Age of Bioterrorism: Are You Prepared? Review of Bioweapons and Their Clinical Presentation for Otolaryngologists

Philip E. Zapanta and Saba Ghorab

Otolaryngology -- Head and Neck Surgery 2014 151: 208 originally published online 22 April 2014
DOI: 10.1177/0194599814531907

The online version of this article can be found at:
http://oto.sagepub.com/content/151/2/208

Published by:
SAGE
http://www.sagepublications.com

On behalf of:
AMERICAN ACADEMY OF OTOLARYNGOLOGY--HEAD AND NECK SURGERY
FOUNDATION
American Academy of Otolaryngology- Head and Neck Surgery

Additional services and information for Otolaryngology -- Head and Neck Surgery can be found at:

Email Alerts: http://oto.sagepub.com/cgi/alerts
Subscriptions: http://oto.sagepub.com/subscriptions
Reprints: http://www.sagepub.com/journalsReprints.nav
Permissions: http://www.sagepub.com/journalsPermissions.nav

>> Version of Record - Jul 23, 2014
OnlineFirst Version of Record - Apr 22, 2014

What is This?
State of the Art Review

Age of Bioterrorism: Are You Prepared? Review of Bioweapons and Their Clinical Presentation for Otolaryngologists

Philip E. Zapanta, MD¹,², and Saba Ghorab³

Abstract

Objectives. This review on Category A bioweapons is intended to help otolaryngologists (1) understand the concepts of bioterrorism, (2) identify a bioterrorism attack, and (3) recognize specific otolaryngologic symptoms and signs of Category A bioweapons.

Data Sources. PubMed and Medline databases.

Review Methods. Review of current literature regarding Category A agents of biological warfare and their relationships to otolaryngology was performed using PubMed, Medline, and articles written by experts in the field of bioterrorism. Each Category A agent was paired with the term otolaryngology and then paired with epistaxis, sinusitis, airway obstruction, pharyngitis, tonsillitis, hearing loss, otitis media, and lymphadenopathy individually. For the latest accepted treatment and diagnostic strategies, bioterrorism was searched with filters for human studies, English language, and the past 5 years. Titles, abstracts, and papers were read for relevancy.

Conclusion. While the use of bioweapons initially leads to nonspecific symptoms, a high index of suspicion and clustering of abnormal pathology will often lead the astute physician to the correct diagnosis of bioweapons. Some disease presentations of Category A agents (anthrax, smallpox, tularemia, botulism, plague, hemorrhagic fever) will involve the realm of otolaryngology.

Implications for Practice. The head and neck manifestations of a Category A bioweapon attack will require knowledgeable otolaryngologists for prompt diagnosis, treatment, and notification of public authorities. This will help decrease the morbidity and mortality of any potential bioterrorism attack.

Keywords

bioweapons, bioterrorism, anthrax, botulism, smallpox, tularemia, plague, hemorrhagic fevers, Category A agents

Received October 14, 2013; revised March 5, 2014; accepted March 26, 2014.

Since the terrorist attacks on September 11, 2001, and the anthrax attacks in the fall of 2001, the threat of biological warfare has been of utmost concern to national security. As health care workers, we have an obligation to educate ourselves on bioweapons and bioterrorism for competent treatment of bioterrorism victims. The medical community lacks the bioterrorism preparedness training necessary for timely diagnosis and management. Although several medical disciplines have addressed bioterrorism education, our community has not reviewed potential bioweapon agents as they relate to otolaryngology. Following a potential bioterrorism event, there may be clusters of unexplained head and neck pathology. The astute otolaryngologist needs to maintain a high level of suspicion to promptly diagnose and treat these patients. The objectives of this article are to help otolaryngologists understand the concepts of bioterrorism, identify a bioterrorism attack, and recognize the specific otolaryngologic symptoms and signs of Category A bioweapons.

Methods

Via PubMed and Medline databases, the senior author (P.E.Z.) conducted a literature review of bioweapons. Since Category A agents pose the most threat to national security, these agents were included, while Category B and C agents were excluded. Table 1 lists the bioweapons in each category. Each Category A bioweapon was paired with the term otolaryngology. Then each Category A bioweapon was paired with epistaxis, sinusitis, airway obstruction, pharyngitis, tonsillitis, hearing loss, otitis media, and lymphadenopathy individually.

