# REVIEW



# **Biological and chemical terrorism: Recognition and management**

# ABSTRACT

Primary care physicians will be on the front line in detecting and managing any future terrorist attacks that use chemical or biological agents. This article reviews how to recognize and treat disease caused by exposure to nerve agents, blistering agents, hydrogen cyanide, ricin, anthrax, smallpox, plague, and botulinum toxin.

# **KEY POINTS**

Inhaled anthrax spores may take up to 60 days to germinate. In a previously healthy patient, an overwhelming febrile illness with a widened mediastinum on chest radiography should alert the clinician to the possibility of anthrax. In suspected cases, early antibiotic treatment is essential and should not wait for disease confirmation.

Smallpox is potentially the most devastating of the biological agents. It can be confused with chicken pox. Even a single case would be considered a significant international health event.

Nerve agents cause overwhelming cholinergic reactions. They can penetrate latex rubber; therefore, isolation suits and butyl rubber gloves are required. Treatment is with atropine in high doses and pralidoxime.

Blistering (mustard) agents have a delayed presentation with eye and skin irritation and burning. There is no known antidote.

\*This paper discusses therapies that are not approved by the US Food and Drug Administration for the use under discussion.

**R** ECENT EVENTS have highlighted the need for clinicians to educate themselves and prepare for the threat of biological or chemical terrorism. For many years these attacks seemed unlikely. No more. The events of September 11, 2001, the increasing number of cases of anthrax due to letters sent in the mail, and increasing intelligence revealing the existence of chemical and biological agents available to governments and terror organizations have awakened health care providers to the need for preparation.

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This article is aimed at primary care providers, internists, emergency physicians, and other health care providers who are likely to be the first to encounter and recognize the effects of such attacks.

# HOW REAL IS THE THREAT?

According to military intelligence and various government agencies, at least 10 countries have the capability of producing and disseminating biological or chemical weapons.<sup>1</sup> It is either unknown or unpublished how many terror organizations have the capability to procure, manufacture, or effectively deploy these agents. Most experts now agree, however, that the nation is facing a real threat.

The fall of the Soviet Union and the investigations of Iraq by the United Nations have given us firsthand observations of biological and chemical weapons programs. The current location of former Soviet stockpiles and the scientists who developed them is largely a matter of speculation. Iraq produced approximately 8,000 L of anthrax solution, 20,000 L

# TABLE 1

# Most likely agents of biological and chemical terrorism

Chemical agents Nerve agents Tabun Sarin Soman GF VX Blood agents Hydrogen cyanide Cyanogen chloride Blister agents Lewisite Nitrogen and sulfur mustards Phosgene oxime Pulmonary agents Phosgene Chlorine Vinyl chloride

# **Biological agents**

Variola major (smallpox) Bacillus anthracis (anthrax) Yersinia pestis (plague) Clostridium botulinum toxin Francisella tularensis (tularemia) Filoviruses Ebola hemorrhagic fever Marburg hemorrhagic fever Arenaviruses Lassa (Lassa fever) Junin (Argentine hemorrhagic fever)

FROM CENTERS FOR DISEASE CONTROL AND PREVENTION. BIOLOGICAL AND CHEMICAL TERRORISM: STRATEGIC PLAN FOR PREPAREDNESS AND RESPONSE. RECOMMENDATIONS OF THE CDC STRATEGIC PLANNING WORKGROUP. MMWR 2000; 49( RR-4):1–14.

> of botulinum toxin, 340 L of *Clostridium perfringens*, and 10 L of ricin; a 1997 report<sup>2</sup> concluded that "it is prudent to assume that the Iraqis retain hidden stores of freeze-dried organisms from its former biological warfare program." Terror organizations such as the Aum Shinrikyo, which caused the sarin gas attack in a Tokyo subway in 1995, have already demonstrated their willingness to use chemical and biological agents.<sup>3</sup>

# OVERT VS COVERT ATTACKS

The type of attack will dictate the response. Chemical agents are likely to be deployed in an overt attack, causing rapid onset of symptoms and mass casualties. Police, fire, and emergency medical services (EMS) personnel would likely be the first to respond and determine at least that an attack has occurred, if not the specific agent used. Immediate management would require hazardous materials (HazMat) units and large-scale decontamination and treatment facilities.

Biological weapons are more likely to be used covertly. Symptoms and signs of disease would have a delayed presentation, depending on the incubation period of the organism and the clinical syndrome.

# EARLY RECOGNITION IS CRUCIAL

Covert attacks will be detected only if health care providers are vigilant and trained to recognize infections with potential "bioterror" organisms. At the very least, any cases of rare, unusual, or unexplained diseases should raise the red flag of suspicion in the clinician's mind. Recognizing and reporting such cases is critical to mitigate the impact of an attack.

