Bioterrorism And The Emergency Physician: On the Front Lines

“...and he that will not apply new remedies must expect new ills; for time is the greatest innovator...” —Sir Francis Bacon, “The Essays,” 1601

September 20, 2002, 7:40 p.m.: A 32-year-old white male presents with “the flu.” This is the second case of flu-like illness you’ve seen tonight. The patient complains of sudden-onset diffuse myalgias and chills. His physical examination is unremarkable aside from a temperature of 102.4°F. No runny nose or sneezing, but he does complain of some shortness of breath. Seems strange to see flu this time of year. Laboratory and radiological examinations are all unremarkable. I guess it’s just an “off-season” viral illness. Motrin and Tylenol should be all he needs.

September 23, 2002, 5:30 p.m.: This flu epidemic is getting out of hand—the ED is swamped. Now, EMS brings in a patient with severe respiratory distress. As you prepare to intubate him, your stomach tightens in a sickening knot; it’s the same “32-year-old white male” you saw three days before. Now, he presents with massive hemoptysis and shock. He gets it all: intubation, crystalloids, pressors, and broad-spectrum antibiotics. Two hours later, he’s dead. This lethal pattern repeats itself throughout the shift, again, and again, and again…

In domestic warfare, the casualties are no longer on a battlefield. Because terrorist attacks using aerosolized biological agents can occur without warning, the first sign of such an attack might be hundreds or thousands of ill or dying patients. The front-line responders in a biological weapons attack are members of the healthcare community.

Emergency medicine will play a leading role in disaster response, training first responders, and the initial care of patients. In the anthrax attacks of late 2001, nine of the 11 patients with inhalational anthrax initially presented to EDs, while the other two eventually sought care in the ED as their illness progressed. The emergency physician is uniquely poised to detect the outbreak, identify the pathogen, and alert the public poised to detect the outbreak, identify the pathogen, and alert the public...
health community.

A bioterror event raises a unique set of questions:

• Is this incident really due to bioterrorism?
• Who should be notified?
• What resources are available to assist in this crisis?
• How do I diagnose and treat diseases I have never seen before?
• Do these patients need to be decontaminated, isolated, or quarantined?
• What can be done to protect the hospital staff from potential exposure?
• How should we handle the psychological consequences of exposure or potential exposure?
• Am I safe?

This issue of Emergency Medicine Practice provides answers to these and other pressing questions.

Critical Appraisal Of The Literature

“In the arts of life, man invents nothing; but in the arts of death, he outdoes Nature herself, and produces by chemistry and machinery all the slaughter of plague, pestilence, and famine.”
—George Bernard Shaw (1856–1950), Anglo-Irish playwright, critic.
The Devil, in Man and Superman, act 3.

For most potential bioterrorist agents, there is a notable lack of evidence in the scientific literature. Many of these diseases have been functionally eradicated in the developed world, and their alien characteristic makes them even more dangerous. In other instances, outbreaks of these pathogens involve a handful of cases seen in faraway lands, perhaps decades ago. Because there is so little evidence on which to base medical decisions regarding bioterrorist agents, public health experts have formed consensus-based guidelines. These guidelines and references to other information may be found at http://www.bt.cdc.gov/.

Epidemiology Of A Bioterrorist Attack

History Of Biological Warfare

The concept of using naturally occurring organisms as a weapon is not new. Indeed, history has documented numerous instances of biological warfare. (See Table 1.) Only recently have we come to realize the lasting effects of some of these agents. During World War II, to compete with German and Japanese bio-weapons research, the British used anthrax to infect a herd of sheep on Gruinard Island, off the coast of Scotland. The island, now referred to as “Anthrax Island,” remained contaminated with the lethal spores for decades. A military report on this experiment suggested that anthrax could render cities uninhabitable “for generations.”

The latter portion of the 20th century is termed the “modern era” of biological warfare. During this period, nation-states developed biological weapons for use on a traditional battlefield. Even after the ratification of the Biological Weapons Convention of 1972, the most impressive bio-weapons program in the history of mankind continued for 20 years—cloaked in secrecy in the former Soviet Union. This program may never be surpassed in scale or offensive capability.

With the Soviet economic implosion of the 1990s, concern turned to the fate of tens of thousands of unemployed Russian scientists and engineers who previously worked in the bio-weapons program. Fear

Table 1. Historical Bioterrorism Events.

<table>
<thead>
<tr>
<th>Year</th>
<th>Incident</th>
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<tbody>
<tr>
<td>400 B.C.</td>
<td>Scythian archers use arrows dipped in blood, manure, or decomposing bodies</td>
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<tr>
<td>190 B.C.</td>
<td>Hannibal hurl venomous snakes onto enemy ships</td>
</tr>
<tr>
<td>1346</td>
<td>Mongols hurl plague-infected corpses over enemy walls</td>
</tr>
<tr>
<td>1405</td>
<td>The Spanish contaminate wine drunk by French soldiers with blood of leprosy patients</td>
</tr>
<tr>
<td>1650</td>
<td>Polish soldiers place saliva from rabid dogs into hollow shell casings</td>
</tr>
<tr>
<td>1710</td>
<td>Russians invading Estonia hurl plague-infected corpses over enemy walls</td>
</tr>
<tr>
<td>1763</td>
<td>British officers give blankets used by smallpox victims to American Indians in Pennsylvania, resulting in a devastating smallpox outbreak</td>
</tr>
<tr>
<td>1860s</td>
<td>Confederate sympathizers during the American Civil War attempt to ship garments and bedding used by yellow fever victims to New York</td>
</tr>
<tr>
<td>1863</td>
<td>Confederate soldiers during the American Civil War leave dead animals in wells and ponds to contaminate Union soldiers’ water supply</td>
</tr>
</tbody>
</table>

grew that weak nations or terrorist organizations might use jobless bio-engineers to build their “great equalizer.”

In response, the United States redirected millions of dollars toward domestic preparedness. Similarly, the emergency medicine community recognized that it might be faced with the consequences of a biological weapons attack—that EDs would become the “front line” in such a conflict. In the wake of 9/11, emergency planners anxiously began to review disaster plans and prepare for bioterrorism.

Incidents involving biological weapons during the latter half of the 20th century were rare. The Monterey Database, which tracks chemical, biologic, and nuclear attacks worldwide, noted that there were only 66 criminal events and 55 terrorist events involving biologic agents over the 40-year period from 1960 to 1999. Most attacks were small and fatalities few.

This changed in October 2001. The United States was attacked through its postal system, and to date, seven cases of cutaneous anthrax and 11 cases of inhalational anthrax have been confirmed, with five fatalities. Thousands of other potentially exposed individuals were provided with antibiotics.

**Awareness And Recognition: Making The Diagnosis**

Attacks may be either overt (announced) or covert (unannounced). In either case, awareness of the event is the first step in incident management. Overt attacks require rapid assessment of the veracity of the claim and then an appropriate and measured response as indicated. A covert attack will be recognized only after victims present for medical care—after the incubation period has passed and clinical signs become manifest.

Kaufmann et al have published an economic model of a large-scale anthrax attack demonstrating that rapid implementation of a post-attack prophylaxis program is the single most important means of reducing losses following a bioterrorist attack. Pivotal to the implementation of post-attack measures is identification of the agent and the attack. However, before the diagnosis or identification can be made, an astute clinician must think outside the routine differentials. We must consider emerging infectious disease and biological terrorism. The attack may be a hoax, a small foodborne outbreak, a lethal aerosol cloud moving silently through a city at night, or the reintroduction of smallpox. Emergency physicians who think like epidemiologists, understand terror pathogens, and are familiar with the diagnostic and treatment options can mitigate the attack.

Making the index diagnosis in a bioterrorism event might be a long shot, but the chances are increasing in this new era. With each missed diagnosis, more people will become ill or die. As emergency physicians, we must add the exotic and nefarious to our differential diagnosis.

**Unique Challenges Of Bio-weapons: Conventional vs. Chemical vs. Biological Attacks**

The results of a biological attack differ from the destruction seen with conventional explosives or with chemical weapons. (See Table 2.) Biologic weapons can be deadly, inexpensive to manufacture, and produce contagion and growing fear as the epidemic spreads. The cost to affect a square kilometer with a biological weapon is approximately $1, compared to $2000 using a conventional weapon. Dispersal agents may involve water, food, crop dusters, and even the U.S. mail. A piece of fruit could become a weapon of terror if sprayed with a potent agent. Biological weapons are easily smuggled and weigh 105-106 times less than chemical weapons of the same “yield” in regard to the number of casualties.

Biological weapons can cause syndromes nearly indistinguishable from naturally occurring illnesses, and patients might not become ill until well after exposure. For these reasons, the HAZMAT model rarely applies to bioterrorism. In contrast to chemical warfare, victims of biological weapons initially might be encountered in the ED rather than the street. The first victims may fall ill days to weeks after an attack. Even then the diagnosis may be delayed, allowing time for hundreds or even thousands of people to become infected before prophylactic measures are instituted. Containment of the outbreak is difficult, and decontamination (other than removal of clothing, plus soap-and-water removal of dermal debris) usually is not helpful. During the resultant disease outbreak following a biological attack, isolation and quarantine—concepts that are rarely necessary with chemical weapons—may be necessary. Because of the insidious nature of these attacks, public fear can be more pervasive than in an attack by conventional weapons with a similar number of casualties.

