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Identifying and managing casualties of biological terrorism

Author: Amesh A Adalja, MD, FACP, FACEP, FIDSA
Section Editors: Daniel J Sexton, MD, Richard D Zane, MD
Deputy Editor: Allyson Bloom, MD

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INTRODUCTION

Terrorism can come in many forms. Biological events have the potential to be more readily disseminated and destructive than chemical or nuclear weapons [1]. The United States Congressional Office of Technology Assessment has estimated that a 100 kg payload of aerosolized anthrax spores, if released upwind of Washington, DC, could result in 130,000 to 3 million deaths, matching the lethality of the hydrogen bomb [2]. Lethal amounts of biological agents are relatively easy to manufacture, conceal, transport, and release. However, there is a growing consensus that manufacture of biological agents requires some amount of tacit knowledge, thus limiting the scope of individuals who have the capacity to initiate a large-scale attack [3].

As with emerging infectious diseases, detection and control of biological attacks depend upon a strong and flexible public health system at the local, state and federal levels. Additionally, well-trained and vigilant front line health professionals are required, especially in detecting covert biological attacks. Primary health care providers will likely be the first to observe and report any unusual illness patterns in the event of such an attack.

This topic will address the history of bioterrorism, the organisms of greatest concern, and the immediate management of persons with possible exposure.

Treatment of established infections, such as anthrax, is discussed in the topics dedicated to those pathogens.

Chemical terrorism is discussed separately. (See "Chemical terrorism: Rapid recognition and initial medical management".)

HISTORICAL PERSPECTIVE

The greatest advancements in biological weapons occurred in the twentieth century. Attacks have been targeted at both animals and humans [4], and have been perpetrated by multiple nations.

The first attempts at restricting the proliferation of biological capacity occurred with the 1925 Geneva Protocol for the "Prohibition of the Use in War of Asphyxiating, Poisonous or Other Gases, and of Biological Methods of Warfare" [1]. However, even after ratification, most countries continued to develop their biologic capacity. The United States built an offensive weapons program at Camp Detrick in 1942 and continued to develop technology in this area, fueled by the ensuing Cold War [5]. President Richard Nixon ended this offensive program in 1969. A multilateral treaty, known as the Biological Weapons Convention (BWC), was developed in 1972, and has been signed by 175 countries.

However, there had subsequently been evidence of ongoing use of biologic weapons in other countries, such as Iraq and the former Soviet Union [6,7]. The accidental release of aerosolized anthrax spores from a Soviet weapons plant in Sverdlovsk resulted in the deaths of at least 68 people from inhalation anthrax [8].

Evidence of prior bioterrorism — Terrorist groups and religious cults have also employed biological agents worldwide.

United States — In the United States, there have been several instances of biologic terrorism over the past few decades including the following events:

- In 1984, a religious cult intentionally infected restaurant salad bars in Oregon with salmonella, resulting in disease amongst 751 people; this episode revealed the vulnerability of the food and water supply [9]. (See "Nontyphoidal Salmonella: Microbiology and epidemiology".)

- In 2001, 22 people in the United States developed inhalational or cutaneous anthrax when this biological agent was sent through the mail to multiple states, resulting in five

deaths [10]. (See "Clinical manifestations and diagnosis of anthrax".)

- In 2003, an envelope with a threatening note and a sealed container containing ricin was processed at a mail processing and distribution facility in South Carolina [11]. An investigation by the Centers for Disease Control and Prevention (CDC) found no evidence of environmental contamination and no cases of ricin-associated illness. Ricin has been employed in multiple similar episodes, which include letters to President Barack Obama, a United States senator, and a Mississippi judge [12].

The United States also has a number of BioSafety Level (BSL) 3 and 4 laboratories spread across the country. A hurricane, or similar natural disaster, if located near such a facility, could theoretically result in an accidental release of organisms [13].

Worldwide — The Japanese cult, Aum Shinrykio, used sarin nerve gas for its attack on the Tokyo subway resulting in over 6000 casualties and 12 deaths in 1995 [14]. The group also attempted to disperse anthrax and botulism on at least eight occasions; these attacks were associated with no known illness. Other groups who have reportedly used biological weapons include the Viet Cong, who used focally contaminated spears during the Vietnam War, and the Mau rebels in Kenya, who used plant latex toxins to kill cattle [15].