Table 1

<table>
<thead>
<tr>
<th>Bioweapon</th>
<th>Symptom</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthrax</td>
<td>Epistaxis</td>
</tr>
<tr>
<td>Smallpox</td>
<td>Sinusitis</td>
</tr>
<tr>
<td>Tularemia</td>
<td>Airway obstruction</td>
</tr>
<tr>
<td>Botulism</td>
<td>Pharyngitis</td>
</tr>
<tr>
<td>Plague</td>
<td>Tonsillitis</td>
</tr>
<tr>
<td>Hemorrhagic fever</td>
<td>Hearing loss</td>
</tr>
</tbody>
</table>

¹Division of Otolaryngology—Head and Neck Surgery, School of Medicine and Health Sciences, The George Washington University, Washington, District of Columbia, USA
²Army Reserve Medical Command, Army Medical Department (AMEDD) Professional Management Command, Forest Park, Georgia, USA
³School of Medicine and Health Sciences, The George Washington University, Washington, District of Columbia, USA

The views expressed in this article are those of the authors and do not necessarily represent the official policy or position of the United States Army Medical Department, the United States Army, the Department of Defense, or the United States government.

Corresponding Author:
Philip E. Zapanta, MD, Division of Otolaryngology, The George Washington University, 2021 K St, NW, Suite 206, Washington, DC 20006, USA.
Email: pzapanta@mfa.gwu.edu
In order for a bioweapon to be effective, it should be relatively easy to produce, store, and weaponize. Currently, aerosolization is the most effective dispersal method of bioweapons. For example, if an airplane were to release 50 kg of anthrax upwind of a major city, 95,000 would die and an additional 125,000 would be injured.

Bioterrorism is an effective mode of warfare for several reasons. First, bioweapons are difficult to detect, are relatively cheaper than conventional weapons, and are easy to produce. A competent group only needs $10,000 and the space of a 2-car garage to produce a major bioweapon. Second, these weapons spread well outside the initial delivery area, potentially leading to devastating results. Third, bioterrorism creates fear and incites public panic. After the first confirmed cases of inhalational anthrax in the fall of 2001, patients flooded emergency rooms and clinics. In the Washington, DC, area alone, the emergency departments experienced an 8.82% increase in patient volume regarding concerns for anthrax exposure.

The Centers for Disease Control and Prevention (CDC) classifies bioweapons as Category A, B, or C based on their infectious nature and ability to cause public panic and chaos. This article focuses on Category A agents since they pose the most serious threat to national security. These agents are easily disseminated with high patient-to-patient transmission, have high mortality rates, and possess a great potential in disrupting the public health infrastructure.

Identification of a Bioweapons Attack

There are several clues to help identify a bioweapons attack. Specific portions of the population may have similar findings and present in the same time frame in the same geographical locations. The disease may be seen in unlikely age groups, in smaller distances or barriers may separate similarly affected populations. The disease may be seen in unlikely age groups, in unlikely ages, or in immunocompromised patients. “Skip lesions” may be evident as significant physical distances or barriers may separate similarly affected populations. There may be unexplained clustering of disease, the disease may be more severe than is classically known, or a zoonotic disease may be found in human patients. If the pathogen is discovered, it may be an uncommon strain and/or display atypical antibiotic resistance.
Anthrax

The first 21st-century bioterrorist attack on the United States occurred when several letters contaminated with anthrax spores were released into the US postal system and cross-contaminated 5000 letters. Of the 22 people infected with either cutaneous or pulmonary anthrax, 5 with pulmonary anthrax died. Pulmonary anthrax occurs via aerosolization and inhalation of 2- to 5-μm spores that are able to bypass the mucociliary system in the sinonasal tract to reach the lung alveoli. The incubation time is up to 100 days in the mediastinal lymph nodes, eventually leading to toxin-mediated edema, hemorrhage, and necrosis. Inhalational signs and symptoms include hoarseness, cough, globus sensation, fevers, severe throat pain, and dysphagia. Other signs and symptoms of inhalational anthrax are the most common route of natural infection, accounting for >90% of cases. In contrast, oropharyngeal anthrax is a rare entity, with only 30 reported cases in the United States. Infection is classically from ingesting undercooked or contaminated meat. After an incubation period of 2 to 5 days, oropharyngeal lesions develop, leading to cervical lymphadenopathy, airway edema, and ultimately airway compromise. Clinically, these patients have fevers, severe throat pain, and dysphagia. Other signs and symptoms include hoarseness, cough, globus sensation, shortness of breath, and significant neck swelling.

