

Anthrax, tularemia, plague, ebola or smallpox as agents of bioterrorism: recognition in the emergency room

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Bioterrorism has become a potential diagnostic consideration in infectious diseases. This article reviews the clinical presentation and differential diagnosis of potential bioterrorist agents when first presenting to the hospital in the emergency room setting. The characteristic clinical features of inhalation anthrax, tularemic pneumonia, plague pneumonia, including laboratory and radiographic finding, are discussed. Ebola virus and smallpox are also discussed as potential bioterrorist-transmitted infections from the clinical and epidemiologic standpoint. In addition to the clinical features of the infectious diseases mentioned, the article discusses the infectious disease control and epidemiologic implications of these agents when employed as bioterrorist agents. The review concludes with suggestions for postexposure prophylaxis and therapy.

Keywords Anthrax, Bioterrorism, Plague, Ebola, Smallpox, Tularemia, Zoonoses, Zoonotic/Atypical pneumonias

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The emergency room is the most likely place where victims of bioterrorism will first be encountered and evaluated. As we have learned from the anthrax experience in New York, mass casualties are not necessarily to be expected. Even if large numbers of individuals are involved in a bioterrorist attack, the initial cases will present as isolated incidents or irregularly in low numbers. Once an outbreak is identified, then it is relatively easy to disseminate information on the nature of the infectious disease agent, in terms of its recognition and control. Emergency room personnel, with the assistance of infectious disease clinicians, are the sentinels at the gate.

Biological agents for potential use in bioterrorism are many. Some are more readily available and easier to employ than are others. The most likely agents to be involved in bioterrorism attacks include *Bacillus anthracis*, *Yersinia pestis*, *Clostridium botulinum*, *Francisella tularensis*, and possibly the viral agents of African hemorrhagic fevers. The emergency room, as the initial point of contact for most bioterrorism victims, has three critical func-

tions early in an attack. The initial function of physicians and consultants at the emergency room level would be to identify sentinel cases involved in the bioterrorism attack. It is critical to recognize that a problem exists and will soon involve larger numbers of individuals. Aside from clinical recognition of the signs and symptoms of agents related to bioterrorism, the emergency room has an important infection control role. Infectious disease clinicians will be essential to assist their emergency room colleagues, and infection control personnel will be needed to limit the spread of biological agents within the emergency room setting to other patients as well as medical personnel. Containment measures will be particularly important with biological agents that are transmitted via the airborne route, or by person-to-person contact. Finally, general supportive measures and specific antimicrobial therapy, antitoxins or vaccines will be needed to treat the affected patients, and this treatment will begin in the emergency room.

Emergency room personnel will need the early and substantial support of specialists related to the problems encountered with the various bioterrorist agents. Infectious disease consultants will be critical in the evaluation of all potential or real bioterrorist cases. Infection control, as mentioned previously, will be essential in containing the

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infection where appropriate, to prevent loss by illness of critical medical personnel during an outbreak. Physicians with experience in toxin-mediated diseases will also be needed if these agents are employed in a bioterrorism attack. On-going supportive care will be needed in the management phase for those severely affected by the attack. The emergency room also requires intensive support from the microbiology laboratory, and must be in communication with authorities to alert others of potential or actual threats from biological weapons [1–8].

BIOLOGICAL WEAPONS TRANSMITTED BY FOOD OR WATER

Clostridium botulinum

C. botulinum is a spore-forming organism that produces a potent exotoxin. The exotoxin is thermolabile, but is extremely potent. Minute amounts, if properly dispersed and disseminated, would be sufficient to eliminate the entire human population. Highly purified botulism toxin is stable, easily transportable, and readily dispersed. Ideal vehicles for the transmission of the toxin would be water supplies and selected food items, but fortunately, such transmission is difficult to achieve. Food-borne botulism requires the introduction of the toxin into foods at the level of the packing plant. This would require terrorists using this biological agent to have access to such a facility. In contrast, water-borne botulism toxin would be much easier to use, but because of difficulties with dispersal of the toxin in large volumes of water, it would be difficult to utilize. Botulism toxin could be easily placed in reservoirs or water tanks, but would not mix completely or evenly in the target volume of water. Therefore, water-borne botulism is likely to occur as sporadic attacks, since it is unlikely that large numbers of people would be affected simultaneously, due to the difficulties in dispersing the toxin in large volumes of water. In the emergency room, botulism will present as descending symmetric paralysis, starting with cranial nerve involvement. Onset would be heralded by the presence of blurry vision, which is rapidly followed by ocular muscle paralysis, difficulty in speaking, and/or the inability to swallow. Fever is not a feature of botulism, since it is a toxin-mediated disorder. There are few other conditions that could be confused with botulism clinically, but neurologic consultation is

advised to rule out other neurologic conditions with similar features. Respiratory paralysis may occur in severe cases. Importantly, mental status is unaffected by botulism; no signs of encephalitis or encephalopathy are present, and nuchal rigidity is not present, i.e. there is no evidence of meningitis. The incubation period is 10–12 h, but this will not be helpful in the initial evaluation of the patient. The incubation period is inversely proportional to the quantity of toxin ingested. Some patients may have profuse vomiting without diarrhea. Differential diagnostic possibilities include bulbar palsy, Guillain–Barre syndrome, or polio, but these conditions do not closely resemble botulism. Guillain–Barre syndrome is usually accompanied by some degree of fever, has a sensory component, and characteristically begins as ascending rather than descending paralysis. Diagnosis of botulism is confirmed by detecting botulism toxin in the stool or serum [9–13].