**Table 2. Comparison Of Weapons: Conventional vs. Chemical vs. Biological.**

<table>
<thead>
<tr>
<th></th>
<th>Conventional</th>
<th>Chemical</th>
<th>Biological</th>
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<tbody>
<tr>
<td>Onset of illness</td>
<td>Instantaneous</td>
<td>Rapid</td>
<td>Often delayed</td>
</tr>
<tr>
<td>Exposure source</td>
<td>Obvious</td>
<td>Obvious</td>
<td>Often covert</td>
</tr>
<tr>
<td>Mimics naturally occurring illness</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>First victim encounter</td>
<td>Prehospital</td>
<td>Prehospital</td>
<td>Hospital</td>
</tr>
<tr>
<td>Containment</td>
<td>Easy</td>
<td>Relatively easy</td>
<td>Difficult</td>
</tr>
<tr>
<td>Decontamination helpful</td>
<td>Usually not</td>
<td>Yes</td>
<td>Usually not</td>
</tr>
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</table>
**General Principles**

While each biological agent requires different diagnostic and treatment approaches, certain principles apply to all bioterror incidents.

**Planning**

The best time to plan a response to a mass casualty disaster is weeks, months, or years before it happens. Disaster drills that specifically address a bio-weapons attack are especially useful. The Association for Professionals in Infection Control and Epidemiology (APIC) and the Centers for Disease Control and Prevention (CDC) have published a document to help prepare hospitals for such events. This electronic publication, titled “Bioterrorism Readiness Plan: A Template for Healthcare Facilities,” is available at: http://bioterrorism.slu.edu/key_references/BioPlan.doc.9

Facilities need to ensure a proper chain of command, adequate communications, efficient triage procedures, and the ability to provide more doctors, nurses, and ancillary staff on short notice. During the planning stage, hospitals should determine whether they have adequate medications—for both patients and staff—in the event of a biological attack. This would include vaccines, immunoglobulins, antitoxins, antibiotics, and antidotes. Sufficient amounts of personal protective gear are also important. Information sheets regarding the various agents and instructions on when to seek medical care are useful as patient handouts.

A disaster-planning book located in the ED should identify who plays what role in the event of a mass casualty incident. A separate chapter on bioterrorism will be invaluable in a time of crisis.

**Patient Triage, Placement, And Precautions**

As in any disaster, efficient triage is essential in managing large numbers of patients. One of the most emotionally straining triage principles in a disaster is that of “the greatest good for the greatest number.” This means that in a mass casualty incident, the moribund patient may receive only palliative care, while critical care resources are reserved for those with a better chance of surviving. In a large-scale disaster, it will also be essential to distinguish the “walking worried” from the truly symptomatic.

Precautions to prevent transmission depend on the particular biologic agent. Some agents, like anthrax, have minimal or no potential for human-to-human transmission. Handwashing should be routine for all patients, while gloves, face protection, and gowns should be utilized if procedures or healthcare activities will cause contact with blood, body fluids, excretions, or secretions.9

For more transmissible diseases (such as smallpox and pneumonic plague), quarantine and a negative pressure room may be necessary to reduce the likelihood for transmission. (Infection control measures are described in further detail later in the text.)

Bioterrorism will also require different interactions with the laboratory and pathology department. Some clinical specimens may be highly infectious and require special handling and processing by a state or regional laboratory. The most dangerous specimens (such as those possibly contaminated with smallpox or Ebola) must be processed in a special Bio-Safety Laboratory (also known as the “Hot Zone”). These Bio-Safety Level (BSL) 4 labs are located at the CDC and at the United States Army Medical Research Institute of Infectious Diseases (USAMRIID).

Remember the risk posed by casualties. The recently deceased may be teeming with infectious organisms, and the pathology department and/or funeral homes should be warned if certain high-risk diseases, such as Ebola, are suspected so that special protective measures may be implemented through the assistance of the CDC.

**Decontamination, Prophylaxis, And Immunization**

Unless the patient is grossly contaminated with a biological weapon, decontamination usually is not necessary. If patients are directly exposed to a powder or spray, they should remove contaminated clothing, place them in an impervious bag, and immediately shower with soap and water. Patients should not be doused in bleach or solvents. Irrigate eyes in the usual manner with water or saline. While the subsections below discuss postexposure management, local health departments can provide additional details regarding decontamination procedures.

Postexposure prophylaxis and immunization depend on the agent, type of exposure, and the patient’s clinical status. Clear guidelines regarding who needs prophylaxis will assist both patients and physicians in avoiding adverse drug events and conserving valuable resources. Some well-prepared hospitals print an information sheet for patients who want but do not receive prophylaxis; this explains why they do not need antibiotics or vaccines and under what circumstances they should return to the ED.

**Differential Diagnosis**

**Syndrome Recognition**

In theory, any biological agent could be used as a terrorist weapon; therefore, it is important to think “epidemiologically” and recognize disease patterns as possible bioterrorist attacks. For example, one case of rapidly progressive influenza-like illness may not herald a bioterrorist attack, but multiple patients with an unusual syndrome of influenza-like illness should raise the suspicion for bioterrorism. Most bioterrorist agents initially induce an influenza-like prodrome, including fever, chills, myalgias, or malaise. One or more of four syndromic patterns then follow the nonspecific prodrome:

- Rapidly progressive pneumonia
- Fever with rash
- Fever with altered mental status
- Bloody diarrhea
When outbreaks of any of these syndromic disease patterns are identified, suspect bioterrorism. (See Table 3.) The CDC has issued a list of high-likelihood potential bioterrorist agents. They are prioritized according to ease of dissemination, transmissibility, mortality, public health impact, potential to cause fear and social disruption, and need for special preparedness. Category A agents are most likely to cause mass casualties if deliberately disseminated as small-particle aerosols and require broad-based public health preparedness. These agents, therefore, are seen as a priority for preparation and training. This article discusses the epidemiology, pathophysiology, evaluation, and management of these diseases.

**Anthrax**

"The explosion of anthrax bombs is hardly louder than the popping of a paper bag."
—Aldous Huxley, in "Brave New World," 1932

**Epidemiology**

For centuries, anthrax has infected animals and occasionally humans throughout the world. *Bacillus anthracis*, the causative organism of anthrax, is a gram-positive spore-forming bacillus that is naturally found in the soil and is distributed worldwide. The hardy spores formed by the bacterium can survive harsh environmental conditions and remain viable for decades—perhaps even centuries. When exposed to a nurturing environment such as a host animal or human, the vegetative bacillus develops from the spore. Animals such as sheep, cattle, goats, and horses acquire the bacillus spore while grazing. In the natural environment, humans acquire the disease via inoculation of minor skin lesions from contact with infected animals, their hides, wool, or other products. Other vectors include ingesting contaminated meat, inhaling spores during the processing of wool, and possibly flies that bite. The drastic reduction in anthrax in the developed world has been attributed to aggressive animal vaccination programs.

Anthrax can be "weaponized" by milling spores to 1-5 micron size. These small spores remain aerosolized for long periods of time (and are also small enough to leach through the 20-micron pores that may be found in envelopes). Other weaponized features may include greater virulence or antibiotic resistance. The strain responsible for the most recent outbreak, the Ames strain, is noted for its high toxin production. The strain dates back to a 1981 anthrax-infected Texas cow, bacteria from which were studied by USAMRIID.

Anthrax infection in humans manifests in three forms: cutaneous, gastrointestinal, and inhalational. The cutaneous form is by far the most common. Between 1944 and 1994, 224 cases of cutaneous anthrax were reported in the United States. Gastrointestinal anthrax is rare, and outbreaks are usually associated with the ingestion of contaminated, undercooked meat. Prior to October 4, 2001, the last known case of inhalational anthrax in the United States was in 1978. The accidental release in 1979 of aerosolized anthrax spores by a military microbiology laboratory in Sverdlovsk, a city of the former Soviet Union, resulted in 79 cases of anthrax infection and 68 deaths, mostly attributable to inhalational infection. Since the catastrophe at Sverdlovsk, there were no deaths reported from cutaneous disease alone.

**Pathophysiology**

Anthrax infection begins when spores are introduced through a break in the skin (cutaneous anthrax), the

<table>
<thead>
<tr>
<th>Table 3. Distinguishing A Natural Disease Outbreak From A Bioterrorist Attack.</th>
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<tbody>
<tr>
<td><strong>Natural outbreak</strong></td>
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<tr>
<td>Gradual presentation of victims with no readily identifiable common exposure</td>
</tr>
<tr>
<td>Cases present at varying stages of disease progression</td>
</tr>
<tr>
<td>Usual expected disease course for that specific pathogen, with appropriate response to standard therapy</td>
</tr>
<tr>
<td>Slowly progressive disease with prodromal symptoms (e.g., natural progression of bubonic plague to pneumatic plague)</td>
</tr>
<tr>
<td>Normal antibiotic sensitivities</td>
</tr>
<tr>
<td>No announcement of attack</td>
</tr>
<tr>
<td>Presentation of common illnesses (such as influenza)</td>
</tr>
<tr>
<td>Presentation of disease in the usual geographic area during the usual transmission season</td>
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</table>
mucosa (gastrointestinal anthrax), or through deposition in alveolar spaces with subsequent lymphatic transport to mediastinal lymph nodes (inhalational anthrax). After germinating, anthrax produces a variety of toxins, two of which are suitably termed edema factor and lethal factor. These toxins perform their noxious duties even if antibiotics kill all of the bacteria.

The cutaneous form is characterized by a pruritic macule or papule that progresses to a round ulcer within 48 hours. The central lesion may have a superimposed vesicle up to 2 cm in diameter and is often surrounded by smaller satellite vesicles that contain serosanguineous fluid laden with gram-positive bacilli. (See Figure 1.) The lesion then develops a painless, depressed black eschar. (The Greek derivation of the word “anthrax” is “charcoal” or “coal,” referring to this characteristic lesion.) The eschar dries, loosens, and falls off within 1-2 weeks, leaving little if any scar.

