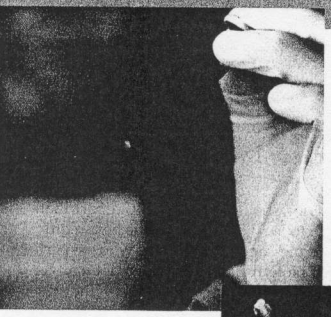
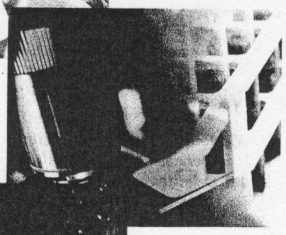
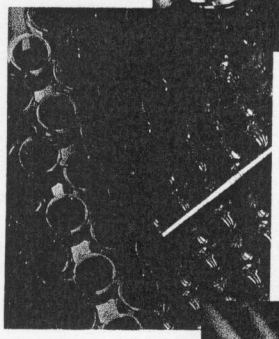
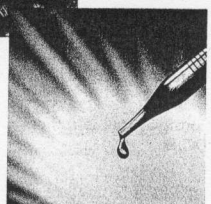
ACP

Bioterrorism Resource Guide









INTRODUCTION

CLINICIANS: STRENGTHENING THE FRONT LINE AGAINST BIOTERRORISM

In 2001, anthrax-filled envelopes that were mailed to several sites along the East Coast made the threat of bioterrorism in this country a reality.

Along with killing five Americans, the attacks exposed serious vulnerabilities in the U.S. health care system. Some of the physicians who treated attack victims did not quickly recognize the symptoms of the rarely encountered anthrax bacteria. Subsequent delays in diagnosis and treatment increased the number of fatalities.

The tragic lesson learned during the 2001 attacks is that rapid recognition and reporting are key to containing the spread of bioweapons and reducing casualties. Because experts say that additional attacks are possible, they are calling on physicians to arm themselves with knowledge on likely bioterrorist agents.

Several factors, however, make physicians' front-line role in the battle against bioterrorism difficult. For one, internists rarely see most of the pathogens that are likely to be used in a bioterrorist attack. Patients may also present with atypical symptoms if unusual dissemination methods are used during an attack, or if pathogens have been changed at a molecular level.

This special supplement to *ACP Observer* is designed to re-acquaint physicians with the six pathogens the CDC has classified as category A pathogens. The agency has reserved this classification for agents that would be the easiest to transmit and would cause the greatest public health devastation. Several of these pathogens have already been developed or used as bioweapons, including anthrax, smallpox, plague and botulinum toxin.

The CDC's message to physicians is clear: Do not wait to confirm your suspicions with laboratory findings before reporting a suspected attack.

Because the outbreak of disease in an attack is likely to differ from naturally-occurring disease from the same microbe, this supplement includes the "ACP Guide to Bioterrorism Identification," with a list of epidemiologic clues to help detect a potential event. (See the insert between pages 6 and 7 of this supplement.) The articles highlighting each pathogen include more specific epidemiologic indicators.

Any infection with a category A agent represents a potential public health emergency that must be contained by public health officials. Most of these pathogens require specialized sample collection, as well as testing procedures or reagents that only public health officials can provide.

Testing laboratories will also need to be warned to take the extra precautions required with a suspected category A pathogen. And physicians and other health professionals will have to follow guidelines for proper patient isolation and contact surveillance.

If physicians suspect that patients have been exposed to a category A pathogen, they should immediately report that information to local and state public health officials. CDC's message to physicians who suspect any form of bioterrorism is clear: Do not wait to confirm your suspicions with laboratory findings before reporting a suspected attack. As the events of 2001 made clear, fighting bioterrorism is not only a struggle against criminal intent, but also a race against the clock. ■

Online resources to help you recognize and prepare for bioterrorism

The Internet is a rich repository for information on bioterrorism, including facts, images and decision support tools. Here is a sampling of some of the resources available on the Web:

- Decision support tools for anthrax and smallpox, detailed information on the pathogens likely to be used in a bioterrorist attack, and clinical images are on ACP's Bioterrorism Resource Center at www.acponline.org/bioterror/.
- Palm pilot documents on bioterrorism identification, including quick facts on individual bioterrorism pathogens and clinical decision support tools, are online at www.acponline.org/pda/bioterrorism.htm.
- A list of bioterrorism agents and diseases, as well as detailed information on likely pathogens and clinical images, can be found on the CDC's Web site at www.bt.cdc.gov/agent/agentlist.asp.
- The College's MKSAP 13: Medical Aspects of Bioterrorism is online at www.acponline.org/bioterror/.
- A clinician registry form to receive regular CDC updates on bioterrorism can be found at www.bt.cdc.gov/clinregistry/index.asp.
- A bioterrorism self-assessment quiz is online at www.acponline.org/bioterro/self_assessment.htm. (Also see page 12.)
- ACP's public policy and advocacy recommendations on bioterrorism can be found at www.acponline.org/hpp/menu/bioterror. htm. ■

Reporting suspected events

Internists are likely to be the first health care professionals to encounter victims of a bioterrorist attack. To ensure a prompt and effective response, public health officials urge physicians to do the following:

- Immediately notify hospital infection control specialists and local and state public health officials whenever they suspect a bioterrorist attack has occurred. Any patients presenting with distinctive symptoms or signs of infection with a category A pathogen should prompt notification procedures.
- Do not wait for confirmation.
- Contact the laboratory conducting diagnostic testing on patients' specimens so personnel can take proper precautions and provide specific instructions on specimen collection, packaging and transport.
- Notify the CDC when local laboratories and public health officials cannot be reached. The CDC's emergency response hotline, which operates 24 hours a day, is 770-488-7100. For a listing of state and local public health department contact information, go to www.cdc.gov/other.htm#states or to www.acponline.org/bioterro/index.html#fbi. ■

ACP Observer Bioterrorism Resource Guide

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- Daniel Havlichek Jr., ACP Member, associate professor of medicine, Michigan State University College of Human Medicine.

Photos courtesy of the Public Health Image Library of the Centers for Disease Control and Prevention.

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ANTHRAX

Bacillus anthracis *from an agar culture, demonstrating spores.*

Anthrax is caused by a gram-positive, spore-forming bacteria, *Bacillus anthracis*. Humans can become infected through skin contact, ingestion or inhalation of spores from infected animals or animal products. "Woolsorter's disease," for instance, is anthrax caused by exposure to animal hair and wool.

Depending on how they infiltrate the body, anthrax bacteria can cause cutaneous, respiratory or gastrointestinal infections. Although cutaneous infections are the most common in nature, bioterrorism-related anthrax would most likely occur as either a cutaneous infection, a more lethal respiratory infection or both. Gastrointestinal infection is very rare and has never been diagnosed in the United States.

Clinical presentation and diagnosis

The primary lesion of cutaneous anthrax is a painless, pruritic papule that appears one to seven days after inoculation. Within one to two days, small vesicles or a larger, 1- to 2-cm vesicle forms that is filled with clear or serosanguineous fluid. As the vesicle enlarges, satellite vesicles may form. Fluid within the vesicles may contain numerous, large gram-positive bacilli. As the lesion matures, a prominent, non-pitting edema surrounds it. Eventually, the vesicle ruptures, undergoes necrosis and enlarges, forming a painless ulcer covered by the characteristic black eschar. Symptoms include low-grade fever and malaise. Regional lymphadenopathy is present early on.

Presumptive diagnosis is based upon the direct Gram-stained smear of a skin lesion (vesicular fluid or eschar) showing encapsulated, broad, gram-positive bacilli. A presumptive diagnosis can also be based on growth on sheep's blood-agar cultures consisting of nonhemoltyic colonies and large, nonmotile, nonencapsulated gram-positive, spore-forming rods. Confirmatory tests include positive cultures from blood, vesicles and tissue biopsies.

Notify your local department of health of patients with suspected anthrax before doing diagnostic tests. For detailed instructions on how to collect diagnostic materials for cutaneous anthrax, go to the diagnosis section of the American Academy of Dermatology's Web site at www.aad.org/BioInfo/Biomessage2. html. (Your health department can also give you additional instructions on testing materials.)