# THE 'IDEAL' BIOTERROR WEAPON

From the point of view of a terrorist, the ideal biologic weapon is one that can be quickly and easily disseminated to a large population, is highly contagious, causes high rates of morbidity and mortality, requires vast resources to combat, and causes mass panic, confusion, or social disruption. The ideal chemical weapon would have similar attributes and would cause the greatest morbidity, mortality, and social disruption in the largest potential area. Both types of weapons require certain expertise, component availability, and manufacturing capability—which a host of potential enemies in fact possess.

# PREPARATION IS THE BEST RESPONSE

Since panic and paranoia are undesirable, preparation is the best response. Governmental agencies, health departments, and the Centers for Disease Control and Prevention (CDC) have identified the most likely agents to be used in a chemical or biological attack (TABLE 1), and they have plans in place to address such attacks.<sup>4</sup> These plans emphasize the important role of the frontline medical providers in recognizing and reporting suspected biological and chemical attacks.

Although it is not known whether or when a biological or chemical attack will take place, clinicians can improve the medical community's readiness for such a situation by disseminating reliable information to others. Many resources provide information on chemical and biological terrorism; one would want to focus on reliable sources because, unfortunately, times like these spawn a few who seek to spread fear and panic through misinformation. For more information, readers are referred to the CDC web site at www.cdc.gov, the World Health Organization at www.who.int, and the United States Army Medical Research Institute of Infectious Diseases at www.usamriid.army.mil.

The rest of this paper discusses the recognition and management of selected agents most likely to be encountered, starting with chemical agents and then biological agents.

# NERVE AGENTS

# 'SLUDGE' effects of nerve agents:

- Salivation
- Lacrimation
- Urinary
  incontinence
- Diarrhea
- GI Distress
- Emesis

A variety of nerve agents were developed between 1930 and 1960 for use in bombs and other military devices. Much work went into refining these agents to increase their potency and environmental persistence.

The first known nerve agent, developed in Germany in 1930s, was called tabun. Sarin was next, followed by soman in the late 1930s and early 1940s. American scientists dubbed these first agents "G" agents, so tabun is also known as GA, sarin as GB, and soman as GD. The "V" agents were developed in the 1950s as more stable versions of the "G" agents. VX is more potent than sarin, and because it is more stable, less volatile, and less water-soluble, it can persist in the environment up to several weeks after release.

# Mechanism of nerve agents

Nerve agents affect transmission of nerve impulses by inhibiting cholinesterase. They are all highly toxic organophosphate compounds that irreversibly bind to cholinesterase, resulting in accumulation of acetylcholine at the nerve synapses and neuromuscular junctions. An initial overstimulation of cholinergic receptors precipitates a cholinergic crisis, followed by paralysis. The cholinergic crisis is characterized by central nervous system (CNS) symptoms and muscarinic and nicotinic effects, the onset and severity of which are determined by the dose, route of exposure, and properties of the specific agent involved.

# Signs and symptoms

# of nerve agent exposure

The onset of symptoms may be within a few minutes or up to 18 hours, depending on the degree of exposure.<sup>5</sup> Common CNS effects are agitation, confusion, delirium, hallucinations, seizures, and coma.

Muscarinic effects tend to be the most prominent, eg, salivation, lacrimation, urinary incontinence, diarrhea, gastrointestinal distress, and emesis, easily remembered using the mnemonic SLUDGE. Bradycardia, bronchospasm, bronchorrhea, and miosis also occur.

Nicotinic effects resulting from acetylcholine stimulation of nicotinic receptors in sympathetic ganglia include tachycardia, hypertension, and pallor. Nicotinic stimulation at the neuromuscular junction causes muscle fasciculations, pain, and weakness particularly involving the respiratory muscles.

Death results most directly from respiratory failure caused by respiratory muscle paralysis, loss of airway control, and profuse bronchorrhea.

The impact of a nerve agent release would depend on the agent used, the method of release, and the environmental concentration. Those in closest proximity or downwind of a vapor release would be expected to have the highest mortality rates. Others in the surrounding area would display varying degrees of symptoms. Inhalational exposure to sarin, the most volatile agent, may result in death in only a few minutes. A 2- to 3-mm<sup>2</sup> area of dermal exposure to VX is potentially fatal.