Localized edema, erythema, and lymphadenopathy are important clues to the diagnosis. Without antibiotic therapy, cutaneous anthrax can lead to bacteremia, with mortality rates as high as 20%. With antibiotics, death due to cutaneous anthrax is rare. Recognition of cutaneous anthrax infection is important because its presence indicates exposure to anthrax spores and could possibly herald other cases of the more serious inhalational anthrax. The differential diagnosis of cutaneous anthrax includes furuncles (usually painful), ecthyma (usually without edema or systemic signs), ecthyma gangrenosum (usually in neutropenic patients), and brown recluse spider bite (painful necrotic lesion). Another unusual possibility is orf, or ecthyma contagiosum, a viral zoonosis of sheep and goats, in which gelatinous edema is rare and the scab forms without eschar.

Gastrointestinal anthrax symptoms (nausea, vomiting, fever, and abdominal pain) appear 2-5 days after the ingestion of vegetative bacilli (usually in undercooked meat). The disease progresses rapidly to bloody diarrhea, with ulceration of the gastrointestinal tract, hemorrhagic

<table>
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<th>Table 4. Critical Biological Agents.</th>
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<tr>
<td><strong>Category A</strong> High-priority agents include organisms that pose a risk to national security because they can be easily disseminated or transmitted person-to-person; cause high mortality, with potential for major public health impact; might cause public panic and social disruption; and require special action for public health preparedness.</td>
</tr>
<tr>
<td>- Variola major (smallpox)</td>
</tr>
<tr>
<td>- Bacillus anthracis (anthrax)</td>
</tr>
<tr>
<td>- Yersinia pestis (plague)</td>
</tr>
<tr>
<td>- Clostridium botulinum toxin (botulism)</td>
</tr>
<tr>
<td>- Francisella tularensis (tularemia)</td>
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<tr>
<td>- Viral hemorrhagic fevers</td>
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<tr>
<td>- Filoviruses</td>
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<td>- Ebola virus (Ebola hemorrhagic fever)</td>
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<tr>
<td>- Marburg virus (Marburg hemorrhagic fever)</td>
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<tr>
<td>- Arenaviruses</td>
</tr>
<tr>
<td>- Lassa fever virus (Lassa fever)</td>
</tr>
<tr>
<td>- Junin virus (Argentine hemorrhagic fever) and related viruses</td>
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</table>

Category B
Second-highest-priority agents include those that are moderately easy to disseminate; cause moderate morbidity and low mortality; and require specific enhancements of the CDC’s diagnostic capacity and enhanced disease surveillance.

- Coxiella burnetii (Q fever) |
- Brucella species (brucellosis) |
- Burkholderia mallei (glanders) |
- Alpha viruses |
- VEE virus (Venezuelan encephalomyelitis) |
- EEE and WEE viruses (Eastern and Western equine encephalomyelitis) |
- Ricin toxin from Ricinus communis (castor beans) |
- Epsilon toxin of Clostridium perfringens |
- Staphylococcus enterotoxin B

A subset of Category B agents includes pathogens that are food- or waterborne. These pathogens include but are not limited to:

- Salmonella species |
- Shigella dysenteriae |
- Escherichia coli 0157:H7 |
- Vibrio cholerae |
- Cryptosporidium parvum

Category C
Third-highest-priority agents include emerging pathogens that could be engineered for mass dissemination in the future because of availability; ease of production and dissemination; and potential for high morbidity and mortality and major health impact.

- Nipah virus |
- Hanta viruses |
- Tickborne hemorrhagic fever viruses |
- Tickborne encephalitis viruses |
- Yellow fever |
- Multidrug-resistant tuberculosis

mesenteric lymphadenitis, and formation of marked ascites. Mortality can be greater than 50%.\textsuperscript{19,23}

Classic inhalational anthrax is a biphasic illness. After up to six days of incubation, the first phase appears as a nonspecific, flu-like illness characterized by mild fever, malaise, myalgias, nonproductive cough, and occasional chest or abdominal pain. Rhinorrhea and nasal congestion usually are \textit{not} associated with inhalational anthrax. Such symptoms suggest an etiology other than anthrax in patients presenting with influenza-like disease.\textsuperscript{24-26} (See Table 5.) Shortness of breath appears to be common in anthrax but unusual in influenza and influenza-like illness.\textsuperscript{2} The second phase of the illness appears 2-3 days later and is characterized by the abrupt onset of high fever, dyspnea, chest or abdominal pain, diaphoresis, cyanosis, and shock. The recent inhalational cases in the United States have manifested with sweats and gastrointestinal symptoms.\textsuperscript{5,27-29} Hemorrhagic meningitis and altered mental status may be seen in up to 50% of cases as the disease progresses to the central nervous system.\textsuperscript{30,31} Death occurs within 24-36 hours. The case-fatality estimates for inhalational anthrax are based on incomplete information; however, the mortality is approximately 75%, even with aggressive care including antibiotics.\textsuperscript{2}

**ED Evaluation**

With the possible exception of Gram’s stain and culture, most readily available laboratory tests are \textit{not} helpful in the diagnosis of anthrax. While a complete blood count and chemistry panel may show hemoconcentration or leukocytosis, such findings are clearly nonspecific. Gram’s stain and culture of fluid from cutaneous vesicles, blood, or cerebrospinal fluid will often show gram-positive bacilli, which grow in bamboo-like chains. (See Figure 2.) Blood cultures may become positive in as few as 14 hours.\textsuperscript{32}

Viral testing is generally unhelpful. While point-of-care rapid influenza tests may occasionally help differentiate influenza from other influenza-like illnesses, the sensitivity of the rapid influenza tests is relatively low (45%-90%). A negative test does not add any diagnostic certainty, and a positive test could occur in someone unfortunate enough to have both influenza and anthrax (a situation that could occur during the flu season, when as many as one-quarter of the population could test positive). Because viral culture results are not immediately available, they are not generally useful in the ED setting.

In asymptomatic patients with suspected exposure to

\begin{table}[h]
\centering
\begin{tabular}{|l|l|l|}
\hline
Sign or symptom & Anthrax & Influenza or other influenza-like illness \\
\hline
Fever or chills & ++++ & +++ \\
\hline
Fatigue or malaise & ++++ & ++++ \\
\hline
Cough & ++++ & +++ \\
\hline
Shortness of breath & ++++ & 0 \\
\hline
Chest discomfort or pleuritic chest pain & +++ & + \\
\hline
Headache & ++ & ++++ \\
\hline
Myalgias & ++ & ++++ \\
\hline
Sore throat & 0 & ++++ \\
\hline
Rhinorrhea & 0 & ++++ \\
\hline
Nausea or vomiting & ++++ & + \\
\hline
Abdominal pain & + & + \\
\hline
\end{tabular}
\caption{Distinguishing Inhalational Anthrax From Influenza.}
\end{table}

Inhalational anthrax, public health authorities have used nasal swab culture as an epidemiologic screening tool to confirm exposure to \( B. \) anthracis. The predictive value of this tool is not known and, at present, the CDC does not recommend the routine use of nasal swab culture to rule out infection with \( B. \) anthracis.\(^{33}\)

Chest radiography in patients with inhalational anthrax often exhibits mediastinal widening, occasional infiltrates, and pleural effusion. (See Figure 3.) All patients in the recent bioterror event had mediastinal abnormalities early in the course of the illness. In contrast, most cases of influenza-like illness are not associated with chest radiographic abnormalities. Computed tomography (CT) of the chest should strongly be considered in any patient with influenza-like illness who presents with mediastinal abnormalities or pleural effusions.\(^{34-36}\) CT of the chest in cases of inhalational anthrax was first reported with the outbreak of October 2001 and seems to be an important diagnostic tool. Findings included prominent mediastinal lymphadenopathy, pleural effusion, mediastinal edema, and basilar air space disease.\(^{27-30}\) (See Figure 4.) With the development of hemorrhagic meningitis, contrast-enhanced CT of the head may show diffuse meningeal enhancement.\(^{37,38}\)

**Treatment And Prophylaxis**

In any suspected case of inhalational anthrax or in cases of cutaneous anthrax with signs of systemic involvement, extensive edema, or head and neck lesions, *intravenous* multidrug antimicrobial therapy should be started immediately. Based on animal and in vitro studies, the recommended agents include ciprofloxacin 400 mg every 12 hours or doxycycline 100 mg every 12 hours plus one of the following drugs: rifampin, vancomycin, penicillin, ampicillin, chloramphenicol, imipenem, clindamycin, or clarithromycin. For uncomplicated cases of cutaneous anthrax that do not involve the head or neck, the CDC suggests that *oral* ciprofloxacin 500 mg every 12 hours or doxycycline 100 mg every 12 hours alone is sufficient therapy.\(^{33}\)

To date, there are no controlled human trials that validate current treatment recommendations for inhalational anthrax. The clinical experience is likewise limited. Studies in monkeys show that death may occur up to 58 days after inhalation of anthrax spores, hence the origin for the recommendation that antibiotic prophylaxis for inhalational exposure should be continued for 60 days.\(^{39}\) This concept of prolonged prophylaxis is supported by the Sverdlovsk inhalational anthrax outbreak, where all cases occurred within six weeks of the release of the spores.\(^{20,31}\)

Promptly initiate prophylactic therapy for patients with confirmed exposure to \( B. \) anthracis. The CDC recommends that, as with uncomplicated cutaneous anthrax, oral ciprofloxacin 500 mg every 12 hours or doxycycline 100 mg every 12 hours is sufficient prophylactic therapy.\(^{40}\) Children or breastfeeding mothers may take amoxicillin at the appropriate dosage for prophylaxis only, but confirmed cases should be treated with ciprofloxacin or doxycycline and the other antibiotic despite their known adverse effects in children.\(^{41}\) In any suspected or confirmed exposure to anthrax, public health authorities should be notified and involved in case management.