Differential diagnosis

Cutaneous anthrax. The necrotic ulcer of cutaneous anthrax is rarely painful, unlike that of a brown recluse spider bite. Pustules are rarely present in anthrax lesions, which can distinguish the disease from more common skin disorders, such as a staphylococcal furuncle. Lymphadenopathy is almost always present early on and helps distinguish cutaneous anthrax from conditions of lesser importance.

The list of cutaneous anthrax mimics is long and includes conditions not always familiar to internal medicine physicians. For a description of cutaneous anthrax and its mimics, and to view clinical images, go to the ACP Bioterrorism Resource Center at www.acponline.org/bioterro/anthrax_mimics.htm.

Inhalation anthrax. Inhalation anthrax is more difficult to diagnose because patients initially present with nonspecific symptoms such as a low-grade fever, nonproductive cough, malaise, fatigue, headache and chest discomfort. Patients may improve after a few days but then rapidly deteriorate, developing a high fever accompanied by abrupt onset of respiratory failure, hemodynamic collapse, delirium and shock that is often fatal. In 1979 in Sverdlovsk (now Yekaterinburg), Russia—where aerosolized anthrax was accidentally released from a Soviet military compound—50% of those infected developed hemorrhagic meningitis.

Chest X-rays of patients with inhalation anthrax usually reveal mediastinal widening or pleural effusion. Any patient with suspicious chest radiograph findings should have a follow-up CT scan of the chest, which may show hyperattenuation of mediastinal or hilar lymphadenopathy, or mediastinal hemorrhage.

Prominent influenza-like symptoms of recent origin in a patient with a widened mediastinum suggest anthrax, particularly if there is more than one case. (Tuleremia may produce a similar clinical picture.) Radiographic findings of air space disease, pleural effusions and a widened mediastinum are common with inhalation anthrax, but they do not occur in uncomplicated influenza.

Anthrax lacks the nasal congestion, pharyngitis and rhinorrhea that typically accompany a cold or the flu. Anthrax is also not spread by person-to-person contact. If a patient's family members and co-workers have recently recovered from a respiratory tract infection, the patient most likely does not have anthrax, but a more common respiratory infection.

Rapid tests for influenza and respiratory syncytial virus, if positive, can also rule out the possibility of inhalation anthrax. However, the sensitivities of many of these tests are relatively low, and they do not test for other infections that cause flu-like symptoms. Consequently, a negative test does not indicate that inhalation anthrax is more likely.

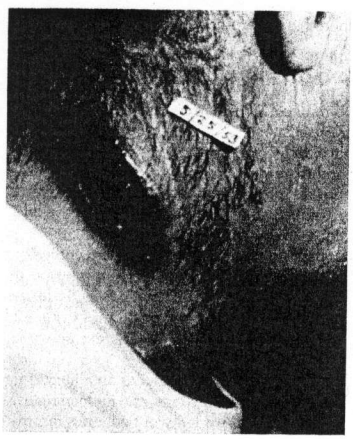
After symptom onset, a presumptive diagnosis can be based upon direct Gram-stained smears of sputum, blood and cerebrospinal fluid, as well as on initial growth of a compatible organism on appropriate cultures (see "Clinical presentation and diagnosis" for cutaneous anthrax, this page). In some anthrax cases, Gram-positive bacilli were visible in a peripheral blood smear during the bactermic phase of the illness. Diagnosis may be confirmed by blood or sputum cultures, which are frequently positive in less than 12 hours if antibiotics have not been administered prior to their collection.

All specimens for *B. anthracis* culture should be collected before initiating antimicrobial therapy, but specimen collection should not unduly delay treatment. Immediately report any patients suspected of having anthrax or of being exposed to the microbe to local or state public health departments, and coordinate all aspects of collecting, packaging and transporting specimens with public health officials and laboratories.

Treatment

Because survival is related to the time from symptom onset to antibiotic administration,

See ***Anthrax,*** *page 4*



A patient with a cutaneous anthrax lesion, showing the characteristic black eschar.