# Decontamination, protection

Efficient deployment of HazMat teams is critical to control a nerve agent attack. All major cities and emergency medical services have plans and equipment in place to address such emergencies, but the physician must be aware of principles involved in handling a patient or multiple patients exposed to one of these agents. Caregivers must first protect themselves by using isolation suits and butyl rubber gloves, because secondary contamination of even small amounts of these substances, especially VX, may result in lethal consequences.

Remember that these compounds are organic and have limited solubility in water. They penetrate latex gloves, resulting in dermal exposure to anyone observing only basic barrier precautions. Patients must be decontaminated by removing their clothing and washing with soap and water in appropriate decontamination facilities. VX is particularly oily and water-insoluble, so exposed patients must be decontaminated using alcohol, ethers, or acetate solutions.

# Treatment for nerve agent exposure

Treatment for nerve agent exposure involves large amounts of atropine and significant critical care resources. Patients with only minimal inhalational exposures resulting in mild rhinorrhea, miosis, or blurred vision may need observation only. All other patients with symptoms will require atropine in doses starting at 2 mg. In severely affected patients, a starting dose of 6 mg is appropriate. Some patients may require up to 40 mg of atropine, potentially exhausting hospital supplies. While atropine is effective in treating the muscarinic effects, it does nothing for the nicotinic effects. Thus, the goal of atropine therapy is the resolution of bronchorrhea.

Anyone requiring atropine should also receive the antidote to organophosphates, pralidoxime. This compound reverses the binding of the organophosphate to acetylcholine, reactivating the enzyme. However, it works only if "aging" has not taken place. Aging is the process by which the temporary phosphorylated bond between the organophosphate and acetylcholine undergoes alkyl group hydrolysis, resulting in a permanent covalent bond. Once aging has taken place, only regeneration of new acetylcholine will result in clinical improvement, a process that may take days or weeks. Soman undergoes aging in 2 minutes, sarin in 5 hours.<sup>6</sup> Therefore, early administration of pralidoxime is critical. Appropriate starting doses are 600 mg for mild to moderate symptoms and up to 1,800 mg for severely affected individuals.<sup>7</sup>

Military personnel have been trained in the use of autoinjectors containing 2 mg of atropine and 600 mg of pralidoxime for immediate intramuscular injection. These autoinjectors may be available for civilian use in the event of nerve agent attacks.

# BLISTERING (MUSTARD) AGENTS

Otherwise known as mustard agents, blistering agents are so named because they cause burns and blisters. These sulfide-based compounds have devastating effects on the skin, mucous membranes, and respiratory tract. They were first developed in the 19th century and used in World War I. Most recently, they were used extensively by Iraq in their war with Iran in the 1980s.

Blistering agents are essentially colorless and odorless. Their name derives from initial attempts at manufacturing that left a residual mustard odor. Some claim that these agents now have the odor of rotten onions. However, the sense of smell is significantly diminished after only a few breaths, and injury can be induced by concentrations so low as to escape olfactory detection.

# Mechanism of blistering agents

These compounds work by binding to a variety of molecules via a reactive sulfonium ion. They have a particularly high affinity for nucleic acids and sulfur and sulfhydryl groups in proteins. They act as alkylating agents, affecting biological processes such as cell division and DNA synthesis.

# Signs and symptoms

# of blistering agent exposure

Generally, no immediate symptoms occur, and presentation may be delayed 2 to 24 hours after exposure.<sup>6</sup> Once symptoms do occur, eye irritation, lacrimation, cough, hoarseness, and a burning sensation on the skin would likely be the first indication of exposure. Skin damage is characterized first by generalized painful inflammation, followed by blistering and desquamation. For updates, see www.cdc.gov www.who.int www.usamriid.army.mil Death is most likely to result from direct lung injury or sepsis. Coughing, hoarseness, and chest discomfort may be the first symptoms, followed by evidence of pulmonary edema and respiratory failure. Effects on tissues such as bone marrow and the immune system may be delayed for 5 to 10 days, and the increased risk of neoplasm resulting from DNA alkylation may not manifest for months or years.<sup>6</sup>

# Treatment for blistering agent exposure

Treatment for blistering agent exposure is largely supportive, as there is no known antidote. Decontamination is important to prevent further exposure to the patients and health care providers. Off-gassing poses a potential danger to responders, particularly in hot weather, and necessitates respiratory protection. The patient's clothes must be removed and sealed, the patient washed with soap and water, eyes flushed, and hair shaved. Decontamination facilities set up by HazMat teams would likely be necessary for multiple patients, and suitable barrier precautions would be provided to health care staff.

Even a 2-cm<sup>2</sup> dermal exposure to VX might be fatal Burn units would be the most appropriate for managing the most severely affected patients, as the initial syndrome and subsequent complications, such as local and systemic infection, are similar to those of more common burn injuries.