Enteropathogens

Toxicogenic or enteropathogenic *Escherichia coli*, *Salmonella* or *Vibrio cholerae* are potential biological weapons. Such agents would have to be introduced into water supplies in large numbers to be recognized as biological weapons. At any given time, there are sufficient sporadic cases of poorly characterized febrile diarrheal illnesses in the population to make the detection of these agents difficult. Only if they occurred in large numbers, suggesting an outbreak, could the possibility of bioterrorist be entertained. Clinicians are familiar with the clinical presentation of these infectious diseases and they are rarely fatal. The use of enteropathogens as biological weapons would create anxiety and cause some illness, but would be minimally disruptive to society. When these infectious diseases are not self-limited, they are readily treatable with antimicrobial agents [4–6].

BIOLOGICAL WEAPONS TRANSMITTED BY CONTACT

Ebola/viral hemorrhagic fevers

Person-to-person transmission is a potential way to spread some bioterrorist agents, particularly pneumonic plague and agents of African hemorrhagic fevers. These agents are highly contagious and difficult to handle, and because of this are not

likely to be utilized as biological weapons. Ebola fever, Rift Valley fever, etc. could be transmitted by a terrorist willing to be infected by these agents. The terrorist would have to travel to the intended area during the incubation period of the infection in order to initiate person-to-person transmission, by secretion contact and/or, to a lesser extent, by airborne dissemination. Ebola fever begins with severe headache and fever, followed quickly by gastrointestinal symptoms, usually accompanied by nausea and vomiting. As Ebola fever progresses, fever and severe myalgias remit for a few days, and then the patient worsens. Liver involvement and bleeding problems characterize the late stages of advanced Ebola fever. Physicians in the emergency room should be suspicious of patients with the abrupt onset of a severe illness characterized by headache, myalgias, and nausea and vomiting. Over several days, patients may

develop a camelback fever curve, and a pulse temperature deficit (relative bradycardia). Ebola and related hemorrhagic fevers are often accompanied by leukopenia, lymphopenia, and thrombocytopenia; these are important laboratory clues to help the clinician differentiate these illnesses from sporadic cases of gastroenteritis in the community. By the time that petechiae/ecchymoses or bleeding diatheses appear, the diagnosis should be obvious. Clinical diagnosis is confirmed by serologic testing. With suspected African hemorrhagic fevers, patients should be subjected to strict airborne isolation and contact precautions until the diagnosis is ruled out. Specimens sent to the laboratory should be considered as extremely biohazardous and handled accordingly. There is no specific treatment for any of the viral hemorrhagic fevers, and therapy is supportive [14–20] (Table 1).

Table 1 Differential diagnosis of African hemorrhagic fever

	Yellow fever	Lassa fever	Marburg virus disease	Ebola virus
Location	Central Africa	West Africa	East Africa	East Africa
Onset	Sudden	Gradual	Sudden	Sudden
Symptoms				
Severe headache/ myalgias/lumbar backache	+	+	+	+
Tinnitus	–	+	–	–
Sore throat	–	+	+	+
Dry cough/chest pain	–	+	+	+
Nausea/vomiting/ abdominal pain	+	–	+	+
Diarrhea	–	±	+	+
Renal failure	–	–	+	+
Signs				
Relative bradycardia	+	+	+	+
Biphasic fever pattern	+	+	+	+
Conjunctivitis	–	+	+	+
Conjunctival suffusion	+	+	+	+
Rash	–	–	Scarlatiniform	Maculopapular
Adenopathy	–	Cervical	Generalized	–
Facial/neck edema	–	+	–	–
Laboratory abnormalities				
Leukopenia → leukocytosis	+	+	+	+
Atypical lymphocytosis	+	+	+	+
Thrombocytopenia	+	+	+	+
↑SGOT	+	+	+	+
Late complications	If not death from acute hepatic necrosis, none	Iritis, deafness, ARDS, seizures, oculogyric crises	Myocarditis, orchitis desquamation, scrotal/labial dermatitis, ARDS	Extreme malaise, profound loss of appetite