Cutaneous anthrax treatment protocol

Adults, pregnant women and immunocompromised hosts

- Ciprofloxacin 500 mg po BID OR doxycycline 100 mg po BID for 60 days
- Cutaneous anthrax with signs of systemic involvement, extensive edema or lesion on the head or neck requires IV therapy, and a multi-drug approach is recommended.
- While ciprofloxacin and doxycycline are first line agents, amoxicillin 500 mg po TID may be substituted for adults who cannot take these drugs.
- While tetracyclines are not recommended during pregnancy, their use may be indicated for life-threatening infections.

Children

- Ciprofloxacin 15 mg/kg po q 12 hrs (maximum of 500 mg/dose) OR doxycycline if > 45 kg, 100 mg po BID; if ≤ 45 kg, 2.2 mg/kg po BID for 60 days
- Cutaneous anthrax with signs of systemic involvement, extensive edema or lesion on the head or neck requires IV therapy, and a multi-drug approach is recommended.
- For children, amoxicillin may be an option for completion of therapy after clinical improvement; weight ≥ 20 kg, 500 mg po TID; weight < 20 kg, 80 mg/kg po TID to complete 60 days of therapy.
- The American Academy of Pediatrics recommends treating young children with tetracyclines for serious infections.

Continued from page 3

empiric therapy should be started as soon as an anthrax diagnosis is suspected and specimens have been collected. Historically, the case fatality rate has been 80% to 100%—although the rate was 45% during the 2001 attacks, presumably because of rapid diagnosis and treatment.

Naturally occurring anthrax strains are susceptible to many antibiotics, including penicillins, tetracyclines and fluoroquinolones. In patients with significant symptoms, ciprofloxacin or doxycycline should be combined with clindamycin, which is a potent inhibitor of toxin production. Other antibiotics may be added to cover central nervous system infections.

All strains are resistant to cephalosporins, and some strains produce an inducible penicillinase. Consequently, do not use extended-spectrum cephalosporins or trimethoprim/sulfamethoxazole. Because bioweapons may be genetically altered and have unusual drug susceptibilities, specific antibiotic therapy should be based on antibiotic susceptibility testing when available.

For more detailed anthrax treatment information see the anthrax treatment protocols, below and on page 3.

Prevention

Pre-exposure vaccination against anthrax is not recommended for the general public. The CDC recommends that groups at risk for repeated exposures to *B. anthracis* spores be given priority for pre-exposure vaccination. Groups at risk for repeated exposure include the following:

- laboratory personnel handling environmental specimens (especially powders) and performing confirmatory testing for *B. anthracis* in the U.S. Laboratory Response Network for Bioterrorism level B (or above) laboratories;
- workers who will be making repeated entries into areas known to be contaminated with *B. anthracis* spores after a terrorist attack;
- workers in other settings where repeated exposure to aerosolized *B. anthracis* spores might occur; and
- military personnel likely to encounter anthrax.

Post-exposure containment

The incubation period for anthrax varies according to the exposure route and dose. For cutaneous anthrax, the incubation period is usually two to three days (range one to seven). For intestinal anthrax, it is one to seven days.

The incubation period following inhalation of anthrax spores is typically six days, but it may vary according to the level of exposure. In animal studies and during the human outbreak in Sverdlovsk, the incubation period was as long as 100 days.

Physicians should maintain universal precautions when evaluating patients with suspected cutaneous anthrax. Direct exposure to vesicle secretions of cutaneous anthrax lesions may result in secondary cutaneous infections.

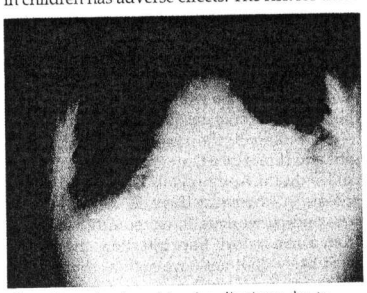
With suspected inhalation anthrax, however, a mask is not required. Inhalation anthrax is acquired through contact with anthrax spores and not viable bacteria. Because direct person-to-person spread of inhalational anthrax has not been reported, there is no need to immunize or treat contacts of patients with anthrax.

For persons known to be exposed to anthrax, however, try to prevent infection with early antibiotic treatment. Treatment delays reduce patients' chances for survival.

The following overview of prophylactic treatment strategies has been adapted from the Center for Civilian Biodefense Studies, Johns Hopkins University Schools of Medicine.

