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Being Prepared
Bioterrorism and Mass Prophylaxis: Part I

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ABSTRACT
Bioterrorism presents a real and omnipresent risk to public health throughout the world. More than 30 biological agents have been identified as possessing the potential to be deployed in a bioterrorist attack. Those that have been determined to be of the greatest concern and possess the greatest potential of use in this arena are known as the Category A agents: *Bacillus anthracis* (anthrax); *Variola major* (smallpox); *Yersinia pestis* (plague); *Francisella tularensis* (tularemia); viral hemorrhagic fevers; and *Clostridium botulinum toxin* (botulism toxin). Although the Centers for Disease Control and Prevention utilizes surveillance systems to identify illnesses, the weight of diagnosing, effectively treating, and notifying the appropriate public health officials lies squarely on the shoulders of emergency care personnel. Part I of this two-part review will focus on the clinical presentation and treatment of anthrax, plague, and tularemia. The subsequent Part II of this review will discuss smallpox, viral hemorrhagic fevers, botulism toxin, and the provision of mass prophylaxis. **Key words:** anthrax, *Bacillus anthracis*, biological warfare, bioterrorism, *Francisella tularensis*, tularemia, *Yersinia pestis*

THE CENTERS FOR DISEASE CONTROL and Prevention (CDC) defines bioterrorism as " . . . the deliberate release of viruses, bacteria, or other germs (agents) used to cause illness or death in people, animals, or plants" (Centers for Disease Control and Prevention, 2007). Although the 1972 signing of the Biological Weapons Convention restricted the use of many of these biological agents around the world, the 2001 anthrax attacks on the United States demonstrated the ever-present threat that these agents still pose to the global community (Bush, Abrams, Beall, & Johnson, 2001; Bush & Perez, 2012). In that event, 22 confirmed or suspected cases of anthrax occurred in the United States when anthrax spores were sent through the mail to the news media and members of Congress,

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resulting in five deaths (Wright, Quinn, Shadomy, & Messonnier, 2010).

To identify biological agents that posed the most significant potential risk to the general population, infectious disease experts, national public health experts, Department of Health and Human Services agency representatives, civilian and military intelligence experts, and law enforcement officials gathered together in 1999 (Rotz, Khan, Lillibridge, Ostroff, & Hughes, 2002). They identified and categorized more than 30 agents as having the potential to be used in a bioterrorist attack (Rotz et al., 2002). These agents were then placed into three different priority categories: A, B, or C (see Table 1). Category A agents were determined to be of the greatest concern and possess the greatest potential for use in this arena. Agents placed in Category B were determined to have some potential but generally resulted in lower illness and death rates and thus have less impact on public health. Category C agents were determined to be biological agents that are not believed to currently present an elevated threat; however, they could represent substantial future threats. Those agents placed in Category A include *Bacillus anthracis* (anthrax); *Variola major* (smallpox); *Yersinia pestis* (plague); *Francisella tularensis* (tularemia); viral hemorrhagic fevers; and *Clostridium botulinum* toxin (botulism toxin).

Emergency departments across the nation play a substantial and critical role in the biodefense effort. Prior to the diagnosis of the first anthrax case in Florida in 2001, four individuals in New York had been seen in emergency departments and were treated for skin lesions that would later be determined to be cutaneous anthrax (Bush & Perez, 2012). Although the CDC utilizes syndromic surveillance systems to identify illnesses caused by biological agents during a large-scale biological warfare attack, they are less sensitive in

Table 1. Categories of bioterrorism agents/diseases

Category A
Anthrax (*Bacillus anthracis*)
Botulism (*Clostridium botulinum* toxin)
Plague (*Yersinia pestis*)
Smallpox (*Variola major*)
Tularemia (*Francisella tularensis*)
Viral hemorrhagic fevers (filoviruses [e.g., Ebola, Marburg] and arenaviruses [e.g., Lassa, Machupo])
Category B
Brucellosis (Brucella species)
Epsilon toxin of *C. perfringens*
Food safety threats (e.g., Salmonella species, *Escherichia coli* O157:H7, Shigella)
Glanders (*Burkholderia mallei*)
Melioidosis (*Burkholderia pseudomallei*)
Psittacosis (*Chlamydia psittaci*)
Q fever (*Coxiella burnetii*)
Ricin toxin from Ricinus communis (castor beans)
Staphylococcal enterotoxin B
Typhus fever (*Rickettsia prowazekii*)
Viral encephalitis (alpha viruses [e.g., Venezuelan equine encephalitis, eastern equine encephalitis, western equine encephalitis])
Water safety threats (e.g., *Vibrio cholerae*, *Cryptosporidium parvum*)
Category C
Emerging infectious diseases such as Nipah virus and hantavirus