# HYDROGEN CYANIDE

Reports of hydrogen cyanide use by Iraq in their war against Iran and against the Kurds prompts a discussion of this agent as a possible chemical terror weapon.

Hydrogen cyanide is most dangerous if inhaled. Because it is highly volatile, high concentrations are difficult to achieve unless it is released into a confined space. Once inhaled, clinical effects can be immediate.

# Mechanism of hydrogen cyanide

Cyanide compounds work by binding to and inhibiting cytochrome  $aa_3$  in the electron transport chain, effectively stopping cellular respiration and resulting in tissue hypoxia and lactic acidosis.

# Signs and symptoms of hydrogen cyanide exposure

After exposure to high concentrations of hydrogen cyanide, death is practically instantaneous. Lower concentrations may produce tachypnea, restlessness, headache, and palpitations followed by seizures, coma, and death. The clinical syndrome essentially mimics hypoxemia and hypoxia, with the exception that cyanosis is absent. The diagnosis is made largely on clinical grounds, but a high venous  $PO_2$  relative to arterial  $PO_2$ , resulting from the inability of tissues to use oxygen, should significantly raise clinical suspicion.

# Treatment for hydrogen cyanide exposure

Treatment for cyanide poisoning is based on its mechanism of action. First, sodium nitrite is given intravenously at a dose of 10 mL of a 3% solution over 2 to 3 minutes. The pediatric dose is 0.2 mL/kg up to 10. Since the dose is based on available hemoglobin, it must be adjusted for anemia (charts are provided in the kit). Amyl nitrite capsules are available for inhalation, but are relatively inefficient and should be given only until intravenous access is achieved.

The nitrites convert hemoglobin to methemoglobin, which has a higher binding affinity for cyanide than does cytochrome oxidase. Cyanomethemoglobin is then converted to thiocyanate via rhodanese, regenerating methemoglobin in the process. Because rhodanese requires a sulfur substrate to exert its effect, sodium thiosulfate is given at a dose of 12.5 g intravenously after the sodium nitrite. Thiocyanate is then easily eliminated in the urine.

Hydroxocobalamin (vitamin  $B_{12}$ ) has been investigated as an antidote for cyanide intoxication, but is not yet approved by the US Food and Drug Administration for this indication.<sup>7</sup> It combines with cyanide to form cyanocobalamin, a nontoxic compound easily excreted in the urine. It also has the benefit of avoiding the potential adverse effects of nitrite-induced methemoglobinemia.

# RICIN

An extract from castor beans, ricin is a potent cytotoxin that inhibits protein synthesis. It

# **Cutaneous anthrax**



FIGURE 1. Cutaneous anthrax. Left, swelling and erythema in the early phase. Right, central ulceration with black, necrotic tissue in the later phase.

has been manufactured and stored as a potential chemical weapon by Iraq.

Clinical effects may be observed following either ingestion or inhalation. Inhalation exposure is characterized by cough, chest tightness, dyspnea, fever, and profuse sweating.<sup>8</sup> Airway necrosis and lung injury follows over the next 2 to 3 days, manifested by hemoptysis and pulmonary edema. Ingestion of ricin from a contaminated food source would result in hemorrhagic gastroenteritis, shock, and death.

There is no specific antidote for ricin, so treatment is largely supportive. Aggressive gut decontamination with activated charcoal might be considered if, for some reason, ricin ingestion is suspected.

# ANTHRAX

Three varieties of anthrax occur in humans: inhalational, cutaneous, and gastrointestinal.

Cutaneous anthrax is the most commonly encountered form, typically following exposure to anthrax-infected animals (FIGURE 1). Anthrax spores can enter wounds or broken skin, a route suspected in some of the recent cases of intentional anthrax exposure. Gastrointestinal anthrax is rare, yet can follow ingestion of undercooked contaminated meat. Inhalational anthrax, while rare, is the most fatal.

Until the recent bioterrorist events, only 18 cases had been reported in the United States in the last century. As of October 24, 2001, seven additional cases of inhalational anthrax and eight cases of cutaneous anthrax have been identified as a result of an apparent intentional release. The mail appears to be the current route of exposure, and other methods for future exposures are possible.

A 1993 report by the US Congressional Office of Technology Assessment<sup>9</sup> estimated that between 130,000 and 3 million deaths could occur as a result of the release of 100 kg of aerosolized anthrax spores over a heavily populated area.

