smallpox vaccination, 1968: National surveillance in the United States. *N Engl J Med* 1969;281:1201-8.
- Tacket C, Shandera W, Mann J, Hargrett N, Blake P. Equine antitoxin use and other factors that predict outcome in type A foodborne botulism. *Am J Med* 1984;76:794-8.
- Black R, Gunn R. Hypersensitivity reactions associated with botulinal antitoxin. *Am J Med* 1980;69:567-70.
- Goeschel H, Wohlfarth K, Freveret J, Dengler R, Bgalke H. Botulinum toxin therapy: neutralizing and nonneutralizing antibodies—therapeutic consequences. *Exp Neurol* 1997;147:96-102.
- Crook L, Tempest B. Plague: a clinical review of 27 cases. *Arch Intern Med* 1992;152:1253-6.
- Reisman R. Allergic reactions due to plague vaccine. *J Allergy* 1970;46:49-55.
- Marshall J, Bartelloni P, Cavanaugh D, Kadull P, Meyer K. Plague immunization. II. Relation of adverse reactions to multiple immunizations with killed vaccine. *J Infect Dis* 1974;129:S19-25.
- Meyer K, Smith G, Foster L, Marshall J, Cavanaugh D. Plague immunization. IV. Clinical reactions and serologic response to inoculations of Haffkine and freeze-dried plague vaccine. *J Infect Dis* 1974;129:S30-6.