Note. Retrieved from http://emergency.cdc.gov/bioterrorism/.

the setting of targeted bioterrorism on a limited scale. Thus, the weight of diagnosing, effectively treating, and notifying the appropriate public health officials lies squarely on the shoulders of emergency care personnel. As a result, it is important for emergency care personnel to be familiar with the biological agents determined to have the greatest potential for use in such an event. Part I of this review will focus on the clinical presentation and treatment of anthrax, plague, and tularemia.

BACILLUS ANTHRACIS (ANTHRAX)

Anthrax is a disease that occurs naturally in the environment and typically exists in herbivores such as horses, cattle, sheep, and goats (Darling, Catlett, Huebner, & Jarrett, 2002). The spores formed by anthrax represent the infective form of the bacteria and are found in soil around the world. They are quite resilient to destruction, potentially remaining in the environment for decades (Franz et al., 1997). These spores cause infection by entering the host through scratches on the skin, inhalation, or eating insufficiently cooked meat. Although transmittable from animal to human, anthrax is not transmitted from person to person. The availability of these spores, the resulting high mortality rate, their ease of mass production, environmental stability, and potential for dispersal as an aerosol cloud make anthrax an ideal candidate for a bioterrorist attack (Pile, Malone, Eitzen, & Friedlander, 1998). In addition, an airborne dispersal of these spores would be both odorless and colorless, further enhancing its appeal as a weapon of mass destruction (Inglesby et al., 1999). Multiple countries have admitted to weaponizing anthrax including the United States, Iraq, the former Soviet Union, as well as terrorist organizations (Inglesby et al., 2002).

Clinical Presentation

Anthrax can present in multiple forms in humans: cutaneous, gastrointestinal, and inhalational (Darling et al., 2002). Approximately 2000 cases of naturally occurring cutaneous anthrax are reported worldwide every year, and it constitutes 95% of all naturally occurring anthrax infections in the world (Inglesby et al., 2002). Humans acquire this form most commonly from working with infected livestock where spore introduction occurs through the skin and typically presents on the hands and forearms (see Figure 1). The infection begins as a papule and after a mean incubation period of 5 days, it goes on to form a fluid-filled vesicle, also known as a "malignant pustule." The subsequent formation of a black scab, known as an eschar, is how anthrax acquired its name (the Greek word for "coal" is *anthrakis*). After 1–2 weeks, the anthrax eschar dries, loosens, and falls off. Fortunately, this form of infection carries a mortality rate of less than 1% if it is treated; however, if left untreated, it can lead to a mortality rate of around 20% (Inglesby et al., 2002). In comparison with cutaneous anthrax, gastrointestinal anthrax is quite rare in humans and is acquired through ingesting spores from undercooked meat from infected animals. No cases have been reported in the United States since 1941 (Wright et al., 2010). The acquired spores can germinate in the upper or lower gastrointestinal track and develop into a systemic illness and sepsis, at which time this form carries an estimated mortality rate of 25% to 60% (Wright et al., 2010).

The final form of anthrax is inhalational, which is also very rare in humans, accounting

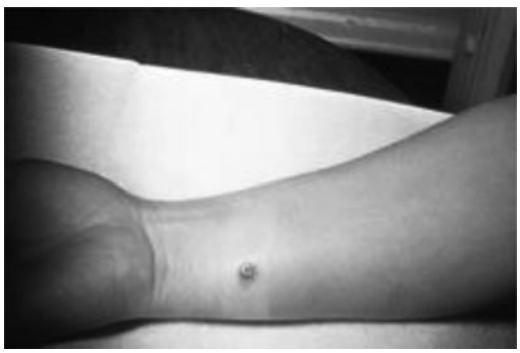

Figure 1. Cutaneous anthrax. Retrieved from http://emergency.cdc.gov/bioterrorism/.