Information on human inhalational anthrax largely comes from an outbreak in Sverdlovsk (in the former Soviet Union) in 1979 and from the recent documented US cases, though this information is evolving rapidly. The Sverdlovsk outbreak resulted from the accidental aerosolized release of anthrax spores from a military microbiology facility, causing at least 79 cases and 68 deaths.<sup>10</sup>

# Mechanism of anthrax disease

Bacillus anthracis is an aerobic, gram-positive, spore-forming, nonmotile bacterium. Spores form when environmental nutrients are exhausted, and they can exist for decades. When exposed to the appropriate nutrientrich environment, the spores germinate and can potentially cause disease.

Once inhaled, spores are transported via lymphatics to mediastinal lymph nodes, where germination can occur up to 60 days or more after exposure. The disease progresses rapidly once germination occurs because replicating Nasal swabs can rule in but not rule out anthrax exposure

# TABLE 2

# CDC recommendations for antimicrobial therapy against anthrax

INDICATION	ADULTS	CHILDREN
Postexposure prophylaxis	Ciprofloxacin 500 mg by mouth twice a day	Ciprofloxacin 10–15 mg/kg by mouth every 12 hours*
	Doxycycline 100 mg by mouth twice a day	Doxycycline: > 8 years and > 45 kg: 100 mg by mouth every 12 hours > 8 years and ≤ 45 kg: 2.2 mg/kg by mouth every 12 hours ≤ 8 years: 2.2 mg/kg by mouth every 12 hours
Cutaneous anthrax	Ciprofloxacin 500 mg by mouth twice a day OR	Ciprofloxacin 10–15 mg/kg by mouth every 12 hours* OR
	Doxycycline 100 mg by mouth twice a day	Doxycycline: > 8 years and > 45 kg: 100 mg by mouth every 12 hours > 8 years and ≤ 45 kg: 2.2 mg/kg by mouth every 12 hours ≤ 8 years: 2.2 mg/kg by mouth every 12 hours
Inhalational anthrax	Ciprofloxacin 400 mg intravenously every 12 hours OR	Ciprofloxacin 10–15 mg/kg intravenously every 12 hours* OR
	Doxycycline 100 mg intravenously every 12 hours PLUS (for either drug) One or two additional antibiotics (eg, rifampin, vancomycin, penicillin, ampicillin, chloramphenicol, imipenem, clindamycin, clarithromycin)	Doxycycline: > 8 years and > 45 kg: 100 mg intravenously every 12 hours > 8 years and ≤ 45 kg: 2.2 mg/kg intravenously every 12 hours ≤ 8 years: 2.2 mg/kg intravenously every 12 hours PLUS (for either drug) One or two additional antibiotics

Treatment for anthrax should be given for 60 days

\*Ciprofloxacin dose in children not to exceed 1 g/day

ADAPTED FROM CENTERS FOR DISEASE CONTROL AND PREVENTION. UPDATE: INVESTIGATION OF ANTHRAX ASSOCIATED WITH INTENTIONAL EXPOSURE AND INTERIM PUBLIC HEALTH GUIDELINES, OCTOBER, 2001. MMWR 2001; 50:889–897 AND CENTERS FOR DISEASE CONTROL AND PREVENTION. UPDATE: INVESTIGATION OF BIOTERRORISM-RELATED ANTHRAX AND INTERIM GUIDELINES FOR ENANAGEMENT AND ANTIMICROBIAL THERAPY, OCTOBER 2001. MMWR 2001; 50:909–919.

bacteria elaborate toxins that lead to hemorrhage, edema, and necrosis. In Sverdlovsk, hemorrhagic thoracic lymphadenitis and hemorrhagic mediastinitis occurred in all patients and hemorrhagic meningitis occurred in half.<sup>10</sup>

Anthrax does not cause a clinically evident pneumonic process, although postmortem examinations in Sverdlovsk patients showed a focal, necrotizing pneumonia in a substantial minority. It is not transmitted person to person.

# Signs and symptoms of anthrax

The clinical diagnosis of inhalational anthrax requires a high degree of suspicion. It generally presents as a two-stage illness.

First, a flulike syndrome begins with



nonspecific symptoms of fever, dyspnea, cough, headache, vomiting, rigors, generalized weakness, and abdominal and chest pain. This stage can last from a few hours to a few days.

The second, fulminant stage can follow immediately or after a brief period of improvement. The second stage tends to develop abruptly with fever, dyspnea, diaphoresis, and shock. Stridor can result from upper airway obstruction caused by mediastinal lymphadenopathy and hemorrhage. Chest radiography may demonstrate a widened mediastinum. The development of hemorrhagic meningitis may be heralded by meningismus, delirium, and obtundation.