**Figure 3.** Chest radiography of a patient with inhalational anthrax, demonstrating a widened mediastinum.

Source: Centers for Disease Control and Prevention.

**Figure 4.** Chest computed tomography of a patient with inhalational anthrax, demonstrating hemorrhagic mediastinal lymphadenopathy.

management in order to assist with epidemiologic investigation. At present, there is no vaccine for B. anthracis available to the public. The U.S. government maintains a limited supply of a licensed anthrax vaccine for use by at-risk military personnel.

Because toxins released from the bacteria cause the major complications of systemic anthrax, corticosteroid therapy may be of some benefit in treating cases of inhalational anthrax.42,43 However, no empirical data regarding this intervention are available.

Infection Control
Anthrax is not transmissible through person-to-person contact, and private rooms are unnecessary. Universal precautions are generally sufficient to protect contacts from exposure to the disease. Decontamination with a soap-and-water bath is sufficient for gross exposures.

Smallpox

“The small pox was always present, filling the church-yards with corpses, tormenting with constant fears all whom it had not yet stricken, leaving on those whose lives it spared the hideous traces of its power, turning the babe into a changeling at which the mother shuddered, and making the eyes and cheeks of the betrothed maiden objects of horror to the lover.”
—Thomas Babington Macaulay, in “History of England,” 1848

Epidemiology

The last known naturally occurring case of smallpox was in Somalia in 1977. After a monumental vaccination campaign, in 1980 the World Health Organization (WHO) declared smallpox officially eradicated.45,46 There is no natural animal reservoir or vector for variola, the virus responsible for smallpox infection. Variola virus is considered a potential biological weapon threat because of its aerosol infectivity, high mortality, transmissibility, and relative stability in the environment. Further, there are reports of efforts by the former Soviet Union to mass-produce the virus and adapt it for use as a bio-weapon.47 Some experts fear that some nations retained stocks of the variola virus instead of placing them in the WHO repositories as requested in the late 1970s. The reintroduction of smallpox would no doubt lead to deadly epidemics. During the 1960s and 1970s in Europe, as many as 10-20 second-generation cases were often reported as infected from an index case.45,46 During the 20th century, smallpox infection was associated with a 1% mortality rate in the vaccinated and a 30% mortality rate in the unvaccinated.45

Smallpox is spread from person to person primarily via airborne particles and direct contact. Contaminated clothing and bed linens also spread the virus.45,46

Pathophysiology

Infection occurs through direct contact with mucous membranes or through aerosol exposure. When inhaled, the virus travels from the respiratory tract to regional lymph nodes, where it replicates after an incubation period of 7-17 days. The resulting viremia causes a prodrome characterized by high fever, malaise, vomiting, headache, and myalgias. Two to three days later, a characteristic macular rash erupts about the face, hands, and forearms. As the rash spreads across the body, the macules morph into papules and eventually to pustular vesicles. (See Figure 5.) Lesions are most prominent about the extremities and face and tend to develop synchronously, a characteristic that aids in discriminating variola infection from varicella infection, as chickenpox tends to show lesions in various stages of evolution. By the time the rash occurs, patients are usually toxic-appearing. Within 7-10 days, the rash begins to form scabs (if the patient lives that long), leaving depressed, depigmented scars. Scabs contain readily recoverable virus throughout the entire healing period; therefore, all patients should be considered infectious until all scabs are shed.51

ED Evaluation

There is no widely available laboratory test to confirm smallpox infection; therefore, clinical presentation is the key to early diagnosis. The presence of a centrifugal, synchronous rash in the appropriate clinical setting suggests the diagnosis of smallpox.

In the first several days of the rash, it may be impossible to distinguish between smallpox and chickenpox. However, smallpox lesions are “deep,” develop at the same pace, and rapidly diffuse. In contrast, chickenpox lesions are superficial, appear in various stages of evolution, and develop in crops. Chickenpox is more dense over the trunk instead of the extremities (as in the case of smallpox)—and, unlike smallpox, chickenpox lesions almost never appear on the palms or soles.52

Because the discovery of even a single case of smallpox is an international emergency, it is imperative to involve public health officials early when the diagnosis is suspected. (Re-read the section on distinguishing smallpox from chickenpox before calling the President.)

Figure 5. Pustular rash of smallpox.

Source: Centers for Disease Control and Prevention.
In this instance, the patient must be placed in isolation and held, even if against his or her will, until public health authorities complete their assessment. Electron microscopy can confirm the presence of smallpox virions. Definitive techniques such as cell culture and nucleic-acid based diagnostic techniques can also be used to identify variola virus, but currently they are neither widely nor rapidly available in the ED setting.\(^{53,54}\) Sampling of pustular fluid should be performed only by people who are recently vaccinated against smallpox, and samples are to be handled by a Bio-Safety Level 4 (BSL-4) laboratory.

**Prophylaxis And Treatment**

Although animal trials with cidofovir are promising, there is currently no treatment for smallpox.\(^{55}\)

In the United States, routine smallpox vaccination ceased in 1972. The immune status for those vaccinated before 1972 is unclear. A limited emergency supply of smallpox vaccine and vaccinia immune globulin (VIG) is under the control of the CDC. Efforts to increase the national stockpile of smallpox vaccine are under way.

**Infection Control**

Smallpox is extremely infectious. Diagnosis of smallpox requires immediate respiratory isolation of the patient. Place a mask on the patient when he or she is being transported and even while he or she is in the treatment room. All healthcare providers who enter the room must be gowned and wear a National Institute for Occupational Safety and Health (NIOSH) particulate respirator (N95). The gown must be removed before leaving the patient’s room. All household and face-to-face contacts should be vaccinated and placed under surveillance. Because smallpox is rapidly spread via aerosol transmission, it poses a particular threat in hospitals that have a limited number of negative pressure isolation facilities. Given the serious nature of this disease, home care and quarantine are a likely and reasonable alternative to inpatient hospital treatment, especially in a mass casualty instance.

**Plague**

“At the onset of the disease both men and women were afflicted by a sort of swelling in the groin or under the armpits, which sometimes attained the size of a common apple or egg. Some of these swellings were larger and some smaller, and all were commonly called boils…. Afterwards, the manifestation of the disease changed into black or livid spots on the arms, thighs and the whole person….Like the boils, which had been and continued to be a certain indication of coming death, these blotts had the same meaning for everyone on whom they appeared.”

—Giovanni Boccaccio, “Preface to the Ladies,” in “The Decameron”

**Epidemiology**

Plague, also known as the Black Death, has killed millions of victims over the ages—often in catastrophic pandemics. There have been three pandemics recorded, beginning in 541 A.D., 1346, and in China in 1855, killing up to 30%-60% of the population of the infected countries (or continents).\(^{56}\) With advances in living conditions, public health, and antibiotic therapy, the rare natural outbreaks are now small and quickly contained.\(^{57,58}\) However, plague has been used as a biological weapon in the past and has potential for causing devastating disease if released as an aerosol.\(^{47,59,60}\)

Naturally occurring plague manifests when infected fleas bite humans, who then develop bubonic plague. A few people infected in this manner will develop systemic disease, known as primary septicemic plague. A percentage of patients with bubonic or septicemic plague will develop secondary pneumonic plague, which can be spread via droplet transmission. In turn, people contracting the disease by this route develop primary pneumonic plague. Between 1947 and 1996 in the United States, there were 390 cases of plague reported. Of these cases, 84% were bubonic, 13% septicemic, and 2% pneumonic.\(^{60}\)

While it is possible that the release of infected fleas could be used as a biological weapon, the most deadly bio-weapons scenario is the release of aerosolized plague, leading to outbreaks of primary pneumonic plague.\(^{61}\)

**Pathophysiology**

*Yersinia pestis*, a gram-negative coccobacillus, causes plague. When viewed under the microscope, the bacteria have a characteristic bipolar appearance that is commonly referred to as the “safety-pin” pattern. (See Figure 6.) When a human is infected by the bite of an infected flea, symptoms of bubonic plague develop within 2-8 days. These include the sudden onset of flu-like symptoms and the development of acutely swollen, painful lymphadenopathy, typically in the groin, axilla, or cervical regions. The infected lymph nodes, known as buboes, can be up to 10 cm in diameter. They are warm, exquisitely tender, non-fluctuant, and are associated with considerable edema.

> Figure 6. *Yersinia pestis*, gram-negative coccobacilli in a “safety-pin” pattern.
Septicemic plague can occur de novo from the bite of an infected flea or secondarily from untreated bubonic plague. It is characterized by disseminated intravascular coagulation, necrosis of small blood vessels, purpuric skin lesions, and gangrene to acral regions such as the digits and nose.\textsuperscript{52}

Pneumonic plague develops secondarily from bubonic or septicemic plague, or primarily when aerosolized bacilli are inhaled. After a two- to four-day incubation period, initial symptoms include fever, hemoptysis, and dyspnea.\textsuperscript{53,54} Other complaints include nausea, vomiting, abdominal pain, and diarrhea.\textsuperscript{55,56} As the disease progresses, a fulminant pneumonia ensues with pulmonary infiltrates and lobar consolidation, respiratory failure, sepsis, and death. Primary pneumonic plague infection, as would be expected from the aerosolized release of \textit{Y. pestis}, typically does not cause the classic buboes that are seen with the naturally occurring form of the disease.