for about 5% of all naturally acquired anthrax cases in the United States (see Figure 2; Wright et al., 2010). However, this form carries with it a mortality rate of 86%–89% without adequate prophylaxis and treatment. Like any severe life-threatening illness, early diagnosis is crucial. It has been estimated that if the time to diagnosis is delayed from 2 days to 4.8 days, the mortality would be expected to double (Kyriacou, Adamski, & Khardori, 2006). This form of anthrax is also known as "woolsorters' disease" because it occurs mainly among industrial workers handling infected hides, wool, and furs, and thus inhaling the spores. The infection begins with an incubation period lasting 2–3 days (range, 1–43 days), during which time the patient may experience fever, malaise, fatigue, and nonproductive cough (Daya & Nakamura, 2005). In the attacks of 2001, malaise and fever were present in all patients who had inhalational anthrax. After this period, the patient may experience a period of clinical improvement, which is followed by a rapid decline in health and the subsequent development of respiratory distress, dyspnea, diaphoresis, stridor, and cyanosis. As the *B. anthracis* bacilli replicate, they release toxins that result in necrotizing, hemorrhagic mediastinitis and edema. Septic shock and death will develop within 2 days after the onset of respiratory distress (Klietmann & Ruoff, 2001).

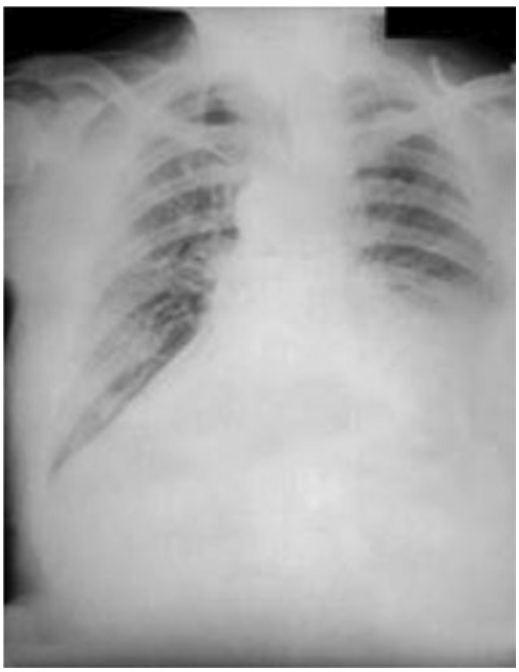

Figure 2. Inhalational anthrax. Retrieved from http://emergency.cdc.gov/bioterrorism/.

Infection Control Precautions

Person-to-person spread of inhalational anthrax is not known to occur; however, standard precautions are recommended for patient care. Anthrax spores are exceedingly persistent and so all instruments should be disinfected with a sporicidal agent. The U.S. Environmental Protection Agency currently recommends sodium hypochlorite solution as a sporicidal agent to decontaminate surfaces and buildings (Kman & Nelson, 2008).

Treatment and Prophylaxis

The first suspicion of anthrax should initiate the notification process of local and state health departments (CDC, 2001). Naturally occurring anthrax is sensitive to penicillin, tetracycline, and multiple other antibiotics. However, genetically engineered drug resistance to penicillin is a high likelihood within the context of a bioterrorist attack, because it is known that the Soviets produced antibiotic-resistant anthrax strains during the Cold War (Inglesby et al., 1999). Therefore, for those who are showing signs of actual infection, the CDC recommends treatment with ciprofloxacin or doxycycline plus one or two other agents. This accounts for multi-drug–resistant strains and the fact that penicillin, doxycycline, or ciprofloxacin is not specifically approved by the U.S. Food and Drug Administration (FDA) for this indication (see Table 2; Franz et al., 1997). Limited data exist to recommend one agent over another in this clinical scenario. In a mass casualty scenario, the number of patients may make intravenous dual therapy not feasible, in which case oral ciprofloxacin is