THE ROLE OF REGULATORY AGENCIES

The United States Centers for Disease Control and Prevention (CDC) has been designated by the United States Department of Health and Human Services to coordinate and lead the planning efforts to upgrade national public health capabilities at the local, state, and federal level. Liaison channels now also exist between the CDC, the Federal Bureau of Investigation (FBI), and Federal Emergency Management Agency (FEMA) in order to better coordinate responses of national relevance. The FBI has jurisdiction over a bioterrorism response.

OVERVIEW OF DETECTION AND RESPONSE

Detection of biological agents can be difficult since biological events are frequently invisible and lead to slow accumulation of casualties, in contrast to chemical spills, which often lead to rapid casualties. The appropriate responses to a potential bioterrorism event include:

- Surveillance, detection, and containment. (See 'Surveillance and detection' below.)
- Confirmation and case detection. (See 'Confirmation and diagnostic testing' below.)

- Directed prophylaxis as required for possible exposure. (See 'Indications' below.)
- Directed therapy as required for possible or confirmed disease
- Clean up and/or epidemiological investigation as necessary

SURVEILLANCE AND DETECTION

Effective surveillance systems for detection of biological outbreaks need to include real time data from emergency rooms, laboratories, pharmacies and even schools to identify patterns of illness. These early responses are important for timely distribution of prophylactic medications or vaccines. The Centers for Disease Control and Prevention (CDC) can often deploy a specialized epidemiological and laboratory response team to assist in the investigations of unexplained or suspicious outbreaks at the request of state health departments, or if federally mandated.

The role of the clinician — Primary health care providers, emergency department physicians, intensivists, infection control practitioners, and infectious disease physicians may be the first persons to recognize disease caused by a variety of biological agents, including pathogens that are infrequently seen. Clinicians must remain mindful that an outbreak of disease might be the result of an intentional exposure [16]. Bioterrorism may be suspected when unusually high rates of a single illness are seen, or an unusual pathogen is isolated in the laboratory.

In general, the specific presentation can suggest certain pathogens. For example, skin lesions could be caused by anthrax, smallpox, or tularemia. Swollen lymph nodes could suggest bubonic plague; paralysis could suggest botulism. Undifferentiated febrile illness could be consistent with many agents.

Organisms of concern — The CDC has identified a number of pathogens that could be used in biological terrorism and have ranked them into various categories based on their overall potential to cause harm (table 1) [17-19]. High-priority agents include organisms that can be easily disseminated or transmitted person-to-person, cause high mortality, might cause public panic and social disruption, and require special action for public health preparedness.

- **Category A agents** are the highest priority. These agents are of particular concern because they can be grown easily in large quantities and are sturdy organisms, resistant to destruction. They are also particularly well suited to airborne dissemination,

thereby infecting large numbers of people. Examples include (table 1):

- *Bacillus anthracis* (anthrax) (see "Clinical manifestations and diagnosis of anthrax")
- Variola virus (smallpox) (see "Variola virus (smallpox)")

- **Category B agents** are the second highest priority. They are moderately easy to spread, and generally cause less morbidity and mortality than Category A but may require enhanced diagnostic capacity or surveillance techniques. Examples include (table 1):

  - *Coxiella burnetii* (Q fever)
  - *Brucella* spp (brucellosis) (see "Brucellosis: Epidemiology, microbiology, clinical manifestations, and diagnosis")

- **Category C agents** include pathogens that could be engineered for mass dissemination either because of ready availability, or ease of production and transport. They are usually agents of significant potential morbidity and/or mortality. Examples include (table 1):

  - Hantavirus (see "Hantavirus cardiopulmonary syndrome")
  - Multidrug-resistant *Mycobacterium tuberculosis* (See "Clinical manifestations and complications of pulmonary tuberculosis".)

Toxins of concern

- **Ricin**, listed as a Category B agent, is a toxin naturally found in castor beans. The clinical manifestations of ricin poisoning differ by route of exposure. Inhalational ricin may cause respiratory distress, fever, cough and pulmonary edema. Effects of this toxin may occur within eight hours of inhalation. Ingestion of ricin can lead to symptoms of vomiting, bloody diarrhea and dehydration within six hours. In severe cases, multi-organ failure can occur.