`Bacillus anthracis` derives its name from the Greek word, `anthrakis`, meaning coal. This represents the common black eschar that forms during a cutaneous anthrax infection, which is the most common route of natural infection, accounting for >90% of cases. In contrast, oropharyngeal anthrax is a rare entity, with only 30 reported cases in the United States. Infection is classically from ingesting undercooked or contaminated meat. After an incubation period of 2 to 5 days, oropharyngeal lesions develop, leading to cervical lymphadenopathy, airway edema, and ultimately airway compromise. Clinically, these patients have fevers, severe throat pain, and dysphagia. Other signs and symptoms include hoarseness, cough, globus sensation, shortness of breath, and significant neck swelling.

Microbiological testing is key in confirming the diagnosis of inhalational anthrax and in determining antibiotic sensitivities. However, blood cultures are often not positive until the late stages of the disease. Most important, health care personnel must notify the laboratory to specifically test for anthrax, since `Bacillus anthracis` is considered a contaminant. Also, a widened mediastinum on imaging studies is almost pathognomonic. Nasal swabbing was popular during the fall 2001 attack, but it provided only epidemiological data and potential exposure information. Throat swabs and blood cultures are useful but may not be available in time to confirm the diagnosis. Cutaneous anthrax is best diagnosed via punch biopsy for histologic evaluation, immunohistochemistry, and polymerase chain reaction (PCR).

Treatment depends on potential exposure and the type of presumed anthrax infection. Penicillin is appropriate for naturally acquired anthrax, but in today’s times, all suspected anthrax patients should be assumed to have penicillin-resistant strains. Cutaneous lesions can be treated with oral ciprofloxacin or doxycycline while parenteral antibiotics are needed for all other forms. Although fluoroquinolones are associated with arthropathy and tendon damage, ciprofloxacin is still recommended as first-line therapy for bioterrorism-associated anthrax in adults and children. An anthrax vaccine is available for postexposure prophylaxis, but currently it is limited to military use.

Smallpox

During the French and Indian War, Sir Jeffrey Amherst, a commander of the British forces, gave contaminated blankets and handkerchiefs to Native Americans to infect them with smallpox. It is unknown whether this was effective or if direct contact with the Native Americans was the source of transmission. Since global eradication of smallpox was declared in 1980, routine public vaccination ceased, and most existing stockpiles of the orthopoxvirus were destroyed. As a result, herd immunity levels have decreased far below levels needed for control during a bioterrorist attack.

Poxvirus aerosolization leads to variola major with a 30% fatality rate. Within 2 weeks of exposure, patients experience fevers, myalgia, prostration, headache, and backache. A centripetal, maculopapular rash starts at the face and oropharynx and spreads distally to the trunk and extremities. Within days, the rash transitions from vesicular to pustular and crusts over to heal, leaving pitted scars. Distinguishing features from classic chickenpox are smallpox’s centripetal rash that appears as synchronous, full-thickness skin lesions; involves the palms and soles; and remains infectious until all the scabs separate.

In addition to skin lesions, smallpox has distinct otolaryngologic manifestations. The papular smallpox rash corresponds to aerodigestive tract mucosal ulcers, which often lead to airway edema and subsequent respiratory compromise. Sloughing of upper aerodigestive tract necrotic epithelial cells can form yellow pseudomembranes, further obstructing the airway. Lesions involving the external and middle ear can cause conductive hearing loss, while the viral infection may cause a sensorineural hearing loss. Scarring of the nasal mucosa may lead to vestibular stenosis. If left untreated, toxemia and airway complications will result in death.

Hemorrhagic smallpox, typically occurring in pregnant patients, has a grave prognosis with almost 100% fatality. Mucocutaneous lesions show erythema, petechiae, and frank hemorrhage that heal without scarring. Variola minor is a mild form of smallpox with <1% fatality and develops in patients with a history of smallpox.

While smallpox is considered a clinical diagnosis, several diagnostic tests exist. Electron microscopy can detect the virus in vesicular or pustular fluid, and light microscopy will show Guarnieri bodies. Alternatively, specimens can be analyzed via PCR and enzyme-linked immunosorbent assay (ELISA). Specimens should be collected by vaccinated personnel and sent to a biosafety level 4 laboratory.