It should be noted that since the release of these recommendations, the CDC has reported that, to date, all anthrax isolates from bioterrorism-related incidents have been susceptible to ciprofloxacin, doxycycline and other agents. However, the use of doxycycline may be preferable to prevent development of ciprofloxacin resistance in more common bacteria. When no information is available about the antimicrobial susceptibility of the implicated strain of anthrax, initial therapy with ciprofloxacin or doxycycline is recommended for adults and children.

The use of tetracyclines and fluoroquinolones in children has adverse effects. The risk for these adverse effects must be weighed carefully against the risk of developing life-threatening disease. As soon as the susceptibility of the organism has been confirmed, prophylactic therapy for children should be changed to amoxicillin.



Chest X-ray showing widened mediastinum due to inhalation anthrax.

Adults and immunocompromised hosts

- Ciprofloxacin 500 mg po BID for 60 days
- Doxycycline 100 mg po BID OR amoxicillin 500 mg po TID, either antibiotic for 60 days

Pregnant women

- Ciprofloxacin 500 mg po BID
- Amoxicillin 500 mg po TID for 60 days

Children

- Ciprofloxacin 15 mg/kg po q 12 hrs but not to exceed 500 mg/dose for 60 days
- If ≥ 20 kg, amoxicillin 500 mg po TID for 60 days; if < 20 kg, amoxicillin 80 mg/kg po TID for 60 days

Patients should be followed closely after completing a post-exposure antibiotic prophylaxis course because there is little experience with this treatment regimen. However, no cases of anthrax surfaced among those recommended to take antimicrobial prophylaxis after the 2001 terrorist attacks.

A six-dose anthrax vaccine can prevent infection, while animal studies suggest that a three-dose vaccine regimen combined with antibiotic administration for 30 days is also effective for post-exposure prophylaxis. Because of the potential preventive benefit of combining antibiotics with the anthrax vaccine, the CDC—under an FDA investigational new drug application—will make anthrax vaccine available in a three-dose regimen (0, 2, 4 weeks) in combination with antimicrobial prophylaxis for unvaccinated persons at risk for inhalation anthrax. However, anthrax vaccine is not licensed for post-exposure use to prevent anthrax.

Use of anthrax vaccine for post-exposure prophylaxis could have additional benefits, including reducing the need for long-term antimicrobial therapy with its associated problems of noncompliance and possible adverse events. After the 2001 anthrax attacks, approximately 10,000 persons were recommended to receive a 60-day regimen of antimicrobial prophylaxis for suspected or confirmed exposure. However, as few as 42% adhered to the prescribed regimen. ■

Treatment protocols for inhalational, gastrointestinal and oropharyngeal anthrax

Adults, pregnant women and immunocompromised hosts

- Ciprofloxacin 400 mg q 12 hrs IV OR doxycycline 100 mg q 12 hrs IV
- If meningitis is suspected, doxycycline may be less optimal due to poor CNS penetration.

And

- One or two additional antibiotics: rifampin, vancomycin, penicillin, ampicillin, chloramphenicol, imipenem, clindamycin and clarithromycin. Penicillin or ampicillin should not be used alone.
- If intravenous ciprofloxacin is not available, and there is no vomiting or ileus, the postexposure use of the prophylaxis oral therapy program described above may be the only reasonable alternative to intravenous ciprofloxacin.
- While tetracyclines are not recommended during pregnancy, their use may be indicated for life-threatening infections.
- Switch to oral antibiotics when clinically appropriate: Ciprofloxacin 500 mg po BID OR doxycycline 100 mg po BID for 60 days (IV and po combined)
- Steroids may be considered as an adjunct for patients with severe edema and for meningitis.

Children

- Ciprofloxacin 10 mg/kg q 12 hrs IV (maximum 400 mg/dose) OR doxycycline if > 45 kg, 100 mg q 12 hrs IV; if≤ 45 kg, 2.2 mg/kg q 12 hrs IV
- If meningitis is suspected, doxycycline may be less optimal due to poor CNS penetration.