  There is no commercially available antidote; in addition to supportive care, gastric lavage and activated charcoal may be useful in some cases. Decontamination procedures should be undertaken for skin or clothing contamination since ricin can also cause burns.

- **Trichothecene mycotoxins**, derived from fungi, have also been used in aerosolized or powdered formulations for bioterrorism. These mycotoxins can lead to minor symptoms such as contact pruritus, burning, or blistering to severe symptoms such as

vomiting and ataxia with hypotension and coagulopathy. Inhalation or ingestion are more likely to cause systemic effects than cutaneous exposures. No vaccine or chemoprophylactic agents exist.

If ricin or mycotoxin exposure is suspected, the CDC should be contacted for assistance, including diagnosis.

PUBLIC HEALTH NOTIFICATION

In the event of a possible terrorist event, local emergency response systems should be activated by dialing 911 in the United States, or equivalent emergency telephone numbers in other countries. In communities without 911 systems, local law enforcement officials should be notified. The local FBI office and local and state public health authorities should also be notified, who in turn will notify other federal agencies if appropriate.

A number of prominent academic centers in the United States have created Preparedness and Emergency Response Research Centers (PERRCs) [20]. These centers act as coordinating points to improve cooperation between public health and emergency medical systems.

The public health response to bioterrorism also requires effective communication and coordination with first responders and law enforcement officials. Public messaging through the general media can alert the wider community. Collaboration between the media and public health agencies has occurred during prior major outbreaks in the United States (ie, anthrax and pandemic influenza).

CONFIRMATION AND DIAGNOSTIC TESTING

Once a potential bioterrorist event has been suspected or detected, the etiologic agent must be confirmed.

Appropriate collection of clinical specimens is crucial to detection:

- Post-exposure specimens should be collected within the first 24 hours. Clinical specimens typically include a nasal swab or sputum.
    - For asymptomatic individuals known or presumed to be exposed in a bioterrorism event based on epidemiology, prophylaxis (if available) should be offered immediately and regardless of results of post-exposure testing.

- Symptomatic individuals known or presumed to be exposed generally warrant more extensive testing. In general, for symptomatic patients, especially with pulmonary symptoms, lower respiratory tract sputum (induced if necessary) is the optimal specimen. Culture and polymerase chain reaction (PCR) testing are usually performed. If a clinical syndrome defies diagnosis, additional testing using serology and possibly molecular testing (ie, next-generation sequencing) may be required to make a diagnosis. Refer to other topic reviews of potential etiologic agents for discussion of diagnosis.

As part of the national preparedness effort, a network of laboratories that communicate directly with the public health infrastructure has been developed [21]. Similar moves in the European Union plan to link all major biosafety laboratories together to enable a more effective response [22]. Every state public health laboratory in the United States now has the ability to respond to a biological terrorism emergency, either individually or through the regional or federal support system.

DECONTAMINATION (OVERT EXPOSURE)

The extent of decontamination required in the event of a biological event depends on the degree of spread in an affected area, the number of individuals affected, and most critically, the organism of concern. Public health experts, emergency responders, and possibly criminal experts guide this response.

Personal decontamination — If personal decontamination is required, the Centers for Disease Control and Prevention (CDC) guidelines recommend that all clothing and personal effects be removed and placed in plastic bags. Persons should be instructed to shower using copious quantities of soap and water. Plastic bags with personal effects should be labeled clearly with the owner's name, contact telephone number, and inventory of the bag's contents. Personal items may be kept as evidence in a criminal trial or returned to the owner if the threat is unsubstantiated.

Careful hand cleansing is important; one study evaluated different agents that might be used for hand washing after contact with anthrax [23]. Regular soap and water were as effective in the removal of spores similar to anthrax as antimicrobial soap or 2 percent chlorhexidine gluconate. However, an ethyl alcohol waterless rub was **not** active against these spores and is not recommended [23,24]. (See "Prevention of anthrax", section on 'Infection control'.)

Environmental decontamination — Environmental surfaces should be cleaned thoroughly

after a suspected exposure once the crime scene investigation is complete. Surfaces may be decontaminated with a 0.5 percent sodium hypochlorite solution (ie, one part household bleach to 10 parts water) [25]. Personal effects may be decontaminated similarly.

Although sodium hypochlorite is a safe and effective decontaminating agent for environmental surfaces and equipment, it is not recommended for human skin [24].