**ED Evaluation**

There are two recent cases of primary pneumonic plague (which were contracted after handling infected cats). Both patients had pulmonary symptoms as well as nausea, vomiting, abdominal pain, and diarrhea; both died.\textsuperscript{53,55}

There is no widely available rapid diagnostic test for plague. Gram’s stain and culture of blood, cerebrospinal fluid (CSF), sputum, or lymph node aspirate may reveal gram-negative bacilli or coccobacilli. Giemsa staining reveals bipolar “safety-pin”-appearing bacilli. Cultures should demonstrate growth within 24-48 hours. Definitive laboratory diagnosis of \textit{Y. pestis} can be made via antigen detection, immunoassay, immuno-staining, or polymerase chain reaction (PCR) at the CDC and other government-operated laboratories.\textsuperscript{57,58}

Radiologic evaluation with chest radiography and computed tomography may reveal evidence of pulmonary infiltrate or lobar consolidation.\textsuperscript{59} Obtain a chest x-ray on any patient in whom the plague is suspected.

**Prophylaxis And Treatment**

In the past, a vaccine protective against naturally occurring plague was produced; however, the vaccine was ineffective against primary pneumonic plague and is no longer available. New vaccines are currently under development.\textsuperscript{69}

Antibiotic therapy with streptomycin 15 mg/kg given intramuscularly twice a day for 10 days has been considered first-line therapy for pneumonic plague in the past. Small numbers of human cases and animal data suggest that gentamicin or doxycycline given intravenously are effective treatments as well. Animal models suggest that quinolones may also be efficacious, but no human data exist for treatment of plague with this class of drugs.\textsuperscript{70} In addition, laboratory and animal studies indicate that doxycycline or fluoroquinolone antibiotics given orally for seven days is adequate prophylaxis for those potentially exposed to plague.

**Infection Control**

Because plague is readily transmissible via droplets, strict isolation for the first 48 hours of treatment is required to prevent secondary spread of the disease. Patients with the pneumonic form of the disease must remain in isolation for four days after the initiation of antibiotic therapy.\textsuperscript{52}

**Botulism**

**Epidemiology**

Botulinum toxin is a neurotoxic protein produced by the anaerobic bacterium \textit{Clostridium botulinum}. The naturally occurring form of the disease is seen with ingestion of improperly prepared or canned foods or with absorption of the toxin from an infected wound. In the United States, fewer than 200 cases are reported annually.\textsuperscript{71} As a biological weapon, botulinum toxin could be released as an aerosol or used as a food contaminant. After the Gulf War, Iraq admitted to producing 19,000 liters of concentrated botulinum toxin, which are still unaccounted for.\textsuperscript{72}

Based on primate studies, the lethal dose of inhaled botulinum toxin for a 70 kg human is approximately 0.21-0.90 mg, making it the most toxic substance known to man.\textsuperscript{73-75} Botulinum toxin has already been used as a bio-weapon in Japan on at least three occasions between 1990 and 1995 by a Japanese cult.\textsuperscript{76} These attacks failed for a variety of reasons, none of which were due to the limitations of the toxin.

**Pathophysiology**

Botulinum toxin acts by binding to the presynaptic nerve terminal at the neuromuscular junction and at cholinergic autonomic sites. In doing so, the toxin prevents presynaptic release of the neurotransmitter acetylcholine, thereby blocking neurotransmission. Symptoms develop within 1-3 days after inhalational exposure, beginning with bulbar palsies. Victims demonstrate dysarthria, dysphagia, blurred vision, and ptosis. As the disease progresses, skeletal muscles are affected, and the patient develops descending, symmetrical, flaccid paralysis that may culminate in respiratory failure.

**ED Evaluation**

Patients with botulism are alert, oriented, and afebrile. Upon neurologic examination, they exhibit bulbar palsies and flaccid paralysis, while sensation remains intact. Look for the “four Ds”: diplopia, dysarthria, dysphonia, and dysphagia.\textsuperscript{77}

In the ED, the diagnosis is clinical, and laboratory tests are not generally helpful. Electrophysiology studies (such as electromyogram) may be helpful (but not readily available during an outbreak).\textsuperscript{78} Definitive testing with mouse toxicity assay or immunoassay is available through the CDC and other government labs. While the mouse assay is the most sensitive test, it requires several days to complete. The differential diagnosis includes Guillain-Barré syndrome (and its Miller-Fisher variant), Guillain-Stuart syndrome, and Lambert-Eaton syndrome.\textsuperscript{78}
Clinical Pathway: ED Management Of Bioterrorism

- Unusual diseases?
- Abnormal presentation of disease?
- Unexplained fatalities?
- Atypical clustering of disease?

No ➤ Yes

• Consider bioterrorism (Class I)
• Notify local health department and FBI (Class I-II)

Influenza-type illness with:
- suspicious circumstances?
- shortness of breath?
- no sore throat or rhinorrhea?

No ➤ Yes

Possible inhalational anthrax
- Chest x-ray (Class I)
- Consider blood culture (Class I-II)
- Consider CT of chest (especially if pleural effusion, mediastinal widening) (Class I-II)
- Determine the need for empirical treatment* of presumed anthrax (Class I-II)

* IV ciprofloxacin 400 mg every 12 hours or doxycycline 100 mg every 12 hours plus one of the following: rifampin, vancomycin, penicillin, ampicillin, chloramphenicol, imipenem, clindamycin, or clarithromycin

No ➤ Yes

Possible cutaneous anthrax
- Gram's stain of lesion looking for gram-positive bacilli (Class I-II)
- Culture/biopsy of lesion (Class II)
- Determine the need for empirical treatment* of presumed anthrax (Class I-II)

*Oral ciprofloxacin 500 mg or doxycycline 100 mg BID (not adequate for head or neck infections)

No ➤ Yes

Possible smallpox
- Respiratory isolation (Class I)
- Gown, gloves, mask (Class I)
- Notify health department about possible smallpox (Class I)
- Samples of pustular fluid to be collected and handled by BSL-4 lab (Class I-II)

No ➤ Yes

Unexplained skin lesion with:
- significant local erythema and edema?
- central vesicle with satellite vesicles?
- painless, black, central eschar?

No ➤ Yes

Go to top of next page

The evidence for recommendations is graded using the following scale. For complete definitions, see back page: Class I: Definitely recommended. Definitive, excellent evidence provides support. Class II: Acceptable and useful. Good evidence provides support. Class III: May be acceptable, possibly useful. Fair-to-good evidence provides support. Indeterminate: Continuing area of research.

This clinical pathway is intended to supplement, rather than substitute for, professional judgment and may be changed depending upon a patient's individual needs. Failure to comply with this pathway does not represent a breach of the standard of care.

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Clinical Pathway: ED Management Of Bioterrorism (continued)

- Fever, hemoptysis, and dyspnea followed by fulminant pneumonia and respiratory failure **OR**
- Huge and painful lymphadenopathy, typically in the groin, axilla, or cervical regions **OR**
- Purpuric skin lesions, and gangrene to acral regions?

**Yes**

- Dysarthria, dysphagia, blurred vision, and ptosis **OR**
- These symptoms followed by descending, symmetrical, flaccid paralysis

**No**

Flu-like illness followed by:
- Bronchitis, bronchopneumonia, pneumonitis, hilar lymphadenitis, or sepsis **OR**
- Massive lymphadenopathy?

**No**

- High fever, headache, fatigue, myalgias, abdominal pain, and malaise, **followed by:**
- Gastrointestinal bleeding, generalized mucous membrane hemorrhage, petechial or ecchymotic rash, conjunctival injection, nondependent edema, and hypotension?

**Yes**

**Possible plague**
- Gram's stain and culture of blood, CSF, sputum, or lymph node aspirate for gram-negative bacilli or coccobacilli (Class II)
- Giemsa staining for bipolar "safety-pin"-appearing bacilli (Class II)
- Chest x-ray or CT of chest (Class II)
- Determine the need for empirical treatment* of presumed plague (Class I-II)

* IM streptomycin 15 mg/kg BID for 10 days **OR** IV ciprofloxacin or IV gentamicin

**Possible botulism**
- Anticipate and determine the need for mechanical ventilation (Class I-II)
- Contact CDC to determine the need for botulism antitoxin (Class I-II)

**Possible tularemia**
- Gram's stain for small, faint-staining gram-negative coccobacilli (Class II)
- Blood cultures (Class II)
- Chest x-ray or CT of chest (Class II)
- Determine the need for empirical treatment* of presumed tularemia (Class I-II)

* IM streptomycin 15 mg/kg BID for 10 days **OR** IV ciprofloxacin or IV gentamicin

**Possible viral hemorrhagic fever**
Supportive care:
- Crystalloids, blood products, and pressors as indicated (Class II)
- Gown, gloves, NIOSH 95 mask (Class I)
- Respiratory isolation (Class II)
- Intravenous ribavirin if presumed Lassa fever or Argentine hemorrhagic fever (Class II-III)

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myasthenia gravis, poliomyelitis, Eaton-Lambert syndrome, tick paralysis, hypokalemia, and hysteria.

Prophylaxis And Treatment

Despite its frightening lethality, the botulinum toxin is heat labile, and it is easily destroyed by heating contaminated food or drink to an internal temperature of 85°C (185°F) for five minutes.\(^7\) A limited supply of antitoxin is available through the CDC. USAMRIID holds an investigational antitoxin product. This antitoxin is effective in animals if administered after exposure but before the development of serious symptoms.\(^7\) Early administration of the antitoxin may prevent further deterioration but will not reverse existing paralysis.\(^8\) Likewise, a limited supply of an investigational toxoid preparation, used for more than 30 years to immunize at-risk laboratory workers and military troops, is available through USAMRIID.\(^8\) Recombinant vaccines are currently in the development phase.\(^8\)

Respiratory failure is the most common cause of death due to botulinum toxin; carefully monitor patients for evidence of respiratory muscle weakness. Assess the adequacy of gag and cough reflexes, look for the dangerous sign of drooling, and monitor respiratory parameters such as oxygen saturation, vital capacity, and inspiratory force. Mechanical ventilation is the most important treatment, as antibiotics have no effect on the disease course.\(^7\) Avoid aminoglycosides and clindamycin, as they may worsen the neuromuscular blockade.