Treatment is primarily supportive care. Since smallpox is very contagious, the index case should be vaccinated and placed in quarantine for 2 weeks. Vaccination can prevent death and severe morbidity if given within 4 days of exposure. Protection from immunization typically lasts 10 to 15 years. Currently, eligibility for vaccination includes
first responders and select military personnel. If a smallpox outbreak occurs, the CDC has an intricate plan to vaccinate the rest of the country. Since its eradication, there has been limited research in the management of smallpox because of inability to test agents in human subjects. Animal studies, however, have shown that cidofovir is effective against 32 smallpox strains. Currently, the US Food and Drug Administration has approved cidofovir as an investigational drug for emergency treatment of adverse effects of smallpox vaccination.

**Tularemia**

Tularemia (rabbit fever or deerfly fever) is a zoonotic disease caused by bites of infected animals or insects and by handling blood and soft tissues of infected animals. Two subtypes exist: *Francisella tularensis* biovar *tularensis* (type A—highly virulent) and *Francisella tularensis* biovar *palaearctica* (type B—avirulent); type A is found only in North America, and type B is usually found in Europe and Asia.

Although 80% of naturally acquired infections cause ulceroglandular tularemia, an aerosolized bioweapon attack would cause typhoidal or pneumonic tularemia 3 to 5 days later. There might be a large number of temporally clustered patients presenting with similar systemic symptoms (malaise, fever, and myalgias), a nonproductive cough, and pneumonia.

Once tularemia is suspected, the diagnosis can be confirmed by various studies. Chest x-ray may show pneumatic infiltrates and mediastinal lymphadenopathy with typhoidal disease. Secretions, exudates, sputum, blood, and biopsy specimens can be cultured on media containing cysteine or other sulphhydryl compounds with bacterial growth within 24 hours. Bacterial agglutination or ELISA can diagnose tularemia. However, it takes 2 weeks after infection for adequate antibody levels to improve the specificity of the serologic diagnosis.

Treatment with antibiotics has dropped fatality rates from 60% to less than 2%. In contained cases, parenteral administration of streptomycin or gentamicin is indicated. However, oral ciprofloxacin or doxycycline is the most viable option in a mass casualty event while saving parenteral antibiotics for sicker patients. Ciprofloxacin or doxycycline is also recommended for postexposure prophylaxis within 24 hours of aerosolization. Chemoprophylaxis is generally not recommended if a patient’s exposure is greater than 72 hours before administration. Patients could succumb to death due to airway obstruction, paralysis, and inadequate diaphragmatic excursion.

**Botulism**

*Clostridium botulinum* produces 7 types of the most lethal toxin known. It is 15,000 times more toxic than nerve gas and 100,000 times more lethal than sarin gas. Aerosolization would cause bulbar palsies (4 “Ds”—diplopia, dysarthria, dysphonia, dysphagia) and descending flaccid paralysis, while remaining afebrile with normal mentation. Patients would suffocate to death due to airway obstruction, paralysis, and inadequate diaphragmatic excursion.

Botulism is a clinical diagnosis. A clustering of patients with descending paralysis and bulbar findings may indicate a bioterrorism event or a natural outbreak of foodborne botulism. No routine laboratory tests will aid in the diagnosis, and specialized assays of gastric contents will require several days to complete.

Supportive treatment includes airway management and gastrostomy feeding tubes. Since the flaccid paralysis is irreversible, recovery is dependent on the synthesis of new axons and synapses. The CDC has a trivalent antitoxin that is effective against the 3 most common types of toxin (A, B, G), and the military has a heptavalent antitoxin that would be helpful in a bioweapons attack. Antitoxin is generally not recommended if a patient’s exposure is greater than 72 hours before administration. There are no recommendations for vaccination of the general public; the protection offered by the toxoid lasts only several months.

**Plague**

*Yersinia pestis* is well known for its infamous pandemics in Eurasia and Northern Africa. Although these pandemics caused bubonic plague via an infected flea bite, plague aerosolization will cause pneumonic plague. After several days of incubation, patients develop fever, a productive cough, hemoptysis, dyspnea, stridor, and bilateral infiltrates on chest x-ray. Nausea, vomiting, abdominal pain, and diarrhea may accompany the aforementioned symptoms. Patients could progress to systemic toxicity, leading to high mortality. Confirmatory laboratory tests include antigen detection, IgM immunoassay, PCR, immunostaining, “safety pin” appearance of the bacteria on gram stain, and cultures of sputum, blood, and/or lymph nodes.