Death occurs rapidly, and the mortality rate may be very high.<sup>11</sup> However, since many of the documented cases occurred before modern antibiotics and critical care facilities were available, the mortality rate, while still significant, is essentially unknown.

# **Diagnosis of anthrax**

Clinicians with a high degree of suspicion for anthrax should immediately notify their local or state health department. In a previously healthy patient, an overwhelming febrile illness with a widened mediastinum on chest radiography should alert the clinician to the possibility of anthrax.

Definitive testing can be arranged through local and state health departments or the US Army Medical Research Institute of Infectious Diseases (USAMRIID). Rapid diagnostic tests such as enzyme-linked immunosorbent assay (ELISA) or polymerase chain reaction (PCR) are generally available only at reference laboratories. Standard blood cultures and serologic tests are likely the most useful diagnostic tests, but the clinician should alert the laboratory to the possibility of anthrax when the culture is sent. Direct Gram stains of the blood may demonstrate the organism.

Sputum culture and Gram stains are unlikely to be useful since the disease does not involve a pneumonic process.

Postmortem examinations revealing hemorrhagic mediastinitis or hemorrhagic mediastinal lymphadenitis are essentially pathognomonic of inhalational anthrax.<sup>12</sup>

#### Treatment of anthrax

The following information comes largely from recent CDC reports.<sup>13,14</sup> Antibiotic prophylaxis is indicated based on exposure to known or suspected anthrax spores and not on laboratory testing. Nasal swabs are to be used for epidemiologic but not for diagnostic purposes because they can rule in but not rule out exposure.

In suspected cases of active disease, early antibiotic treatment is essential and should not wait for disease confirmation. On the basis of past experience and susceptibility testing of recently isolated strains, the CDC has issued a new set of antimicrobial recommendations (TABLE 2). For postexposure prophylaxis, ciprofloxacin or doxycycline are recommended and should be continued for 60 days. There is evidence that recently identified strains possess penicillinase and cephalosporinase activity. Concern for a beta-lactamase induction event in the presence of large numbers of organisms prompted the recommendation that beta-lactams not be used for treatment of active disease.

For treatment of active disease, ciprofloxacin or doxycycline is recommended, given intravenously for inhalational anthrax and orally for the cutaneous form. This applies even to children and pregnant women, in whom these antibiotics have been relatively contraindicated, given the relative risks and benefits.<sup>13–15</sup>

The recently identified strains have also demonstrated susceptibility to rifampin, clindamycin, vancomycin, and chloramphenicol, although clinical experience with these antibiotics is limited. Erythromycin, azithromycin, trimethoprim-sulfamethoxazole, and cephalosporins should not be used.

The CDC suggests combination therapy with two or more antibiotics until susceptibility testing is performed. Intravenous antibiotics can be switched to oral equivalents when clinically appropriate and continued for a total of 60 days.

Patients should be advised not to take or stock up on antibiotics simply because an anthrax attack has been threatened. State and local health departments and the CDC have stockpiles of antibiotics and plans in place to address large-scale and small-scale events. In suspected anthrax cases, do not wait for confirmation to start treatment

# If a suspicious substance is found

"Anthrax scares" are becoming increasingly common. White powder has been found in various locations, including US government offices, media outlets, mail, airlines, and shopping centers. Some samples have been positively identified as anthrax spores, but most are hoaxes.

If a suspicious substance is found, local health authorities should be notified. If the threat is deemed credible, persons in contact with it should be appropriately decontaminated using HazMat protocols, and samples of the suspicious substance sent to the appropriate testing facility, usually the state or local health department.

If anthrax spores are positively identified, antibiotic prophylaxis would be provided by the health authorities.

If a patient presents to an emergency department or doctor's office after being exposed to a suspicious substance, the clinician should isolate the patient and the substance while notifying the local health department. Biohazard precautions should be maintained to seal the substance and the patient's clothes in a plastic container while assuring that the powder is not aerosolized.

If the emergency department has decontamination facilities, the patient should be showered before entering the clinical care area.

The local health department will assist in testing the substance and instituting appropriate infection-control measures.

# Anthrax vaccine

An inactivated, acellular vaccine has been used by the US military for several years. Because the supply is limited and large-scale anthrax exposure is relatively unlikely, the vaccine has not been given to the population at large. If a large-scale attack does occur, postexposure vaccination would possibly be made available.

# For more information

Since information on anthrax exposures is rapidly evolving, readers are referred to the CDC website (**www.cdc.gov**) for the most up-to-date information and recommendations.

# SMALLPOX

Smallpox was eradicated in 1977, and immunization ceased in 1980 based on recommendations from the World Health Organization.<sup>16</sup> Routine immunizations in the United States ceased in 1972.