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BIOLOGICAL WEAPONS TRANSFERRED BY THE AIRBORNE ROUTE

Smallpox

Like most infectious diseases, smallpox is most contagious during the incubation period before the onset of the rash. The initial patients in a biological attack using smallpox will present before the rash appears. The rash in smallpox does not appear for at least 3 days after the on-set of symptoms. Patients initially complain of headache and myalgias, and may have a diffuse maculopapular rash prior to their subsequent vesicular eruption. Fevers are high and have a characteristic pattern. The fever initially decreases without treatment on day two, before increasing again prior to the vesicular eruption on or after day three. Patients may complain of gastrointestinal symptoms at the outset of the illness. Patients also appear irritable and uncomfortable before the rash appears. The appearance of the rash is heralded by a decrease in temperature and the appearance of vesicles beginning on the head and face. Vesicles increase and become prominent on the chest, have a centrifugal distribution on the extremities, and involve the palms and the soles. In the early vesicular stage, smallpox is most likely to be confused with chicken pox. The constitutional symptoms, as well as the distribution of the rash, readily differentiate it from other vesicular rashes, e.g. orf, dermatitis, or herpeticiformis, and atypical measles. In chicken pox, the rash progresses in successions of crops of new vesicles every few hours, and abruptly stops after 3 days. The vesicles are not as large or umbilicated as in smallpox. Patients are not as toxemic in appearance as with smallpox. The vesicles of chicken pox resemble a dewdrop on a rose petal, and lesions in chicken pox all present at different stages of eruption. In smallpox, characteristically, the lesions, are all in the same stage of development when they appear. Hemorrhagic smallpox may present with diffuse bleeding into the skin. Smallpox and chicken pox are clinical diagnoses. If there is any confusion in differentiating the two, a Tzanck test should be performed. Cytoplasmic inclusion bodies seen in stained scrapings from the vesicle base are present in chicken pox but not in smallpox. Both chicken pox and smallpox are highly contagious via the airborne route, and require strict airborne isolation. Patients are no longer contagious after the

lesions crust. The treatment of smallpox is currently symptomatic. Although cidofovir has in vitro activity against the smallpox virus, it is fairly toxic and can only be administered intravenously. Children and young adults have not been vaccinated against smallpox. The immunity of older adults previously immunized against smallpox is not known at the present time. If smallpox is identified in a patient, it must be assumed to represent a bioterrorism attack, since natural cases no longer exist. Accordingly, officials must be contacted for immediate distribution of the smallpox vaccine. Some older individuals may develop immunity more rapidly than their younger counterparts, due to the anamnestic response to the previous smallpox vaccine [21–26] (Table 2, Figure 1).

Tularemia

F. tularensis is a highly virulent organism with different manifestations depending upon inoculum/site of infection. It is unlikely that *F. tularensis* would be used as a weapon of bioterrorism, since it has no stable spore phase, and is highly virulent and difficult to handle. It would be difficult to aerosolize this organism without infecting those processing and handling the organism for use in biological warfare. Should tularemia be used, aerosol spread would be the most likely mode of deployment. In the emergency room, patients would present with an atypical pneumonia. Most clinicians are now familiar with the fact that atypical pathogens are characterized by extrapulmonary manifestations. The most common atypical pneumonias encountered in the emergency room setting are *Mycoplasma pneumoniae* pneumonia and legionnaires' disease. Legionnaires' disease is most likely to be confused with tularemic pneumonia, but these two may be differentiated fairly well by clinical signs and symptoms. Patients with tularemia, in contrast to those with legionnaires' disease, have a clear sensorium, but both may present with a headache. The headache of tularemia, however, is severe and usually associated with prominent myalgias. The chest X-ray pattern of tularemic pneumonia is nondescript, as is that of legionnaires' disease. Infiltrates in tularemic pneumonia may be unilateral or bilateral, but they are usually accompanied by pleural effusion and/or hilar adenopathy. Tularemic pneumonia is more likely to be confused with inhalation anthrax than

Table 2 Smallpox: infection control considerations

	Potential for patient-to-patient spread	Potential for patient-to-medical personnel spread	Infection control precautions	Recommended disinfection procedures	Postexposure prophylaxis of medical contacts
Emergency room/ hospital	High	High	Standard universal precautions Airborne Isolation	Sodium hypochlorite or quaternary ammonia compounds Clothing/bedding should be washed in hot water with bleach/autoclaved Use biohazard bags for all else	Smallpox vaccination recommended, if unable to take vaccine (compromised hosts) administer vaccinia immune globulin (VIG) 0.6 mL/kg (IM) in 2 divided doses over 24 h

with legionnaires' disease. Both inhalation anthrax and tularemic pneumonia have mediastinal widening and pleural effusions as common features. In legionnaires' disease, serum transaminases are frequently mildly and transiently elevated, in contrast to tularemic pneumonia, in which the serum transaminases remain normal. Relative bradycardia is a cardinal feature of legionnaires' disease but is not characteristic of tularemia. Increases in CPK, erythrocyte sedimentation rate, and CRP, and a decreased serum phosphorus, strongly favor the diagnosis of legionnaires' disease versus tularemia, anthrax, or typical bacterial pneumonias. If the pleural effusions are tapped, the pleural effusions of tularemia are sero-sanguinous or frankly hemorrhagic, which is uncommon with other pulmonary infections, except for inhalation anthrax. *F. tularensis* is readily treatable, if recognized early, with doxycycline. Quinolones probably represent an acceptable alternative in doxycycline-intolerant patients. From the infection control standpoint, the main biohazard presented by tularemia is in the handling of specimens by personnel in the emergency room and microbiology laboratory [27–35] (Tables 3–5).