PROPHYLAXIS

Indications — Determination of who should receive prophylaxis will depend on the suspected agent of concern and the associated route of transmission. As an example, the definition of a "close contact" depends on whether the suspected agent is acquired through inhalation versus contact.

Selection of prophylaxis type — The type of prophylaxis will depend on the agent or toxin that is suspected.

State and regional public health officials guide clinicians as to the suspected pathogen and preferred prophylaxis to use depending on local supplies. The Department of Health and Human Services houses the Strategic National Stockpile (SNS) for rapid response to such large-scale events with supplies to where they are most needed [26].

Chemoprophylaxis — Chemoprophylaxis is available for many infections, such as the etiologic agents of anthrax, plague, tularemia, brucellosis and Q fever. Ciprofloxacin and doxycycline are used for the agents of anthrax, tularemia, and plague [27]. Trimethoprim-sulfamethoxazole may have a role in chemoprophylaxis for glanders and melioidosis [28]. For brucellosis, combination therapy with doxycycline and rifampin for 21 days is preferred [29]. The chemoprophylaxis of children or pregnant women requires a careful risk-benefit assessment, given the potential problems with antibiotics in special populations. (See "Fluoroquinolones" and "Tetracyclines".)

For anthrax, monoclonal antibodies can also be used for post-exposure prophylaxis when no other options are available, as below.

Antitoxins — A number of antitoxins have been developed to counteract the effect of biologic agents. To date, these have been designed to protect against ricin, botulism and anthrax, although only some have progressed to commercial availability at this point [30]. Two monoclonal antibodies that neutralize Bacillus anthracis toxin, raxibacumab and

obiltoxaximab, are approved by the US Food and Drug Administration for the prevention and treatment of inhalational anthrax [31,32]. A polyclonal anthrax antibody is approved for the treatment of anthrax [33]. A supply of these products is held in the SNS in the event of an anthrax emergency. The use of these therapies is discussed in detail elsewhere. (See "Treatment of anthrax", section on 'Antitoxins' and "Prevention of anthrax", section on 'Monoclonal antibodies'.)

Immunization — Although the principle of immunization to prevent disease has been shown to be effective in some large-scale outbreaks (eg, H1N1 influenza vaccine, SARS-CoV-2 vaccine), the value of mass vaccination after a biological event is unclear.

In cases of suspected or documented bioterrorism, vaccines are available for the prevention of anthrax [34], smallpox, Ebola, and cholera. Other vaccines are only available through special dispensation from the CDC (eg, vaccines effective against the causative agents of Q fever, the various viral encephalitides). Some vaccines, such as those directed against Ebola, anthrax, and smallpox, are stockpiled.

INFECTION CONTROL

The Centers for Disease Control and Prevention (CDC), in conjunction with the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Disease Society of America (IDSA) produced guidelines designed to assist in the care of hospitalized patients and outpatients regardless of their diagnosis or presumed infectious status [35].

Required precautions are disease specific; the types of precautions that are instituted will depend on the suspected or documented pathogen as follows:

- Airborne precautions (eg, smallpox, hemorrhagic fevers, tuberculosis, measles, SARS-CoV-2)
- Droplet precautions (eg, plague, influenza; although these are the precautions used for natural infection, in a biological weapons scenario, enhanced transmission may be a risk, and a lower threshold to use airborne precautions for nonairborne pathogens is warranted)
- Contact precautions (eg, salmonella)

Secondary person-to-person transmission is possible with a number of biologic agents, especially smallpox, pneumonic plague, and the agents of hemorrhagic fever, so attention to

hospital-acquired or community-based transmission is needed [36]. Samples from toxin-exposed subjects can be dealt with routinely. (See "Infection prevention: Precautions for preventing transmission of infection".)

PSYCHOLOGICAL CONSIDERATIONS

One consequence of a terrorist attack is the residual psychological impact on the affected patients and the surrounding community. This will include overload of medical facilities by the "worried well" and grief responses by the survivors. Furthermore, past experience with the severe acute respiratory syndrome (SARS) suggested that some people who were ill delayed seeking care, because they perceived medical centers as being the source of the contagion [37].

Psychological morbidity for first-responders, medical personnel, and the public can be significant in the event of a terrorist event, so clinicians should be mindful of depression, pathologic bereavement, acute stress disorder (ASD) and post-traumatic stress disorder (PTSD) [16,38].