Caused by variola virus, smallpox is potentially the most devastating of the bioterror agents, as it has a high infectivity rate, a fatality rate of up to 30%, and a high personto-person transmission rate. Like anthrax, smallpox can be easily disseminated in aerosol form. Infection occurs after deposition of the virus particles on upper respiratory mucous membranes.

# Signs and symptoms of smallpox

Early features of the disease, generally beginning 12 to 14 days after exposure, include malaise, fever, rigors, vomiting, myalgias, delirium, and rash. Over the next few days, the patient develops mucous membrane lesions and a rash, which progresses from macules to papules to pustules.

Smallpox can be easily confused with varicella (chicken pox), but there are differences. The pustules in smallpox tend to be round, tense, deep dermal lesions all in the same stage of development; in contrast, the pustules of varicella tend to be in various stages of development. In addition, varicella lesions tend to predominate on the trunk, while smallpox lesions tend to occur more commonly on the face and extremities, including the palms and soles.

Death occurs from the systemic inflammatory response and cardiovascular collapse.<sup>17</sup>

# Diagnosis of smallpox

Virus is shed from the oropharynx and from the skin lesions until they are completely healed.

The preliminary diagnosis may be made by electron microscopy. Diagnostic confirmation is done through virus isolation, ELISA, and PCR from skin scrapings and oropharyngeal swabs in a facility equipped to manage this organism. Once an outbreak has occurred, diagnosis can be made on clinical grounds.

People vaccinated for smallpox before 1972 are probably not immune anymore

# Controlling the spread of smallpox

Patients with suspected smallpox should be quarantined with appropriate respiratory isolation precautions. Any known contacts may be placed in respiratory isolation and observed for signs of the disease until after the typical incubation period, although this is controversial.

Patients with smallpox should be treated in facilities separate from the usual hospital setting, if possible, in an effort to minimize the spread of the disease. Even a single case of smallpox would be considered a significant international health event.

# Treatment of smallpox

There is no specific treatment for smallpox, although cidofovir is effective in vitro.<sup>17</sup>

Smallpox vaccine (vaccinia) is available through the CDC, but only a limited supply is currently available. The vaccine would be given to patients with smallpox and to their close contacts. Routine vaccination in the United States stopped in 1972, and it is unlikely that people immunized before this time would still have protective immunity.<sup>18</sup> Vaccination up to 4 days after exposure may prevent or attenuate the illness.<sup>19</sup>

For plague, streptomycin, gentamycin, or doxycycline are recommended

Vaccinia immune globulin (VIG) should be given to patients with severe cutaneous reactions to the vaccine and to those with contraindications to vaccination.

Secondary bacterial infections are rare, and antibiotic treatment would only be warranted as specific rather than empiric therapy.

PLAGUE

Plague is well known in history, having caused several pandemics and millions of deaths. Several countries, including the United States, have experimented with plague as a biological weapon, using flea vectors in World War II and, more recently, an aerosolized form of the causative organism, Yersinia pestis.

Y pestis is classically transmitted through the bite of infected fleas, resulting in several forms of the disease, including bubonic, pneumonic, and primary septicemic plague. Bubonic plague is historically the most common manifestation, characterized by markedly tender and swollen lymph nodes, or buboes, resulting from local lymphangitic spread of the organism. Necrosis of the involved nodes is followed by endotoxemia leading to cardiovas-cular and neurologic collapse.<sup>20</sup>

As a biological weapon, plague would most likely manifest as the primary pneumonic form of the disease resulting from an aerosolized attack. Pneumonic plague is usually a secondary result of bubonic or primary septicemic plague. Primary pneumonic plague is rare in the United States, so such a case should raise the suspicion of a biological attack.

# Signs and symptoms of plague

Onset of symptoms follows exposure by 2 to 4 days. It is characterized by fever, cough, and dyspnea and may include prominent gastrointestinal symptoms including abdominal pain, nausea, vomiting, and diarrhea. The cough may be productive of watery, bloody, or purulent sputum.

Although both inhalational anthrax and pneumonic plague initially present similarly, a productive cough, especially hemoptysis, would preferentially suggest plague.

Radiographic findings also differ. Plague results in a pneumonic process while anthrax produces a prominent mediastinum in the absence of an infiltrate.

# Diagnosis of plague

Confirmatory tests are generally available only through health departments, which should be notified immediately if plague is strongly suspected. Cultures of blood, sputum, or lymph node aspirate would be useful.<sup>21</sup>

# Treatment of plague

Treatment recommendations for pneumonic plague resulting from a biological weapons attack are based on limited scientific evidence. The plague vaccine was discontinued in 1999 and is no longer available.