Recovery may take weeks or months; prolonged nursing care is required.

Infection Control

Botulism is not transmissible from person to person; therefore, no special isolation procedures are required. Contaminated surfaces should be washed with 0.1% bleach.

Tularemia

“The horseman on the pale horse is Pestilence. He follows the wars.”
—The General (Boris Karloff), in “Isle of the Dead”

Epidemiology

Tularemia is a zoonotic disease caused by Francisella tularensis, a small facultative intracellular gram-negative coccobacillus. The clinical disease is known by a variety of names, including “rabbit fever” and “deer fly fever.” Naturally occurring disease is seen when humans are inoculated through the bite of an infected insect. This ulceroglandular form of the disease causes flu-like symptoms, fever, and massive lymphadenopathy. There are also reports, including a recent series of 11 patients, of naturally occurring primary pneumonic tularemia due to inhalation of contaminated dust.\(^7\) The mortality rate of untreated pneumonic tularemia is over 60%.\(^4\) In a biological weapons scenario, the aerosolization of F. tularensis is most likely, leading to outbreaks of primary pneumonic tularemia. The bio-warfare potential of tularemia has been studied since the 1930s, and the former Soviet Union reportedly developed strains resistant to antibiotics and vaccines.\(^1\)

Pathophysiology

After a three- to five-day incubation period, people exposed to aerosolized tularemia present with an acute, nonspecific febrile illness. Initial symptoms include fever, headache, myalgias, coryza, sore throat, and dry cough. Nausea, vomiting, and diarrhea are sometimes noted. Shortly thereafter, the disease progresses to bronchitis, bronchopneumonia, pneumonitis, hilar lymphadenitis, sepsis, and death.\(^9\) When compared to other threat agents, such as anthrax or plague, illness due to tularemia progresses more slowly and has a lower case-fatality rate.

ED Evaluation

Tularemia as an aerosolized bio-weapon would present as an outbreak of acute febrile illness. Clinical symptoms vary considerably depending on the portal of entry, and patients may demonstrate pharyngitis, bronchitis, pneumonitis, pleuritis, hilar lymphadenitis, or sepsis. Others may have fever with no identifiable source.\(^7\)

Chest radiography or CT may reveal peribronchial infiltrates, multilobar pneumonia, pleural effusion, and hilar lymphadenopathy.\(^9,9^9\)

As with many other potential bioterror agents, rapid diagnostic testing is not widely available. In public health laboratories, confirmatory diagnosis is made by direct fluorescent antibody or immunohistochemical stains.\(^9,9^2\)

Routine Gram’s stain reveals small, faint-staining gram-negative coccobacilli. Growth of F. tularensis by culture of body fluids is the definitive means of diagnosis. Serum antibody titers are not diagnostic until 10 or more days after the onset of illness and are not valuable during the acute phase of the illness.\(^9^3\)

Prophylaxis And Treatment

In a contained casualty situation, current recommendations for the treatment of tularemia include a 10-day course of streptomycin given intramuscularly, gentamicin given intravenously or intramuscularly, or ciprofloxacin given intravenously.\(^9^4\) Tetracyclines or chloramphenicol may also be used but are less effective and must be administered for at least 14 days to prevent relapse.\(^9^5,9^6\)

Patients exposed to tularemia should receive doxycycline 100 mg orally twice a day or ciprofloxacin 500 mg orally twice a day for 14 days as prophylaxis.\(^9^7\) In the setting of a mass casualty situation, this oral form of therapy is also recommended.

A limited supply of live-attenuated vaccine is available from the CDC as an investigational new drug. The vaccine improves immunity to aerosolized F. tularensis but does not provide complete protection from the disease when large numbers of the bacteria are inhaled.\(^9^8,9^9\)
**Infection Control**

Tularemia is not transmissible from person to person; therefore, standard precautions should be adequate to prevent the spread of the disease. No special isolation measures are necessary.

**Viral Hemorrhagic Fevers**

“Ebola is called a ‘slate wiper’ for humans. There is no known cure. Once infected, the virus kills its host in seven days.” —Richard Preston, in “The Hot Zone”

**Epidemiology**

Viral hemorrhagic fevers (VHFs) include a group of illnesses caused by RNA viruses. These highly infectious agents cause high fever, flu-like symptoms, increased vascular permeability, and bleeding from multiple sites. All of the four viral families known to cause VHF are possible bioterrorist agents. Of particular concern are the Ebola, Marburg, Lassa, and Junin viruses. The mortality rate for the Zaire subtype of Ebola is 90%.103 Infected rodents or arthropods transmit some of these diseases in the natural environment to humans. Notably, the natural reservoir of the Ebola virus remains unknown. Once the human host is infected, the virus is readily transmissible from person to person through direct contact with body fluids. This accounts for the high number of fatalities among healthcare workers who care for patients infected with these viruses. Cases of VHF in the United States are extremely rare and are usually seen in travelers who have visited endemic areas. Because of their highly infectious nature, diagnosis of a single case should be considered a public health emergency.101

Some have speculated that the Plague of Athens (430-427/425 B.C.) was actually the first outbreak of the Ebola virus.102

**Pathophysiology**

Following a two- to 21-day incubation period, early infection with VHFs is marked by high fever, headache, fatigue, myalgias, abdominal pain, and malaise. As the disease progresses, the more worrisome clinical findings involve increased vascular permeability. These include gastrointestinal bleeding, generalized mucous membrane hemorrhage, petechial or ecchymotic rash, conjunctival injection, nondependent edema, and hypotension. The disease rapidly progresses to shock and death.103

**ED Evaluation**

The clinical presentation of hemorrhagic fever depends on the particular agent. Patients will present with fever and toxicity and some constellation of headache, myalgias, rash or jaundice, bleeding, and disseminated intravascular coagulation. Physical findings include petechiae, mucous membrane and conjunctival hemorrhage, hematuria, hematemesis, and melena. Delirium, seizures, ataxia, and coma are ominous signs.

There are no widely available rapid tests for hemorrhagic fever. Antibody and nucleic acid-based assays are available through the CDC in Atlanta and USAMRIID in Fort Detrick, MD. Because of the highly infectious nature of these diseases, great care should be taken in handling all body fluid specimens.

Routine laboratory testing may indicate leukopenia, thrombocytopenia, elevated hepatic transaminases, and prolonged prothrombin time (PT) and partial thromboplastin time (PTT).104

**Prophylaxis And Treatment**

An investigational vaccine available in limited quantities has been effective in preventing the Junin virus (Argentine hemorrhagic fever). Other vaccines are currently under development.105 Intravenous ribavirin has been used to treat some cases of Lassa fever and Argentine hemorrhagic fever. Postexposure prophylaxis with orally administered ribavirin also seems to be effective.106,107

Otherwise, treatment is supportive and includes administration of crystalloids, blood products, and pressors as indicated.

**Infection Control**

There have been numerous infections among healthcare workers in Africa secondary to contact with victims of hemorrhagic fever. During a 2000 outbreak of Ebola in Uganda, 14 of 22 medical personnel (64%) were infected despite the use of isolation wards and infection control measures including gowns, gloves, shoe covers, standard surgical masks, and either goggles or eyeglasses.108 It is not clear if this was due to breaks in technique or airborne transmission (for which a standard surgical mask is inadequate protection). Contact and droplet precautions, including the use of HEPA filter masks, should be employed when caring for patients with VHFs, particularly in cases with respiratory involvement. In patients with prominent cough, vomiting, diarrhea, or hemorrhage, a negative pressure room is recommended to prevent aerosol transmission of the disease. Decontamination of infected materials with household bleach is adequate.109,110

**Psychosocial Consequences Of Bioterrorism**

“If it’s a 50-pound package of a white, powdery substance being delivered to a bakery, assume it is flour.” —Recent notice to UPS drivers117

An often overlooked—but crucially important—dimension of ED bioterrorism preparedness concerns the management of psychological consequences.111,112 Many EDs have special provisions for addressing psychological issues after mass casualty incidents (e.g., a building collapse or bus accident).

A bioterrorism attack, however, is anything but “normal” and differs from other mass casualty incidents. The psychological effects of such an attack could be...
enormous, often dwarfing the usual scope of hospital training exercises or disaster plans. EDs at the center of a bioterrorism response will face at least two major challenges: identifying and managing large numbers of psychological casualties, and managing extraordinary stresses on staff.

Psychological Casualties

Large numbers of psychological casualties—possibly far exceeding the toll of direct illness and fatalities—can result from incidents involving invisible agents (biological agents, chemicals, radiation). Following the sarin attack on the Tokyo subway system, which killed 12 individuals, over 5000 people sought care from area hospitals. The vast majority did not wait for ambulances or other emergency vehicles; instead, they drove or walked to the nearest medical facility. One of the most common problems was anxiety and stress related to the attack. Similarly, in the aftermath of a radiological accident in Goiania, Brazil, a staggering 112,000 concerned people sought medical examinations. In some cases, even individuals who lived far from the affected area requested such exams. During the anthrax outbreak of 2001, a HAZMAT team was mobilized when a man thought there was something suspicious about his M&Ms.

In the aftermath of a large-scale bioterrorism incident, people can be expected to stream into area EDs seeking assistance. Significant numbers may be suffering from acute mental effects such as shock, horror, grief, confusion, and irritability. Others will complain of sleep disturbance, loss of trust, social isolation, fear of contagion, paranoia, and anger. More may suffer from subacute or chronic psychological effects. In situations involving invisible agents, significant numbers experience stress-induced physical symptoms that mimic the effects of exposure. During the Goiania experience, large numbers of people waited in line for their medical examinations. The fear was “so intense that some people fainted in the queues as they approached their moment of monitoring. Many complained of vomiting and diarrhea.”