And

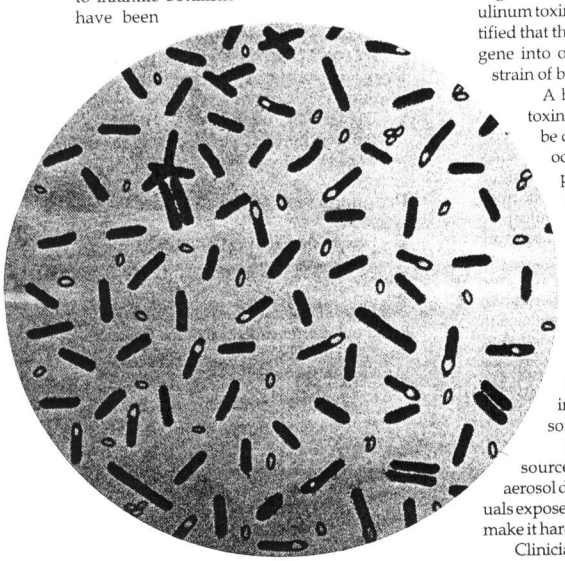
- One or two additional antibiotics: rifampin, vancomycin, penicillin, ampicillin, chloramphenicol, imipenem, clindamycin and clarithromycin. Penicillin or ampicillin should not be used alone.
- If intravenous ciprofloxacin is not available, and there is no vomiting or ileus, the postexposure prophylaxis oral therapy program described above may be the only reasonable alternative
- Switch to oral antibiotics when clinically appropriate: Ciprofloxacin 15 mg/kg po q 12 hrs (not to exceed 500 mg/dose) OR doxycycline if > 45 kg, 100 mg po BID; if≤ 45 kg, 2.2 mg/kg po BID for 60 days (IV and po combined)
- Steroids may be considered as an adjunct for patients with severe edema and for meningitis.
- The American Academy of Pediatrics recommends treating young children with tetracyclines for serious infections. ■

BOTULISM

The botulism neurotoxin, which is generated by *Clostridium botulinum* and related anaerobic bacteria, is the most poisonous substance known. The toxin's extreme potency, combined with its ease of production and transport, make it a significant bioterrorism threat. In addition, victims' need for prolonged intensive care, ventilators and antitoxin would all pose a major health care crisis if large numbers of people were affected.

Eight distinct C. *botulinum* toxin types have been described: A, B, C1, C2, D, E, F and G. Of these eight, types A, B, E, and rarely F and G cause human disease, while C and D cause disease in animals such as cattle, ducks and chickens. Foodborne, wound and infantile forms of botulism occur naturally. Food-borne botulism is the result of ingesting pre-formed toxin, while infantile botulism results from ingestion of bacterial spores that later colonize the intestinal tract, producing the botulinum toxin.

For unknown reasons, infantile botulism is the most common, naturally occurring form. A few cases of adult intestinal botulism analogous to infantile botulism have been reported, but are extremely rare. Wound botulism is the result of a wound becoming contaminated with *C. botulinum* bacteria that subsequently produce the toxin in vivo.



Clostridium botulinum bacteria, stained with Gentian violet. The bacterium produces a nerve toxin that causes botulism.

There have been no reports of water-borne botulism, presumably because the toxin is inactivated by chlorination and aeration. But the toxin could remain stable for several days in untreated water or beverages.

Any botulism infection caused by exposure to an aerosol form of the bacteria would indicate a bioterrorist attack.

Botulism is spread by absorption of the botulinum toxin into the circulation system from either a mucosal surface, such as the gut or the lungs, or an open wound. Botulinum toxin does not penetrate intact skin, nor does it naturally spread by person-to-person contact.

The United States, the former Soviet Union, Iran, Iraq, North Korea and Syria have developed or are believed to be developing botulinum toxin as a weapon. (The United States disbanded its bioweapons program in 1970.)

Terrorists have been able to isolate *C. botulinum* from the soil with relative ease. They could also access therapeutic botulinum toxin, which is used to treat dystonias, migraines and other conditions. However, terrorists are not likely to use medicinal preparations of the toxin because such extremely low concentrations limit their effectiveness as a weapon.