The antibiotic most often recommended and used for the treatment of plague is streptomycin. Since the availability of streptomycin is now limited, gentamicin is recommended as an alternative.<sup>21</sup> In a large-scale attack, when hospital supplies of intravenous drugs might be limited, doxycycline is recommended as an alternative in patients suitable for oral therapy.



Fluoroquinolones have not been adequately studied in controlled human trials, but they have demonstrated comparable clinical efficacy in animal models of pneumonic plague.<sup>22–24</sup>

Postexposure prophylaxis in the form of intravenous antibiotics should be given to anyone with a fever in an area of a plague outbreak. Tachypnea would be considered a sufficient indication in infants.

Persons without symptoms in close contact with infected patients should receive oral antibiotic prophylaxis with doxycycline for 7 days.<sup>25</sup>

# Controlling the spread of plague

Person-to-person transmission of plague can occur via respiratory droplets, prompting the recommendation that cases and asymptomatic close contacts of an infected patient, whether confirmed or suspected, observe strict respiratory isolation precautions until after 48 hours of adequate antibiotic treatment or prophylaxis.

Environmental decontamination is not necessary as the organism is very sensitive to environmental conditions and is only infective for up to 1 hour after aerosolization.<sup>26</sup>

# BOTULINUM TOXIN

As the most potent poison known, botulinum toxin has been well documented as a biological weapon. Aum Shinrikyo, the Japanese cult responsible for the sarin gas attack in Tokyo in 1995, has attempted to use it on at least three occasions. Iraq has admitted to producing 20,000 L of concentrated botulinum toxin, of which 12,000 L were loaded into weapons.<sup>3,27</sup>

Botulinum toxin is a zinc endopeptidase that irreversibly blocks fusion of acetylcholine-containing vesicles with the terminal membrane of the motor neuron, resulting in flaccid paralysis. Naturally occurring botulism takes three common forms: food-borne, wound, and intestinal. All forms result from toxin absorption through mucosal surfaces or wounds, as botulinum toxin cannot penetrate intact skin. A botulinum toxin attack could take the form of a focused aerosol release in a populated area, or it may possibly be released into a food source.

# Signs and symptoms of botulism

Botulism is characterized by descending, symmetric, flaccid muscle paralysis manifesting first in the bulbar muscles. Cranial nerve palsies result in diplopia, dysphagia, dysarthria, and ptosis. Other symptoms may include blurred vision, dry mouth, and mydriasis. Fever and sensory complaints or findings are absent. Presentations may be variable, but hypotonia, paralysis of respiratory muscles, and loss of the gag reflex may result in the need for mechanical ventilation. The sensorium is preserved, so the clinician must understand that the patient is aware of his or her surroundings although the degree of hypotonia may make the patient appear obtunded.

# Diagnosis of botulism

Botulism is a clinical diagnosis. Specialized laboratory testing may take days to confirm the diagnosis, although electromyography (EMG) may aid in the differential diagnosis. Possible misdiagnoses include Guillain-Barré syndrome, myasthenia gravis, Lambert-Eaton syndrome, tick paralysis, and stroke. Laboratory testing is only available through the CDC and certain health departments, and suspected cases should be reported immediately to the local health department.

# Treatment of botulism

Treatment for botulism is largely supportive.

An antitoxin available through the CDC and health departments is a trivalent compound active against the three most common types of botulinum toxin. The US Army has an investigational heptavalent antitoxin that may be available in an outbreak. Antitoxin should be given to patients with neurologic signs of botulism at the time of diagnosis unless the patient is already improving.<sup>27</sup>

As with any antitoxin, rare adverse reactions such as anaphylaxis and serum sickness may occur. A small test dose should be given before giving the full dose, and appropriate supportive resources should be immediately available.

With improvements in supportive and critical care in the last few decades, mortality from botulism has declined from 25% in the 1950s to 6% in the 1990s.<sup>28</sup> Because botulinum toxin binding is irreversible, patients

Botulinum toxin is the most potent poison known may remain in critical care units on mechanical ventilation for months while motor neuron fibers regenerate.

Botulism is not transmissible person to person, so isolation is not necessary. Antitoxin prophylaxis, based on risk vs benefit, is not recommended in people without symptoms who may have been exposed to

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the toxin, but they should remain under close supervision and be treated promptly should symptoms occur.

In the event of an outbreak, health agencies would work to identify the source of the toxin and perform any necessary decontamination procedures, because it may take days for the toxin to naturally degrade.<sup>29</sup>

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# A botulism antitoxin is available from the CDC