EMERGENCY RESOURCES

Centers for Disease Control and Prevention (CDC) – Division of Emergency Preparedness and Response

www.emergency.cdc.gov/

CDC Emergency Response Coordinating Group:

770-488-7100 (health professionals or government officials only)

Regional Poison Control Centers:

1-800-222-1222

CDC Coordinating Office for Terrorism Preparedness and Emergency Response:

404-639-7405

CDC Division of Bioterrorism Preparedness and Response:

404-639-0385

Federal Bureau of Investigation (FBI):

1-855-835-5324

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Anthrax".)

SUMMARY AND RECOMMENDATIONS

- Detection of biological agents can be difficult since biological events are frequently invisible and lead to slow accumulation of casualties, in contrast to chemical spills, which often lead to rapid casualties. (See 'Overview of detection and response' above.)
- An astute clinician may be the first to recognize either a large outbreak of one disease or an unusual pathogen, which may be the first sign of biological terrorism. (See 'The role of the clinician' above.)
- Effective surveillance systems for detection of biological outbreaks need to include real time data from emergency rooms, laboratories, pharmacies and even schools to identify patterns of illness. These early responses are important for timely distribution of prophylactic medications or vaccines. (See 'Surveillance and detection' above.)
- The Centers for Disease Control and Prevention (CDC) has identified a number of pathogens that could be used in biological terrorism and have ranked them into various categories based on their overall potential to cause harm. The pathogens of greatest concern include anthrax and smallpox (table 1). (See 'Organisms of concern' above.)
- In the event of a possible terrorist event, local emergency responses systems should be activated by dialing 911 in the United States, or equivalent emergency telephone numbers in other countries. (See 'Public health notification' above.)
- Post-exposure specimens should be collected within the first 24 hours and prophylaxis should be offered (if available). Most clinical specimens include a nasal swab or sputum; culture and polymerase chain reaction (PCR) testing are usually performed. (See 'Confirmation and diagnostic testing' above.)

- In overt exposures, both personal and environmental decontamination may be required. (See 'Decontamination (overt exposure)' above.)
- State and regional public health officials will guide clinicians as to the suspected pathogen and preferred prophylaxis to use depending on local supplies. (See 'Indications' above.)
- The type of prophylaxis will depend on the agent or toxin that is suspected; possibilities include chemoprophylaxis (eg, antibiotics), immunizations, or antitoxins. (See 'Prophylaxis' above.)
- Airborne, droplet or contact precautions will be established depending on the agent of concern. (See 'Infection control' above.)

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GRAPHICS

Potential bioterrorism agents by category

Category A agents
Variola major (smallpox)
Bacillus anthracis (anthrax)
Yersinia pestis (plague)
Clostridium botulinum toxin (botulism)
Francisella tularensis (tularemia)
Filoviruses (Ebola, Marburg)
Arenaviruses (Lassa, Junin and related viruses)
Category B agents
Coxiella burnetii (Q fever)
Brucella spp. (brucellosis)
Burkholderia mallei (glanders)
B. pseudomallei (melioidosis)
Chlamydia psittaci (psittacosis)
Rickettsia prowazekii (typhus fever)
Alphaviruses (eastern equine encephalitis, western equine encephalitis, Venezuelan equine encephalitis)
Ricin toxin
Epsilon toxin of Clostridium perfringens
Staphylococcus enterotoxin B
Salmonella spp.
Shigella dysenteriae
Escherichia coli O157:H7
Vibrio cholerae
Cryptosporidium parvum
Category C agents
Nipah virus
Hantaviruses

Tickborne hemorrhagic fever viruses
Tickborne encephalitis viruses
Yellow fever
Multidrug-resistant tuberculosis

The United States Centers for Disease Control and Prevention has ranked various pathogens into these categories based on their potential to cause harm.

Category A agents are the highest priority. They can cause high mortality, can be grown easily in large quantities, and are resistant to destruction. They are also well suited to airborne dissemination and can thus infect large numbers of people.

Category B agents are the second highest priority. They are moderately easy to spread but generally cause less morbidity and mortality than Category A agents.

Category C agents include pathogens that could be engineered for mass dissemination and have significant potential morbidity and/or mortality.

Graphic 79744 Version 3.0

Contributor Disclosures

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