Plague pneumonia

Pneumonic plague would be a devastating agent to use in biological warfare. Unlike bubonic plague, pneumonic plague has the potential for person-to-person airborne spread. If plague is transmitted in this fashion, it has great potential for spreading. However, *Y. pestis* has no spore stage, and is difficult to process, handle and disperse if used in aerosol form. Should anyone in a non-endemic area develop pneumonic plague that is not a complication of an ongoing bubonic plague epidemic, then the plague may be considered to be the result of the bioterrorism. Plague pneumonia is nondescript in terms of chest X-ray appearance. Patients are critically ill. The sputum is pink and frothy and contains abundant bipolar-staining Gram-negative bacilli. Hilar adenopathy and pleural effusions are not features of pneumonic plague. Circulatory collapse is common as the infection progresses, as is the case with inhalation anthrax. Diagnosis is established by demonstrating the organism in sputum or blood samples. Plague may be treated with streptomycin or doxycycline. From an infection control standpoint, person-to-person spread of plague from patients

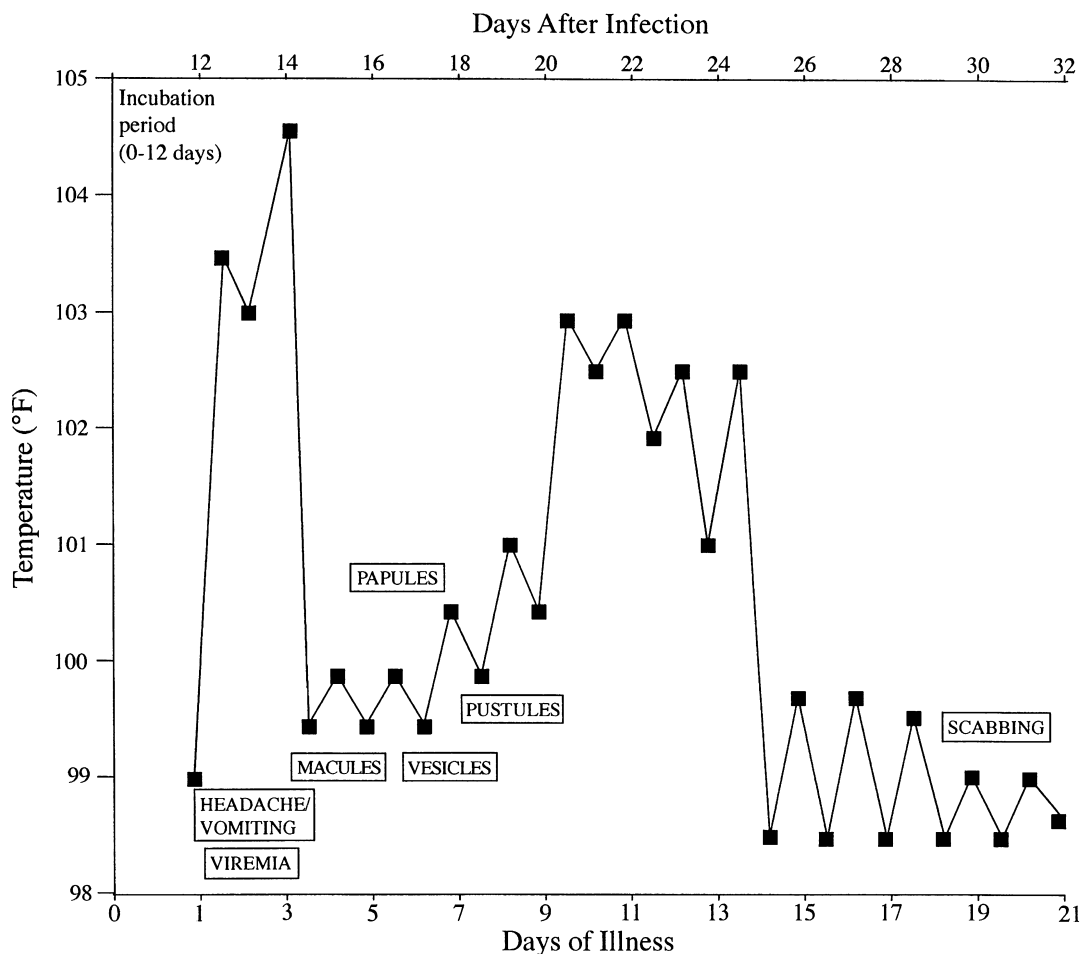


Figure 1 Smallpox: relationship of fever to signs and symptoms. Reproduced with permission from: Cunha BA. Smallpox: an osterian primer. *Infect Dis Practice* 2002; 26.

with pneumonic plague may be contained by using appropriate airborne precaution procedures [36–44] (Tables 6–8).

Anthrax

Because anthrax is a naturally occurring infectious disease, there is much experience with recognizing and treating naturally acquired inhalational and cutaneous anthrax. However, in the 2001–2002 US experience, weapons-grade anthrax was used as a weapon of bioterrorism for the first time. Cutaneous anthrax derived from weapons-grade anthrax is clinically the same as naturally acquired cutaneous anthrax. However, the clinical presentation of inhalational anthrax due to weapons-grade *B. anthracis* spores is different from that of cases previously occurring with naturally acquired inhalation anthrax. Except for the previous

incident occurring in Sverdlosk in the Soviet Union due to an accident at a biological weapons facility, the New York experience is the only carefully studied and reported experience with inhalation anthrax from the inhalation of weapons-grade spores. Patients presenting with inhalation anthrax do not feel well for several days during the prodromal period, and frequently complain of substernal discomfort and fever; sometimes, gastrointestinal symptoms are present at this stage. Patients still do not feel well, but subsequently improve over the next day or two, and then in most cases the infection progresses.