Streptomycin and doxycycline are the gold standard for the treatment of plague. Given emerging bacterial resistance and streptomycin’s limited availability, fluoroquinolones are viable alternatives. Like tularemia, parenteral antibiotics are recommended in a contained outbreak, while oral antibiotics are more practical in a mass incidence. Prophylactic antibiotics are given to individuals who develop a fever, new cough, or tachycardia in the context of a possible plague bioweapon attack. Since 1999, no vaccine has existed for *Yersinia*.}

![Downloaded from oto.sagepub.com at SOCIIDADE BRASILEIRA DE CIRUR on August 5, 2014](https://example.com)
Hemorrhagic Fever

Viral hemorrhagic fever (VHF) is caused by RNA viruses that are traditionally transmitted to humans via infected arthropods or animals. Potential weaponizable viruses are filoviridae (Ebola, Marburg) and arenaviridae (Lassa fever, New World arenaviruses). Although disease presentation varies depending on the virus, they all carry a risk for a bleeding diathesis. Viral hemorrhagic fever is a febrile illness that starts with nonspecific symptoms of malaise and prostration that can progress to cutaneous (variable maculopapular rash), gastrointestinal (anorexia, vomiting, abdominal pain, diarrhea), respiratory (chest pain, shortness of breath, cough, nasal discharge), vascular (conjunctival injection, postural hypotension, edema), and neurological (headache, confusion, coma) manifestations. Although bleeding is not severe until the late stages, it is reflective of end-organ vascular damage. Hemorrhagic symptoms observed during the peak of the illness include petechiae, ecchymoses, epistaxis, mucosal hemorrhages, and/or visceral hemorrhagic effusions.

Diagnosis is primarily made by clinical suspicion. Patients presenting early with nonspecific symptoms are often misdiagnosed with malaria, typhoid, or shigellosis. However, a febrile illness with obvious vascular involvement points to VHF. Enzyme-linked immunosorbent assay and PCR are helpful, and if viral cultures of specimens are requested, the turnaround time is 3 to 10 days.

Due to VHF’s sporadic presentations in humans, the development of vaccines and treatment options have been in animal models. Except for the yellow fever vaccine, vaccines and therapeutic agents are not available. Treatment is primarily supportive care. Patients should be monitored for hypovolemic shock, which is often fatal if left untreated. Fresh-frozen plasma, clotting factors, and platelets are viable options to control hemorrhages. Recent studies have shown that ribavirin is effective against arenaviruses but is not approved for pregnant patients or children. Ribavirin is also not recommended for prophylactic treatment of asymptomatic contacts.

Implications for Practice

The key to identifying a victim of a bioterrorism attack is clinical suspicion. Not only does the clinician need to rely on patient history, but he or she must also know the significance of current events. The clustering of rare diseases, unusual antibiotic resistance, and an increase in number of previously healthy patients contracting illnesses are key indicators. Public authorities must be notified immediately, and the infectious disease team can play an integral role in the diagnosis and treatment of the bioterror diseases. The otolaryngologist should keep in mind several clinical pearls that can aid in the diagnosis and treatment of a bioterrorism victim (Supplemental Table S1, available at otojournal.org):

- In general, doxycycline and ciprofloxacin are good choices for plague, tularemia, and anthrax.

- Obtaining cultures are important not merely for the diagnosis but also to confirm the correct choice of antibiotics as the bioweapon will likely have been engineered to have some antibiotic resistance.

- The smallpox rash is classic and should be distinguishable from chickenpox.

- The diagnosis of botulism relies on a nonfebrile patient with flaccid paralysis and the 4 “Ds”—diplopia, dysphonia, dysarthria, and dysphagia.

- Pneumonic plague is unique since it is the only bioweapon pneumonia (plague, tularemia, anthrax) that presents with hemoptysis.

- Inhalational anthrax and pneumonic plague will present more acutely than tularemia pneumonia.

- A bioweapon attack may masquerade as acute pharyngitis or its complications. If patients do not improve with traditional therapy and the clinical picture decompensates, the otolaryngologist should have a lower threshold in expanding the differential to include oropharyngeal anthrax, oropharyngeal tularemia, and plague pharyngitis.

- Viral hemorrhagic fever should be suspected if groups of patients present with a febrile illness and acute vascular involvement. Treatment for VHF is supportive, and invasive procedures should be minimal.

Author Contributions

Philip E. Zapanta, conception and design, acquisition/interpretation of data, drafting and revising the manuscript, final approval; Saba Ghorab, acquisition/interpretation of data, revising manuscript, final approval.

Disclosures

Competing interests: None.

Sponsorships: None.

Funding source: None.

Supplemental Material

Additional supporting information may be found at www.otojournal.org/supplemental.

References