Table 2. Category A agent treatment

Agent	Therapeutic options	Dosage
Bacillus anthracis (Anthrax)	Antibiotic therapy involves a two-drug regimen, one from list A and one from list B	
	List A	
	First-line	
	Ciprofloxacin	400 mg IV every 8 hr
	Alternative agents	
	Levofloxacin	750 mg IV every 24 hr
	Moxifloxacin	400 mg IV every 24 hr
	Meropenem	2 g IV every 8 hr
	Imipenem	1 g IV every 6 hr
	Doripenem	500 mg IV every 8 hr
	Vancomycin	60 mg/kg/day IV divided every 8 hr[a]
	Penicillin-susceptible:	
	Penicillin G	4 million units IV every 4 hr
	Or	
	Ampicillin	3 g IV every 6 hr
	List B	
	First-line	
	Clindamycin	900 mg IV every 8 hr
	Linezolid	600 mg IV every 12 hr
	Alternative agents	
	Doxycycline	200 mg initially, then 100 mg IV every 12 hr
	Rifampin	600 mg IV every 12 hr
	Antibiotic therapy for possible/confirmed meningitis should include three or more antibiotics with at least one having bactericidal activity and one being a protein synthesis inhibitor	
	Bactericidal agent (fluoroquinolone)	
	First-line	
	Ciprofloxacin	400 mg IV every 8 hr
	Alternative agents	
	Levofloxacin	750 mg IV every 24 hr
	Moxifloxacin	400 mg IV every 24 hr
	Bactericidal agent (β-lactam)	
	First-line	
	Meropenem	2 g IV every 8 hr
	Alternative agents	
	Imipenem	1 g IV every 6 hr
	Doripenem	500 mg IV every 8 hr
	Penicillin G	4 million units IV every 4 hr
	Ampicillin	3 g IV every 6 hr

(*Continues*)

Table 2. Category A agent treatment (*Continued*)

Agent	Therapeutic options	Dosage
	Protein synthesis inhibitor	
	First-line	
	Linezolid	600 mg IV every 12 hr
	Alternative agents	
	Clindamycin	900 mg IV every 8 hr
	Rifampin	600 mg IV every 12 hr
	Chloramphenicol	1 g IV every 6–8 hr
	Antitoxins	
	Raxibacumab	Adults and pediatrics >50 kg: 40 mg/kg IV Pediatrics 15–50 kg: 60 mg/kg IV Pediatrics <15 kg: 80 mg/kg IV
	Anthrax immune globulin[b]	Still under investigation
Yersinia pestis (Plague)	First-line	
	Streptomycin	1 g IM every 12 hr
	Gentamicin	5 mg/kg IM or IV once daily
	Alternative agents	
	Doxycycline	100 mg IV every 12 hr
	Chloramphenicol	25 mg/kg IV every 6 hr
	Ciprofloxacin	400 mg IV every 12 hr
Francisella tularensis (Tularemia)	First-line	
	Streptomycin	1 g IM every 12 hr
	Gentamicin[b]	5 mg/kg IM or IV once daily
	Alternative agents	
	Doxycycline	100 mg IV every 12 hr
	Chloramphenicol	15 mg/kg IV every 6 hr
	Ciprofloxacin[b]	400 mg IV every 12 hr

Note. [a]Maintain serum trough concentrations of 15–20 mcg/ml.
[b]Not Food and Drug Administration approved for this indication.
From Darling et al. (2002); Dennis et al. (2001); Eliasson Broman, Forsman, and Back (2006); Franz et al. (1997); Hendricks et al. (2014); Kman and Nelson (2008); and Shapiro, Hatheway, Becher, and Swerdlow (1997).

recommended. Once susceptibility testing results are available, patients may be switched to intravenous penicillin G or other antibiotics. Unfortunately, by the time symptoms appear in a patient with inhalational anthrax, treatment is not often successful. However, if the patient lives, antibiotic therapy should be continued for 60 days to prevent recurring disease. After clinical improvement, patients may be switched to oral antibiotics for the duration of their therapy (Darling et al., 2002). In the 2001 attacks, the fatality rate was 45% among those with confirmed inhalational anthrax who started therapy after symptoms arose (Pile et al., 1998). Although this demonstrates the efficacy of treatment, it also further emphasizes the importance of the provision of prophylaxis prior to the development of symptoms.