The second phase of anthrax is characterized by high fever, oppressive sternal chest pain mimicking an acute myocardial infarction, and shortness of breath. Chest X-ray may reveal small bilateral pleural effusions, with or without a widened mediastinum. Since inhalation anthrax results in a

Table 3 Tularemia: empirical therapy for presumed tularemic pneumonia

Exposed hosts	Preferred initial therapy	IV → PO switch	Total duration of therapy (IV/PO)
Adults	Streptomycin 1 g (IM) every 12 h	NA	10 days
	or Gentamicin 5 mg/kg (IM/IV) every 24 h	NA	10 days
	or Doxycycline 200 mg (IV) every 12 h	Doxycycline 100 mg (PO) every 12 h	14 days
	or Chloramphenicol 500 mg (IV) every 6 h	Chloramphenicol 250 mg (PO) every 6 h	14 days
	or Ciprofloxacin 400 mg (IV) every 12 h	Ciprofloxacin 500 mg (PO) every 12 h	10 days
	or Levofloxacin 500 mg (IV) every 24 h	Levofloxacin 500 mg (PO) every 24 h	10 days
	or Gatifloxacin 400 mg (IV) every 24 h	Gatifloxacin 400 mg (PO) every 24 h	10 days
Children >12 years	Same as adults		
<12 years	Streptomycin 15 mg/kg (IM) every 12 h	NA	10 days
	or Gentamicin 5 mg/kg (IM/IV) every 24 h	NA	10 days
	or Doxycycline 2.2 mg/kg (IV) every 12 h	Doxycycline 2.2 mg/kg (PO) every 12 h	14 days
	or Ciprofloxacin 30 mg/kg (IV) every 12 h	Ciprofloxacin 30 mg/kg (PO) every 12 h	10 days
	or Levofloxacin 250 mg (IV) every 24 h	Levofloxacin 250 mg (PO) every 24 h	10 days
	or Gatifloxacin 200 mg (IV) every 24 h	Gatifloxacin 200 mg (PO) every 24 h	10 days

Table 4 Tularemia: infection control considerations

	Potential for patient-to-patient spread	Potential for patient-to-medical personnel spread	Infection control precautions	Recommended disinfection procedures	Post-exposure prophylaxis of medical contacts
Emergency room/hospital	None	None	Standard universal precautions	Sodium hypochlorite or quaternary ammonia compounds (avoid aerosolization of infectious materials)	+

Post-exposure host	Preferred antibiotic	Duration of prophylaxis
Adults (normal/compromised hosts)	Doxycycline 100 mg (PO) every 12 h	14 days
	or	14 days
	Ciprofloxacin 400 mg (PO) every 12 h	
	or	
	Levofloxacin 500 mg (PO) every 24 h	14 days
	or	
	Gatifloxacin 400 mg (PO) every 24 h	14 days
Children (normal/compromised hosts)		
>12 years	Same as adult	
<12 years	Amoxicillin 40 mg/kg (PO) every 8 h	14 days
	or	
	Ciprofloxacin 30 mg/kg (PO) every 12 h	14 days
	or	
	Levofloxacin 250 mg (PO) every 24 h	14 days
	or	
	Gatifloxacin 200 mg (PO) every 24 h	14 days

Table 5 Tularemia: postexposure prophylaxis

hemorrhagic mediastinitis and not pneumonia, demonstration of a widening mediastinum should suggest the diagnosis of inhalation anthrax in acutely ill febrile patients. The mediastinal widening due to hemorrhagic mediastinitis is detected earliest and best by chest CT/MRI. As mentioned previously, the hemorrhagic mediastinitis may be inapparent or minimally apparent on the conventional chest X-ray, and if there is any question about the possibility of anthrax or interpretation of the plain film, then a chest CT/MRI should be obtained immediately. Liver function tests have been reported as being abnormal in inhalation anthrax cases; otherwise, routine laboratory tests are unhelpful, except for thrombocytopenia, which is a variable finding. In hemorrhagic mediastinitis, the fact that the inhaled spores have been milled to a very small diameter and processed with a surface tension-reducing agent allows individual spores to reach the alveoli. The spores are ingested by the alveolar macrophages and transported via the lymphatics to the lymph nodes of the mediastinum. There they interfere with hemostasis locally, resulting in hemorrhage at the mediastinum. If the inoculum of

inhaled weapons-grade spores is sufficiently high, a localized pneumonitis in the segment of the lung receiving the high spore concentration can result in a pulmonary infiltrate in addition to the findings of hemorrhagic mediastinitis described.