Thus, ED staff dealing with a bioterrorism incident will face a challenging triage situation involving a complicated mix of people: some with signs of having been infected by an agent, others with psychogenic symptoms, and some with both. Effective triage protocols will be vital. The response team must distinguish psychological casualties from medical ones and differentiate the more serious psychological problems from less serious ones.

For people with transient symptoms, response managers may facilitate recovery by creating respite locations. Such locations should be removed from areas of high-tempo triage activity, but they should also be close enough to permit symptoms to be observed and monitored and to enable return for re-evaluation should symptoms worsen. It will also be important to have appropriate materials and assistance available for children.

Sustained Stress On ED Personnel

Dealing with a bioterrorism situation will subject ED personnel to levels of sustained psychological stress greater than anything they have ever known. Healthcare providers may encounter dead bodies on a daily basis over a significant period of time. They may also see gruesome deaths, numerous dead children, and dead or dying colleagues. Such grim experiences are especially traumatic. Over time, some physicians may suffer psychosomatic symptoms.

In a bioterrorism situation, ED personnel can also expect to have to deal with large numbers of worried patients, parents, and so on asking for tests and demanding antibiotics. During the anthrax letter situation in late 2001, emergency rooms in the Washington, DC, area saw substantial numbers of people reporting headaches, nasal congestion, and coughs who feared they had anthrax. Parents, worried about their children, were flooding doctors with requests for Cipro. After a 2001 outbreak of meningococcal disease in Ohio killed two students, hundreds of people reportedly traveled to local hospitals seeking testing or treatment. Several days later, thousands of people reportedly stood in the rain outside one hospital awaiting the arrival of additional antibiotics.

Clinicians will be bombarded by patients, family members, and members of the press. We will be questioned about isolation, quarantine, contamination, symptomatology, and treatments. Education of clinicians must include ways of addressing these questions and, more broadly, strategies for dealing effectively with people’s concerns and anxieties.

Wearing personal protective clothing/equipment can be a significant psychological stressor. Studies of military training exercises have seen significant personnel attrition (up to 10%) due to anxiety, claustrophobia, or panic related to protective gear. Among civilian healthcare personnel, figures could be even higher.

Of course, it is not only medical doctors who are subject to enormous stresses in a hospital dealing with a bioterrorism incident. Every staff member would be at risk. As DiGiovanni notes: “There is little reason to believe that medical personnel (including ancillary staff, e.g., housekeepers, central supply workers), inexperienced and perhaps untrained in chemical and biological incidents, will be spared from the anxiety and other distresses that will afflict the rest of the community, particularly if the offending agent threatens their own families.” While no one can be certain, it is quite possible that some staff members, fearful of exposure or concerned about the well-being of their families, may opt out of hospital operations. This, in turn, would add further to the stresses on the remaining healthcare workers.

In short, even well-prepared healthcare facilities will face unprecedented challenges in dealing with a large-scale bioterrorism situation, while less adequately prepared facilities could easily be overwhelmed and rendered ineffective. At a minimum, therefore, EDs need
to have the following in place:

• a bioterrorism incident triage protocol that integrates ED personnel and behavioral health staff;
• mechanisms for identifying and managing large numbers of psychological casualties;
• respite areas for people experiencing transient mental health effects;
• materials and assistance for children and worried parents who arrive at the hospital;
• bioterrorism education and training for all ED staff (including support/ancillary staff);
• pre-briefing for ED personnel who are expected to have to deal with unusually grotesque scenes outside of their usual experience; and
• adequate psychological support for ED personnel.

The unique psychological issues posed by bioterrorism should also be addressed in hospital disaster plans, training courses, and training exercises.

**Preparation For Bioterrorism**

The best deterrent and response to the unknowns of bioterrorism is preparation. In contrast to preparation for chemical terrorism, where preparation relies largely on HAZMAT equipment, immediate treatment in the

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**Ten Assumptions A Bioterrorist Wants You To Make**

1. **“I don’t have to consider rare diseases; the infectious disease specialists can worry about that.”**
   The earlier a rare pathogen is identified, the more effective the public health response. Failure to consider a rare disease will lead to inevitable delays and possibly extend the epidemic.

2. **“There’s no reason for me to notify public health authorities— it would just mean a lot of extra phone calls and paperwork.”**
   Coordination of the medical community by public health authorities is essential in rare disease outbreaks. Failure to notify public health authorities can lead to fatal delays in appropriate civic response.

3. **“I think I’ll call the local radio station and tell them about this suspected case of anthrax. They can handle the distribution of information to the public.”**
   This is a sure way to cause panic in the streets (and prompt a call from an enraged hospital administrator). Appropriate delivery of accurate information is essential to conserve limited medical resources. Work directly with public health and media authorities at your hospital before notifying others.

4. **“I’m not sure this is smallpox. Putting him in negative pressure isolation might cause panic.”**
   Failure to properly isolate patients who are suspected to be infected with highly transmissible diseases such as smallpox can be a deadly mistake— for you and your staff.

5. **“Sure, this patient has a flu-like illness and a widened mediastinum on chest radiography— but it will take two hours to get a CT scan of his chest, and he really wants to go home.”**
   If we are to detect bioterrorist attacks, we must think of rare diseases and recognize suspicious patterns. Failure to order appropriate diagnostic testing can delay critical treatment and have deadly consequences.

6. **“Even though this case could be inhalational anthrax, I don’t want to expose the patient to all of those antibiotics before we have a definitive diagnosis.”**
   In many bioterror situations, early, aggressive antibiotic therapy is essential to survival. Delays in treatment may lead to unnecessary morbidity and mortality.

7. **“None of these patients were in the building when the suspicious envelope arrived, but we’re going to decontaminate them anyway. We want everyone to know we’re taking this seriously.”**
   In cases of potential exposure, the public turns to you as a healthcare provider for advice on decontamination procedures. Unnecessary decontamination can cause unwarranted stress for patients and can overburden the emergency healthcare system.

8. **“This patient doesn’t have any signs or symptoms of plague and has not been near anyone with the disease, but he is asking for antibiotics, so I’ll give them to him anyway.”**
   Reserve antibiotic prophylaxis for those patients who genuinely warrant treatment. This will prevent unnecessary side effects. In some cases, conservation of antimicrobials may be important.

9. **“All of the employees in the office said they were covered in this powder that tested positive for anthrax, but they don’t look sick now. They can wait to get antibiotics if they develop symptoms.”**
   Patients who are genuinely at high risk for exposure to deadly infectious agents should certainly receive antibiotic prophylaxis. All suspected threat agent exposures should be discussed with local or state public health officials.

10. **“In the ED, my role is just to stabilize the patients, not to diagnose rare diseases.”**
    The emergency physician is likely to be the first-line responder in a bioterrorist attack. ED diagnosis of rare diseases can and must be done in order to rapidly recognize and respond to the threat of bioterrorism.
streets, and cordoned-off crime scenes, preparation for biological terrorism relies much more on education, a robust public health system, and broad inter-agency collaboration. The integrated system must include intelligence and forensics, medical surveillance, medical and physical countermeasures, and a strong public health infrastructure, all bound together by vigorous inter-agency collaboration and effective educational programs. Fortunately, much of what should be done in anticipation of a biological terrorist attack is also applicable to any public health disaster or infectious disease outbreak, making these expensive but necessary preparations “dual use” in nature.

In a recent survey of 30 hospitals within a local region, none of the hospitals believed they were fully prepared to handle a biological incident, and only 27% of the hospitals surveyed had incorporated weapons of mass destruction (WMD) preparedness into their hospital disaster plans. Of the hospitals that had performed WMD drills, only one had conducted a drill specifically addressing biological weapons.132 A large-scale bioterrorism drill performed in Denver that simulated aerosolized plague attacks resulted in over 3000 simulated casualties within four days.133 One of the most valuable insights from this drill was that the systems and resources currently in place are inadequate to manage the stress of a large-scale bio-weapons attack. Based on these observations, it is clear that in order to treat victims of bioterrorism, we must augment our diagnostic capabilities and surveillance programs and make infrastructure modifications to prepare adequately for the consequences of an epidemic of infectious disease.

Today, rapid progress in the development and enrichment of our public health infrastructure is ongoing, and multiple parties have called for improved surveillance systems both before and after the events of the U.S. anthrax attack.134,139-141 But the system is not yet where it needs to be. Currently there is no unified surveillance system in place, leaving multiple fragmented systems that rely on widely varying methodology and technology to function. The complexities of disease reporting and the lack of consistent feedback have led to

Table 6. Patient Isolation Precautions.

**Standard Precautions**
- Wash hands after patient contact.
- Wear gloves when touching blood, body fluids, secretions, excretions, and contaminated items.
- Wear a mask and eye protection, or a face shield, during procedures likely to generate splashes or sprays of blood, body fluids, secretions, or excretions.
- Handle used patient-care equipment and linen in a manner that prevents the transfer of microorganisms to people or equipment.
- Use care when handling sharps, and use a mouthpiece or other ventilation device as an alternative to mouth-to-mouth resuscitation when practical.

Standard precautions are employed in the care of all patients.

**Airborne Precautions**

Standard Precautions plus:
- Place the patient in a private room that has monitored negative air pressure, a minimum of six air changes/hour, and appropriate filtration of air before it is discharged from the room.
- Wear respiratory protection when entering the room.
- Limit movement and transport of the patient. Place a mask on the patient if he or she needs to be moved.

Conventional diseases requiring Airborne Precautions: measles, varicella, pulmonary tuberculosis.
Biothreat diseases requiring Airborne Precautions: smallpox.

**Droplet Precautions**

Standard Precautions plus:
- Place the patient in a private room or cohort him or her with someone with the same infection. If this is not feasible, maintain at least three feet between patients.
- Wear a mask when working within three feet of the patient.
- Limit movement and transport of the patient. Place a mask on the patient if he or she needs to be moved.