In December 2012, the FDA approved raxibacumab injection as an additional therapeutic strategy along with antibiotics to treat

inhalational anthrax. This is a human IgG monoclonal antibody that neutralizes toxins produced by *B. anthracis*. These toxins have the ability to cause irreversible tissue injury that can be quite extensive as well as death. This is the first monoclonal antibody to be approved under the FDA's Animal Efficacy Rule, meaning that this medication's efficacy is based entirely on animal models of inhalational anthrax. Because infusion reactions have been noted in studies (e.g., rash, urticaria, and pruritus), patients receiving this medication should be premedicated with diphenhydramine and the intravenous infusion should be administered for more than 2 hr and 15 min (see Table 2). The dose, infusion volume, diluents, and infusion rate can all vary on the basis of patient's weight, and so pharmacist consultation is highly recommended when using this agent. The most frequently reported adverse reactions associated with therapy include rash, pain in the extremity, pruritus, and somnolence.

Secondary to the high rate of mortality following the development of symptoms, the CDC recommends prophylaxis for those who have been potentially exposed to inhalational anthrax but have yet to show signs of infection (see Table 3; Inglesby et al., 2002). The determination of who should receive this prophylaxis will be decided by public health or law enforcement authorities (Branda & Ruoff, 2002).

A protein-based anthrax vaccine might be available to be administered to exposed individuals as well (see Table 4; Branda & Ruoff, 2002). This is an inactivated cell-free product that protects against cutaneous and inhalational anthrax and is approved by the FDA for at-risk patients prior to anthrax exposure (e.g., laboratory personnel working with *B. anthracis*, certain military personnel; Turnbull, 1991). Currently, the CDC recommends that this vaccination be considered in those who are receiving postexposure prophylaxis for inhalational anthrax exposure because it may provide optimal protection (Wright et al., 2010). Currently, this vaccine is licensed for the preexposure setting only, and it is unlikely that ample vaccine supplies will be available for a mass vaccination

Table 3. Category A agent postexposure prophylaxis

Agent	Therapeutic options	Duration
Bacillus anthracis (anthrax)	*First-line*	60 days
	Ciprofloxacin 500 mg PO every 12 hr	
	Doxycycline 100 mg PO every 12 hr	
	Alternative agents[a]	
	Levofloxacin 750 mg PO once daily[b]	
	Moxifloxacin 400 mg PO once daily	
	Clindamycin 600 mg every 8 hr PO	
	If penicillin susceptible:	
	Amoxicillin 1 g every 8 hr PO	
	Penicillin VK 500 mg every 6 hr PO	
Yersinia pestis (plague)	Doxycycline 100 mg PO every 12 hr	7 days
	Ciprofloxacin 500 mg PO every 12 hr[c]	
Francisella tularensis (tularemia)	Ciprofloxacin 500 mg PO every 12 hr[c]	10 days
	Doxycycline 100 mg PO every 12 hr	14–21 days

Note. [a]In order of preference.
[b]No safety data are available for levofloxacin beyond 30 days.
[c]Not Food and Drug Administration approved for this indication.
From Henderson (1999); Eliasson et al. (2006); and Inglesby et al. (2000, 2002).

Table 4. Category A agent vaccines

Agent	Therapeutic options
Bacillus anthracis (anthrax)	*Preexposure prophylaxis*: Anthrax vaccine 0.5 ml subcutaneous at 0 and 4 weeks, then 6, 12, and 18 months, with annual boosters thereafter *Postexposure prophylaxis*[a]: Anthrax vaccine 0.5 ml subcutaneous at 0, 2, and 4 weeks in addition to a 60-day course of antibiotics

Note. [a]Not Food and Drug Administration approved for postexposure prophylaxis.
From Branda and Ruoff (2002); Franz et al. (1997); and Kman and Nelson (2008).

campaign. Local adverse reactions secondary to the vaccine have been reported in less than 30% of subjects, with the majority of those being erythema, edema, and induration of less than 30 mm (Wright et al., 2010). Systemic reactions have been reported in less than 1% of subjects.