Anthrax meningitis frequently accompanies cases of inhalation anthrax, so emergency room physicians must be alert to patients presenting with central nervous system findings in addition to their pulmonary symptoms. In some cases, anthrax hemorrhagic leptomeningitis occurs alone and/or overshadows the pulmonary component of the infection. Lumbar puncture performed in patients with anthrax meningitis reveals a PMN predominance and abundant red blood cells. The cerebrospinal fluid (CSF) glucose is depressed, and the CSF protein is variably elevated. A Gram stain of the CSF shows Gram-positive bacilli. In the Sverdlosk experience, anthrax meningitis was readily diagnosed at autopsy in patients who died of anthrax meningitis. The characteristic appearance has been termed 'the cardinal's cap', in which there is hemorrhage diffusely over the brain, involving the leptomeninges. This finding may be useful in terms of retrospective diagnosis, but is

Table 6 Empirical therapy for presumed plague

Exposed hosts	Preferred initial therapy	IV → PO switch	Total duration of therapy (IV/PO)
Adults	Streptomycin 1 g (IM) every 12 h	NA	10 days
	or		
	Gentamicin 5 mg/kg (IM/IV) every 24 h	NA	10 days
	or		
	Doxycycline 200 mg (IV) every 12 h	Doxycycline 100 mg (PO) every 12 h	14 days
	or		
	Chlorophenicol 500 mg (IV) every 6 h	Chloramphenicol 250 mg (PO) every 6 h	14 days
	or		
	Ciprofloxacin 400 mg (IV) every 12 h	Ciprofloxacin 500 mg (PO) every 12 h	10 days
Children	or		
	Levofloxacin 500 mg (IV) every 24 h	Levofloxacin 500 mg (PO) every 24 h	10 days
	or		
	Gatifloxacin 400 mg (IV) every 24 h	Gatifloxacin 400 mg (PO) every 24 h	10 days
	>12 years	Same as adult	
	<12 years		
	Streptomycin 15 mg/kg (IM) every 12 h	NA	10 days
	or		
	Gentamicin 5 mg/kg (IM/IV) every 24 h	NA	10 days
	or		
	Doxycycline 2.2 mg/kg (IV) every 12 h	Doxycycline 2.2 mg/kg (PO) every 12 h	14 days
	or		
	Ciprofloxacin 30 mg/kg (IV) every 12 h	Ciprofloxacin 30 mg/kg (PO) every 12 h	10 days
	or		
	Levofloxacin 250 mg (IV) every 12 h	Levofloxacin 250 mg (PO) every 24 h	10 days
	or		
	Gatifloxacin 200 mg (IV) every 24 h	Gatifloxacin 200 mg (PO) every 24 h	10 days
	or		
	Chloramphenicol 25 mg/kg (IV) every 6 h	Chloramphenicol 25 mg/kg (PO) every 6 h	14 days

Table 7 Plague: infection control considerations

	Potential for patient-to-patient spread	Potential for patient-to-medical personnel spread	Infection control precautions	Recommended disinfection procedures	Post-exposure prophylaxis of medical contacts
Emergency room/hospital	Low	Low	Standard universal precautions plus surgical masks	Sodium hypochlorite or quaternary ammonia compounds	+ (during first 48 h of antibiotic therapy)

Post-exposure host	Preferred antibiotic	Duration of prophylaxis
Adults (normal/compromised hosts)	Doxycycline 100 mg (PO) every 12 h	7 days
	or Ciprofloxacin 400 mg (PO) every 12 h	7 days
	or Levofloxacin 500 mg (PO) every 24 h	7 days
	or Gatifloxacin 400 mg (PO) every 24 h	7 days
	or Chloramphenicol 500 mg (PO) every 6 h	7 days
Children (normal/compromised hosts)		
>12 years	Same as adult	
<12 years	Doxycycline 2.2 mg/kg (PO) every 12 h	7 days
	or Ciprofloxacin 30 mg/kg (PO) every 12 h	7 days
	or Levofloxacin 250 mg (PO) every 24 h	7 days
	or Gatifloxacin 200 mg (PO) every 24 h	7 days
	or Chloramphenicol 25 mg/kg (PO) every 6 h	7 days

Table 8 Plague: post-exposure prophylaxis

unhelpful in the initial management in the emergency room setting (Table 9).

If anthrax spores are ingested, gastrointestinal anthrax may result, but this would be exceedingly uncommon. Gastrointestinal anthrax is characterized by a single large lesion, not unlike the cutaneous lesion of anthrax, but which is present in the gastrointestinal tract. There is usually a single, large ulcer present, which may hemorrhage. Bacteremia may complicate any clinical type of anthrax, and is overwhelming in septicemic anthrax. When there is hematogenous dissemination from the skin or the lungs, some of the organisms localize to the gastrointestinal tract. For this reason, in cases of anthrax it is not uncommon to find multiple small hemorrhagic ulcers throughout the gastrointestinal tract. This is in contrast to the single predominant lesion found when the organisms are ingested and do not reach the intestine via the bloodstream.

The presumptive diagnosis of anthrax depends on demonstrating Gram-positive bacilli under the eschar in cutaneous anthrax, or in the CSF in anthrax meningitis, or in the blood in bacteremic or septicemic anthrax. The sputum does not usually contain *B. anthracis* in inhalation anthrax. Samples of body fluids should be considered to be extremely biohazardous, and the microbiology laboratory should be warned prior to specimens are being sent to them from the emergency room. The presumptive diagnosis of anthrax depends on demonstrating hemolysis on blood agar. Other tests suggested for anthrax in Gram-positive bacilli are the demonstration of a capsule using a negative stain, e.g. Congo red or India ink, or the demonstration of the characteristic fir tree appearance of gelatin liquefaction in a stat gelatin culture tube. Serologic tests for anthrax usually take some time and are unhelpful in the initial management of patients.