Conventional diseases requiring Droplet Precautions: invasive Haemophilus influenzae and meningococcal disease, drug-resistant pneumococcal disease, diphtheria, pertussis, mycoplasma, GABHS, influenza, mumps, rubella, parvovirus.
Biothreat diseases requiring Droplet Precautions: pneumonic plague.

**Contact Precautions**

Standard Precautions plus:
- Place the patient in a private room or cohort him or her with someone with the same infection if possible.
- Wear gloves when entering the room. Change gloves after contact with infective material.
- Wear a gown when entering the room if contact with patient is anticipated or if the patient has diarrhea, a colostomy, or wound drainage not covered by a dressing.
- Limit the movement or transport of the patient from the room.
- Ensure that patient-care items, bedside equipment, and frequently touched surfaces receive daily cleaning.
- Dedicate use of noncritical patient-care equipment (such as stethoscopes) to a single patient or cohort of patients with the same pathogen. If this is not feasible, adequate disinfection between patients is necessary.

Conventional diseases requiring Contact Precautions: MRSA, VRE, Clostridium difficile, RSV, parainfluenza, enteroviruses, enteric infections in the incontinent host, skin infections (SSSS, HSV, impetigo, lice, scabies), hemorrhagic conjunctivitis.
Biothreat diseases requiring Contact Precautions: Viral hemorrhagic fevers.


physician frustration and poor compliance with current public health reporting mechanisms.\textsuperscript{135,136}

Given the impact of delays in detecting bioterrorism, new approaches to surveillance that emphasize the early detection of specific syndromes and reporting cases through real-time communication systems are being implemented.\textsuperscript{137} The government recognizes that EDs will play an increasingly important role in bioterrorism surveillance, and standard approaches to data sharing are likely to emerge in the near future.\textsuperscript{138}

Summary

The emerging threat of bioterrorism is an inescapable reality. All EDs should prepare for this eventuality. Emergency physicians must be alert to unusual presentations and, in particular, clusters of unusual presentations that could result from biological weapons. ED personnel should participate in bioterrorism surveillance systems. When bioterrorism is suspected, ED personnel must work closely with the public health and behavioral health community to appropriately triage, rapidly diagnose, and effectively treat patients. This system will not work efficiently without planning and preparation for the unusual contingencies presented by a bioterrorist attack. We can act rapidly and effectively if we pay close attention to epidemiologic patterns and remember the potential for biological weapons. ▲

Table 7. Discussion Of Investigational Information.

\textbf{Anthrax:} Doxycycline, ciprofloxacin, and penicillin G procaine are all FDA-approved for the treatment of anthrax. The anthrax vaccine is FDA approved for individuals at high risk of infection with B. anthracis. The use of rifampin, vancomycin, ampicillin, chloramphenicol, imipenem, clindamycin, clarithromycin, or corticosteroids for the treatment of anthrax would be considered off-label.

\textbf{Smallpox:} The smallpox vaccine and vaccinia immune globulin are both FDA-approved for the prevention and treatment of smallpox. Cidofovir is not FDA-approved for the treatment of smallpox, and the use of the drug in this setting would be considered off-label.

\textbf{Plague:} Doxycycline and gentamicin are both FDA-approved for the treatment of plague. Streptomycin and the quinolone drugs are not FDA-approved for the treatment of plague, and the use of these drugs to treat plague would be considered off-label.

\textbf{Botulism:} Botulism antitoxin is FDA-approved for the treatment of patients with botulism. The botulism toxoid is approved by the FDA as an Investigational New Drug.

\textbf{Tularemia:} The Live Vaccine Strain (LVS) for tularemia is approved by the FDA as an Investigational New Drug. Gentamicin and ciprofloxacin are not FDA-approved for the treatment of tularemia, and the use of these drugs for the treatment of tularemia would be considered off-label.

\textbf{Viral Hemorrhagic Fevers:} The vaccine for Argentine hemorrhagic fever is approved by the FDA as an Investigational New Drug. Ribavirin is not FDA-approved for the treatment of viral hemorrhagic fevers, and the use of the drug to treat viral hemorrhagic fevers would be considered off-label.

References

Evidence-based medicine requires a critical appraisal of the literature based upon study methodology and number of subjects. Not all references are equally robust. The findings of a large, prospective, randomized, and blinded trial should carry more weight than a case report.

To help the reader judge the strength of each reference, pertinent information about the study, such as the type of study and the number of patients in the study, will be included in bold type following the reference, where available. In addition, the most informative references cited in the paper, as determined by the authors, will be noted by an asterisk (*) next to the number of the reference.


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4. Measures that can ease the challenges in dealing with a potential bioterrorist attack include:
   a. a bioterrorism incident triage protocol that integrates ED personnel and behavioral health staff.
   b. mechanisms for identifying and managing large numbers of psychological casualties.
   c. written materials for worried parents who arrive at the hospital.
   d. bioterrorism education and training for all ED staff (including support/ancillary staff).
   e. all of the above.

5. During bioterror mass casualty incidents:
   a. triage should proceed as usual, with the worst cases treated first.
   b. healthcare providers must differentiate the “walking worried” from the truly symptomatic.
   c. healthcare providers should provide prophylactic antibiotics to anyone who requests them.
   d. healthcare providers should collect and send laboratory samples to their local labs.

6. All of the following tend to indicate a natural disease outbreak, rather than a bioterrorist attack, except:
   a. Cases present to the ED at varying stages of disease progression
   b. Usual expected disease course for that specific pathogen, with appropriate response to standard therapy
   c. Slowly progressive disease course, with prodromal symptoms
   d. Sudden presentation of large numbers of victims with a similar disease or syndrome who may have a readily identifiable common exposure

7. All of the following are true regarding cutaneous anthrax except:
   a. Localized edema, erythema, and lymphadenopathy are important clues to the diagnosis.
   b. Without antibiotic therapy, cutaneous anthrax can lead to bacteremia, with mortality rates as high as 20%.
   c. With antibiotics, death due to cutaneous anthrax is rare.
   d. Cutaneous anthrax is not caused by the same spores as inhalational anthrax.

8. The recommended prophylactic therapy for patients with confirmed exposure to \textit{B. anthracis} is:
   a. oral ciprofloxacin 500 mg every 12 hours, or doxycycline 100 mg every 12 hours, for 60 days.
   b. the anthrax vaccine.
   c. prophylactic therapy is unnecessary.
   d. there is no prophylactic therapy.

9. All of the following are true regarding inhalational anthrax except:
   a. It begins as a nonspecific, flu-like illness.
   b. Rhinorrhea and nasal congestion usually are not associated with inhalational anthrax.
   c. Shortness of breath is rare in anthrax but common in influenza and influenza-like illness.
   d. Chest radiography in patients with inhalational anthrax often exhibits mediastinal widening, occasional infiltrates, and pleural effusion.

10. Patients who are diagnosed with smallpox:
    a. require the standard precautions.
    b. should receive aggressive antibiotic therapy.
    c. should be questioned so that recent contacts can be vaccinated and placed under surveillance.
    d. are expected to have a 95% mortality rate.

11. Smallpox:
    a. is not very contagious.
    b. begins with high fever, malaise, vomiting, headache, and myalgias; the characteristic rash appears 2-3 days later.
    c. lesions rarely develop on the extremities and face.
    d. lesions are superficial, appear in various stages of evolution, and develop in crops.

12. All of the following are true regarding plague except:
    a. The bacteria have a characteristic bipolar appearance that is commonly referred to as the “safety-pin” pattern.
    b. Septicemic plague can occur \textit{de novo} from the bite of an infected flea or secondarily from untreated bubonic plague.
    c. Pneumonic plague develops secondarily from bubonic or septicemic plague, or primarily when aerosolized bacilli are inhaled.
    d. Primary pneumonic plague infection typically does not cause the classic buboes that are seen with the naturally occurring form of the disease.
    e. Isolation is not required, because the plague is not very contagious.

13. By weight, the most toxic substance known to man is:
    a. anthrax spores.
    b. inhaled botulinum toxin.
    c. ricin toxin.
    d. epsilon toxin.

14. Patients with botulism exhibit:
    a. diplopia.
    b. dysarthria.
    c. dysphonia.
    d. dysphagia.
    e. all of the above.
15. Tularemia typically presents:
   a. after a three-week incubation period.
   b. as an acute, nonspecific febrile illness.
   c. without a sore throat or cough.
   d. with nausea and vomiting, but not fever.

16. Viral hemorrhagic fevers:
   a. present with fever and toxicity and some constellation of headache, myalgias, rash or jaundice, bleeding, and disseminated intravascular coagulation.
   b. can be detected by a rapid bedside test.
   c. are rarely lethal.
   d. require no special infection control measures other than handwashing.

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Class Of Evidence Definitions

Each action in the clinical pathways section of Emergency Medicine Practice receives an alpha-numerical score based on the following definitions.

Class I
- Always acceptable, safe
- Definitely useful
- Proven in both efficacy and effectiveness

Level of Evidence:
- One or more large prospective studies are present (with rare exceptions)
- High-quality meta-analyses
- Study results consistently positive and compelling

Indeterminate
- Continuing area of research
- No recommendations until further research

Level of Evidence:
- Evidence not available
- Higher studies in progress
- Results inconsistent, contradictory
- Results not compelling

Class II
- Safe, acceptable
- Probably useful

Level of Evidence:
- Generally higher levels of evidence
- Non-randomized or retrospective studies: historic, cohort, or case-control studies
- Less robust RCTs
- Results consistently positive

Class III
- May be acceptable
- Possibly useful
- Considered optional or alternative treatments

Level of Evidence:
- Generally lower or intermediate levels of evidence

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