YERSINIA PESTIS (PLAGUE)

Y. pestis is known to have caused more than 200 million deaths worldwide during its numerous epidemics and three pandemics (Darling et al., 2002; Inglesby et al., 2000). The most well-known pandemic was the second plague that started in 1346 and is known as the "Black Death," earning its name from the massive ecchymoses and fetid odor of patients with advanced disease (Kman & Nelson, 2008). This outbreak began in Europe and eventually claimed the lives of nearly one-third of the European population. The plague is an enzootic infection with a rodent (e.g., rats, ground squirrels, prairie dogs) host and a flea vector. Fleas transmit the infection to the rodents and then they can transmit the bacteria from one host to another, including humans. Although fleas are the most common mechanism for transmission, direct host-to-host transmission can occur through aerosolization. Humans can also become infected by coming into contact with infected tissues, bodily fluids, or respiratory droplets from infected or dead animals (Darling et al., 2002). There are three different forms of plague: bubonic, septicemic, and pneumonic (see Figure 3).

Naturally occurring plague exists on five continents, including Asia, Africa, North America, South America, and Europe. The CDC recorded 390 cases of plague in the United States from 1947 to 1996. The vast majority of these cases were bubonic plague, with pneumonic plague accounting for only 2% of cases (Koirala, 2006). Bubonic plague occurs after the *Y. pestis* bacteria enter the host following a flea bite that results in the characteristic lesion or "bubo" that gives this

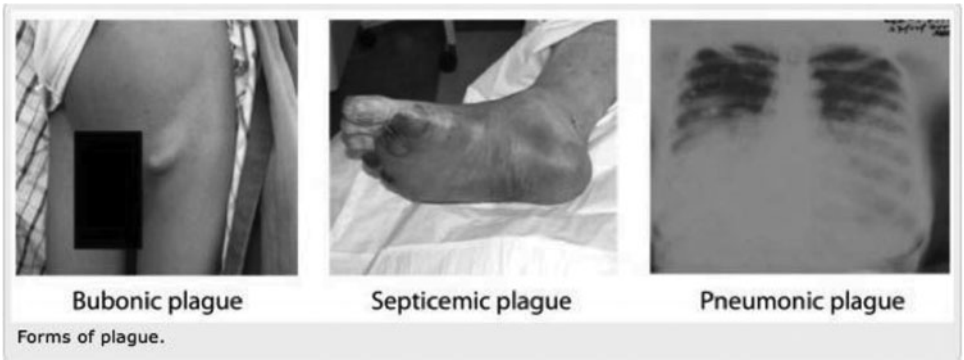

Figure 3. Forms of plague. Retrieved from http://emergency.cdc.gov/bioterrorism/.

infection its name. Pneumonic plague is a respiratory tract infection that can result from inhalation of the bacteria, and it represents the most likely route during a bioterrorist attack. In the absence of rapid and appropriate antibiotic therapy, death would occur within a few days (Inglesby et al., 2000).

Clinical Presentation

With naturally occurring bubonic plague, patients typically develop symptoms 2–6 days after a flea bite. Hemorrhagic necrosis tends to follow, leading to the formation of buboes, which are swollen and tender lymph nodes in the groin, axilla, or cervical region with associated rubor and edema. Buboes range in size from 1 to 10 cm, are very painful, erythematous, and associated with surrounding inflammation (Inglesby et al., 2000). From the lymph system, it has the potential to enter the blood, causing septicemia and leading to shock and even disseminated intravascular coagulation. Sepsis does have the potential to develop without buboes in a minority of cases, an illness termed "primary septicemic plague" (see Figure 4; Conrad, LeCocq, & Krain, 1968). Bubonic plague is not typically transmitted from person to person without the assistance of a flea vector. However, in the presence of pulmonary infection, the disease may be spread by respiratory transmission. Between 5% and 15% of patients will develop a secondary pneumonia and will shed infectious virulent bacilli in droplet nuclei while coughing. Pulmonary involvement arises from bacterial seeding via the bloodstream in bubonic or primary septicemic plague, causing secondary pneumonic plague.

Figure 4. Plague septicemia. Retrieved from http://emergency.cdc.gov/bioterrorism/.

Primary pneumonic plague symptoms start after a 2- to 4-day (range, 1–6 days) incubation period (Darling et al., 2002). Most patients develop a productive cough with blood-tinged sputum within 24 hr of the onset of symptoms. Near the end of the incubation period, initial symptoms include the onset of fever, headache, malaise, nausea, and vomiting (Darling et al., 2002).