Table 9 Diagnostic approach to biological agents transmitted by inhalation

	Plague	Tularemia	<i>Legionella</i>	Anthrax
Symptoms				
Sore throat	—	±	—	±
Shortness of breath	+	±	—	+
Hemoptysis	+	+	—	+
Chest pain	++	±	±	+++
Abdominal pain	+	—	±	±
Nausea/vomiting	+	—	±	±
Diarrhea	+	—	+	±
Signs				
Relative bradycardia	—	—	+	—
Shock	+	±	—	+
Laboratory features				
Sputum	Hemorrhagic (raspberry syrup sputum)	Hemorrhagic	Mucoid/purulent	Hemorrhagic
Gram stain sputum	Gram-negative coccobacilli (bipolar staining)	Gram-negative coccobacilli (non-bipolar staining)	Negative/normal flora	Gram-positive bacilli
Blood cultures	+	—	—	+
Chest X-ray:				
Infiltrates	Bilateral segmented/lobar (± consolidation infiltrates)	Bilateral/segmented/lobar (— consolidation)	Multilobar infiltrates	Usually none (if present, focal infiltrates)
Mediastinal widening				
Pleural effusion	—	+ (Bilateral bloody)	± (Non-bloody)	+ (Bilateral bloody)
BHA	—	+	—	—
WBCs				
↑ LFTs	—	—	+	+
↑ CPK	—	—	+	—
↓ PO ₄	—	—	+	—

BHA, bilateral hilar adenopathy.

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Specimens that are presumptively identified as being positive for anthrax should be forwarded to central laboratories for definitive identification (Table 10).

Fortunately, *B. anthracis* is susceptible to the majority of antibiotics. The organism is exquisitely sensitive to penicillin and most β -lactams. The most extensive experience in treating anthrax has been with penicillin and with doxycycline. In the recent New York experience, quinolones were used. Some patients were treated with double-drug therapy, but there is little evidence to support this approach. *B. anthracis* is so exquisitely sensitive that consideration of synergy is irrelevant. In some patients, clindamycin was added to the regimen for its purported anti-endotoxin activity rather than its antibacterial effects.

Because of earlier treatment and recognition, rather than because of more efficacious antibacter-

Table 10 Microbiological differences between *B. anthracis* and non-*B. anthracis* bacilli

<i>B. anthracis</i>
Non-motile/encapsulated/long chains
No growth on penicillin agar (10 µg/mL)
'Inverted fir-tree' growth in gelatin
Gelatin liquefaction slow
No hemolysis of sheep red blood cells
Ferments salicin slowly or not at all
Pathogenic to laboratory animals
Non- <i>B. anthracis</i> (pseudo-anthrax bacilli)
Generally motile/non-encapsulated/short chains
Usually good growth on penicillin agar
Growth absent or atypical fir tree in gelatin
Gelatin liquefaction usually rapid
Hemolysis of sheep red blood cells
Usually ferment salicin rapidly
Non-pathogenic to laboratory animals

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ial therapy, the fatality rate with inhalation anthrax in the New York experience was better than had been previously reported.

From an infection control standpoint, inhalation anthrax and cutaneous anthrax are not very contagious, but the potential for contagiousness exists via organism- or spore-contaminated/infected body fluids [45–53] (Tables 11–13).

SYNDROMIC CLINICAL DIAGNOSTIC AND THERAPEUTIC APPROACH

Bioterrorism in the emergency room presents special challenges. The main focus of emergency room personnel in a possible bioterrorism attack is to quickly and rapidly arrive at a presumptive diagnosis of the agents involved. Early recognition

Table 11 Anthrax: empirical therapy for presumed anthrax pneumonia

Exposed hosts	Preferred initial therapy	IV → PO switch	Total duration of therapy (IV/PO)
Adults	Doxycycline 200 mg (IV) every 12 h or Penicillin G 4 MU (IV) every 4 h or Ciprofloxacin 400 mg (IV) every 12 h or Levofloxacin 500 mg (IV) every 24 h or Gatifloxacin 400 mg (IV) every 24 h	Doxycycline 100 mg (PO) every 12 h or Amoxicillin 1 g (PO) every 8 h or Ciprofloxacin 500 mg (PO) every 12 h or Levofloxacin 500 mg (PO) every 24 h or Gatifloxacin 400 mg (PO) every 24 h	≥14 days ≥14 days ≥14 days ≥14 days ≥14 days
Children			
>12 years	Same as adult		
<12 years	Doxycycline 2.2 mg/kg (IV) every 12 h or Penicillin 50 000 U/kg (IV) every 6 h or Ciprofloxacin 30 mg/kg (IV) every 12 h or Levofloxacin 250 mg (IV) every 24 h or Gatifloxacin 200 mg (IV) every 24 h	Doxycycline 2.2 mg/kg (PO) every 12 h or Amoxillin 40 mg/kg (PO) every 8 h or Ciprofloxacin 30 mg/kg (PO) every 12 h or Levofloxacin 250 mg (PO) every 24 h or Gatifloxacin 200 mg (PO) every 24 h	14 days 14 days 14 days 14 days 14 days