Infection Control

Patients with bubonic plague will require body fluid precautions and segregation from other patients until completion of at least 3 days of appropriate antibiotics (Darling et al., 2002). Those with respiratory symptoms or confirmed pneumonic plague should be maintained on droplet precautions and negative pressure isolation (Kman & Nelson, 2008). Gowns, gloves, and eye protection, as well as surgical masks appear adequate to stop the spread of pneumonic plague.

Treatment and Prophylaxis

In a pneumonic plague epidemic, persons developing new cough or body temperature of 38.5 °C (101.3 °F) or greater should begin antibiotic treatment (see Table 2; Darling et al., 2002). Although intravenous antibiotics are recommended for the contained casualty setting, oral ciprofloxacin and doxycycline would be more practical in the mass casualty setting. Individuals who are affected should be isolated until they have completed at least 48 hours of antibiotic treatment and clinical improvement is evident (Darling et al., 2002).

The primary preventative measure in the outbreak of this agent will be flea and rodent control. Regardless of symptoms or lack thereof, all individuals who have had contact with patients who have pneumonic plague should receive prophylactic antibiotics (see Table 3; Inglesby et al., 2000). For

this purpose, close contact means contact with an affected patient at less than 2 m. Contacts who develop symptoms while being treated should seek prompt medical attention and begin intravenous therapy. Close contacts who refuse treatment will need to be watched carefully for the cough or fever within 7 days after exposure (Kman & Nelson, 2008).

FRANCISELLA TULARENSIS (TULAREMIA)

This is a disease caused by bacteria that infect humans through contact with small mammals that are infected by insect vectors (e.g., ticks, deerflies, mosquitoes), or via contaminated environments or aerosols (Branda & Ruoff, 2002; Darling et al., 2002). There has been no documentation of person-to-person transmission. Although it is not contagious, it is easily spread and has a profound ability to cause epidemics (Dennis et al., 2001). In addition, it has the ability to survive for weeks in water, soil, animal carcasses, frozen meat, and hay or straw (Cronquist, 2004). It is an extremely virulent organism, as demonstrated by a WHO report from 1969 that revealed that aerosol dispersal of 50 kg of *F. tularensis* in an area with 5 million people would result in 19,000 deaths and 250,000 persons with severe illness (Dennis et al., 2001). Although uncommon, respiratory exposure can also occur from the inhalation of contaminated dust particles. This agent was weaponized by the United States in the 1950s as part of the biowarfare program. The former Soviet Union also maintained stocks of weaponized tularemia but is never known to have used them in an attack (Dennis et al., 2001).

Most cases occur in rural areas where animals that serve as natural reservoirs live (Kman & Nelson, 2008). In the United States, cottontail rabbits and jackrabbits are the most common reservoirs for the vector. Squirrels, beavers, muskrats, meadow voles, cats, and rodents have also been linked to the disease. In the United States, ticks are responsible for 75% of cases and most infections occur in the south-central and western states. Much like plague, large quantities of dead animal hosts can herald impending human outbreaks. Nevertheless, an aerosolized attack would be the most likely method used by terrorists because it has the highest potential for adverse consequences.

Clinical Presentation

Infection with *F. tularensis* typically occurs 3–5 days after exposure (range, 1–21 days) and can occur through the mucous membranes, gastrointestinal tract, lungs, and skin (Dennis et al., 2001). The severity, type of symptoms, and time to onset often rely on the route of exposure, dose, and virulence of organism. Depending on the route of infection, patients can present with one of six clinical syndromes: ulceroglandular, oropharyngeal, oculoglandular, glandular, typhoidal, and pneumonic (Eliasson et al., 2006). The majority of naturally occurring cases (75%–85%) are ulceroglandular tularemia, and it is often acquired through the skin or mucous membranes by contact with the blood or fluids of infected animals (Eliasson et al., 2006). Ulceroglandular tularemia is characterized by headache, fever, chills, an ulcerated skin lesion, malaise, and painful regional lymphadenopathy (see Figure 5). The case fatality rate for this form of tularemia is about 5% without treatment. Composing 5%–15% of cases, typhoidal tularemia occurs mainly after inhalation of infectious aerosol (Eliasson