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Table 12 Anthrax: infection control considerations

	Potential for patient-to-patient spread	Potential for patient-to-medical personnel spread	Infection control precautions	Recommended disinfection procedures	Post-exposure prophylaxis of medical contacts
Emergency room/hospital	Low	Low	Standard universal precautions	Sodium hypochlorite or quaternary ammonia compounds	Unnecessary

Table 13 Anthrax: post-exposure prophylaxis

Post-exposure host	Preferred antibiotic	Duration of prophylaxis
Adults (normal/compromised hosts)	Doxycycline 100 mg (PO) every 12 h	60 days
	or Amoxicillin 1 g (PO) every 8 h	60 days
	or Ciprofloxacin 400 mg (PO) every 12 h	60 days
	or Levofloxacin 500 mg (PO) every 24 h	60 days
	or Gatifloxacin 400 mg (PO) every 24 h	60 days
Children (normal/compromised hosts)		
>12 years	Same as adult	
<12 years	Amoxicillin 40 mg/kg (PO) every 8 h	60 days
	or Ciprofloxacin 30 mg/kg (PO) every 12 h	60 days
	or Levofloxacin 250 mg (PO) every 24 h	60 days
	or Gatifloxacin 200 mg (PO) every 24 h	60 days

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provides the ability to warn other centers to be watchful for patients with similar syndrome complexes. It also alerts hospital personnel to the danger of infected patients, and alerts laboratory personnel to the danger of handling biohazardous materials. As is the case with other infectious diseases, differential diagnosis is the key function of physicians and consultants. When an outbreak due to bioterrorism agent is well underway and understood, awareness is heightened and the likelihood of misdiagnoses decreases greatly. However, the real challenge comes in diagnosing the index cases correctly. Patients subjected to bioterrorist agents are likely to present with either neurologic symptoms, e.g. botulism, or respiratory symptoms, e.g. plague pneumonia, inhalation anthrax, tularemic pneumonia, gastrointestinal illnesses, enteric pathogens, bleeding diatheses, such as the African hemorrhagic fevers, or pneumonias, such as tularemic pneumonia, inhalation anthrax, or plague pneumonia. The most difficult diagnostic challenge would be to differentiate between diseases that have similar features, e.g. tularemic

pneumonia versus inhalation anthrax, or to separate these entities from other conditions in the community that may cause confusion in the emergency room setting, e.g. legionnaires' disease versus tularemia. Except for botulism and the African hemorrhagic fevers, and smallpox, all of the remaining agents likely to be used in bioterrorism are bacteria, and are susceptible to antibiotics (Table 14).

While quinolones are preferable for enteral pathogens, and streptomycin is preferred for plague, doxycycline is the antibiotic most likely to be efficacious when a precise etiologic agent has not yet been identified. Doxycycline, when used for serious infections, is optimally given at a dose of 200 mg intravenously every 12 h for ≥ 72 h. Because the drug has a long half-life and is highly lipid soluble, this loading regimen needs to be used in order to achieve a rapid therapeutic effect. If a patient is given doxycycline, 100 mg intravenously or orally every 12 h, as is usually recommended, it will take 4–5 days before the maximum therapeutic effect is achieved. This is far too long,

Clinical syndrome	Bioterrorist agents	Non-bioterrorist mimic
Severe headache/myalgias, nausea, vomiting, generalized bleeding	Ebola Hemorrhagic smallpox (pre-eruptive)	Meningococcal meningitis/ meningococemia Hemorrhagic measles
Severe headache, myalgias, and vomiting	Smallpox (pre-eruptive)	Rocky Mountain spotted fever (RMSF) Viral influenza Tick-borne arboviruses
Weakness, blurry vision, dysphagia	Botulism	Bulbar palsies (massive CVA, ALS) Pseudobulbar palsies
Community-acquired pneumonia with hemoptysis	Plague pneumonia Tularemia pneumonia	Pulmonary emboli/ infarction
Community-acquired pneumonia with nausea, vomiting, diarrhea, abdominal pain	Plague pneumonia	<i>Legionella</i>
Community-acquired pneumonia with chest pain/shock	Anthrax	Acute MI

CVA, cerebrovascular accident; ALS, amyotrophic lateral sclerosis.

Table 14 Differential diagnosis of bioterrorist agents by clinical syndrome on presentation to the emergency room

and anyone who has a critical infectious disease for which doxycycline is an appropriate treatment should always use the loading regimen described for seriously ill patients [54,55].

Infection control measures are important in containing the infection and allaying fears when biological agents are used that have little or no contagious potential. The microbiology laboratory, in particular, and medical and nursing personnel as well are likely to have the highest potential for becoming infected. A rapid alert system should be in place, so that even presumptive cases are effectively and rapidly identified, and this information is disseminated to other medical centers in the area. A high grade of suspicion and constant vigilance are necessary as bioterrorism becomes a fact of life, and new manifestations of infection due to these agents should be expected and looked for.

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