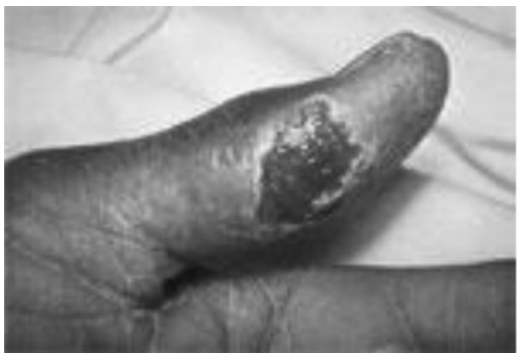

Figure 5. Ulceroglandular tularemia. Retrieved from http://emergency.cdc.gov/bioterrorism/.

et al., 2006). As with most Category A agents, this represents the most likely route of attack. Pneumonic tularemia pneumonia may be fulminate and is associated with a high mortality rate if not treated. It develops after the inhalation of organisms or its hematogenous spread throughout the body. This process occurs in 30%–80% of typhoidal cases and in only 10%–15% of ulceroglandular cases (Eliasson et al., 2006). Pulmonary infection often leads to death secondary to respiratory failure (Dennis et al., 2001). Complications arise from hematogenous spread of the bacteria that can lead to sepsis, pneumonia, and, in some cases, meningitis (Dennis et al., 2001).

Infection Control

During a tularemia outbreak, neither isolation nor quarantine is required. Heat and disinfectants easily inactivate the organism (Darling et al., 2002). A protective mask should be used when performing activities that create dust (Eliasson et al., 2006). In the setting of a bioterrorist release of tularemia aerosol, it is unclear how long aerosol would survive. In this event, exposed parties should decontaminate skin and clothing with soap and water. Decontamination of exposed surfaces and objects can occur with 10% bleach solution followed in 10 min by 70% alcohol solution. The standard level of chlorine in municipal water supplies should be adequate to prevent waterborne infection (Cronquist, 2004).

Treatment and Prophylaxis

Antibiotic therapy can reduce mortality in tularemia to less than 2%, compared with an untreated mortality rate of approximately 35% in inhalational tularemia cases (see Table 2; Darling et al., 2002; Dennis et al., 2001; Eliasson et al., 2006). The Working Group on Civilian Biodefense has recommended several treatment regimens for tularemia (Dennis et al., 2001). Although intramuscular (IM) administration is recommended initially, the patient may be changed to oral antibiotics once improvement is seen (Dennis et al., 2001). Because of the limited feasibility of IM administration in a mass casualty event, oral antibiotics should be utilized (Dennis et al., 2001).

Whether by covert terrorist attack or laboratory exposure, postexposure prophylaxis is recommended for tularemia exposure (see Table 3; Eliasson et al., 2006). If it can be given within 24 hr of exposure, a 14-day course of ciprofloxacin or doxycycline is an effective treatment. If the release of tularemia occurs covertly and diagnosis is not made until casualties present with symptoms, suspected contacts should watch for a fever. If symptoms arise within 14 days of presumed exposure, standard treatment regimens would apply.

CONCLUSION

Following the anthrax attacks in 2001, bioterrorism changed from a theoretical threat to a real, tangible concern for everyone. The anthrax attacks demonstrated that a rapid response by prepared medical, public health, government, and law enforcement professionals can mitigate the impact of bioterrorism. There are multiple countries that either possess or are attempting to acquire biological agents with the intent of doing harm to civilians. The Category A agents present the greatest threat, and thus the greatest challenge, for health care practitioner preparation. Anthrax, plague, and tularemia are all agents within this category that have high associated morbidity and mortality if left untreated. Fortunately, safe and effective antibiotic therapy is available for the treatment of infections from these organisms. Health care practitioners can elevate the societal level of preparedness for bioterrorism by ensuring that they are familiar with the biowarfare agents, their clinical recognition, and the management. The upcoming Part II of this review will complete the discussion of Category A agents by focusing on smallpox, viral hemorrhagic fevers, and botulism toxin. In addition, it will examine the public health response to these emergencies by reviewing the provision of mass prophylaxis and the role of the health care provider.

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