If inhaled, a single gram of crystalline botulism toxin could kill more than one million people. Fortunately, it is very hard to overcome the technical difficulties of dispersing the toxin in aerosol form. In the 1990s, a Japanese cult collected *C. botulinum* from the soil, but it was unable to use an aerosolized form of its toxin as a bioweapon.

Botulism is characterized by paralysis that always begins with the cranial nerves.

In addition to spreading aerosolized botulism, terrorists could contaminate food with the toxin or bacteria, or disperse it via genetically engineered, contagious bacteria that produce botulinum toxin. Although Soviet scientists have testified that they tried to splice the botulinum toxin gene into other bacteria species, a contagious strain of botulism has not yet been detected.

A bioterrorist attack using botulinum toxin or organisms that produce it would be difficult to distinguish from naturally occurring, food-borne botulism. In the past 20 years, botulism outbreaks have gone from being primarily associated with home-preserved food to being caused by mass-produced, processed foods or foods served in restaurants. Common foods have been linked to botulism outbreaks, including fish, yogurt, cream cheese, jarred peanuts, cheese sauce, baked potatoes and potato salad, and oils infused with chopped garlic. In infants, honey has been identified as a source of botulism.

It may also be hard to track down the source of an outbreak in the event of an aerosol dissemination. The mobility of individuals exposed during the incubation period would make it hard to pinpoint a common exposure site.

Clinicians should suspect a bioterrorist botulism attack under the following circumstances:

- Many simultaneous outbreaks of botulism occur without a common source.
- Large numbers of people develop botulism.
- Afflicted patients are linked by locale—co-workers, for instance, or travelers who use the same airport—but not dietary exposures. This would indicate an aerosol attack.
- A botulism outbreak caused by an unusual botulinum toxin type, such as type C, D, F or G.

Clinical presentation and diagnosis

Botulism is an afebrile, neuroparalytic disease characterized by symmetric, descending flaccid paralysis of motor and autonomic nerves. The paralysis always begins with the cranial nerves.

Symptoms include diplopia, blurred vision, drooping eyelids, dysphagia, dysphonia, dysarthria, weakened jaw clench, dry mouth and muscle weakness. The prominent bulbar palsies that typify botulism can be summarized in part as the "4 Ds": diplopia, dysarthria, dysphonia and dysphagia.

When untreated, botulism can progress to descending paralysis of respiratory muscles, arms and legs. Death can ultimately result from respiratory failure. Patients have a clear sensorium and no sensory deficits, but they may have trouble communicating because of the bulbar palsies.

In patients with acquired food-borne disease, abdominal cramps, nausea, vomiting or diarrhea may precede the neurological signs of botulism. These gastrointestinal symptoms may be due to other bacterial metabolites in the contaminated food and may not occur if the botulinum toxin is intentionally placed in foods or aerosols.

The signs and symptoms of botulism, and the speed with which they develop, vary considerably, according to the amount of toxin absorbed into the circulation.

The clinical presentation of inhalation botulism is not well defined, as there have been only three cases in humans who were exposed to small amounts of the botulinum toxin. These patients developed increased oral secretions, dysphagia, dizziness, difficulty moving their eyes, dysarthria, unsteady gait and extreme weakness. More severe and extensive symptoms may accompany a higher-dose exposure to aerosol botulinum toxin.

To confirm a botulism diagnosis, laboratory tests use mouse neutralization assays of stool, vomitus or serum samples. These tests are conducted only at the CDC and some state health department laboratories. Results take days to complete.

Clinical diagnosis is therefore key to recognizing a bioterrorist attack with botulism early on and responding appropriately. Clinicians caring for patients with suspected botulism should notify their local public health department and hospital epidemiologist or infection control practitioner immediately to coordinate shipment of therapeutic antitoxin, laboratory diagnostic testing and epidemiological investigation.

Differential diagnosis

Botulism is frequently misdiagnosed as Guillain-Barré syndrome and its variants, or as myasthenia gravis, stroke, intoxication, poliomyelitis, a central nervous system infection or tumor, Lambert-Eaton syndrome or tick paralysis. The descending and symmetric nature of botulism paralysis, as well as its early and prominent cranial nerve involvement, distinguishes botulism from its mimics.

The disease can also be differentially diagnosed from similar conditions by its lack of the following symptoms:

- sensory nerve damage;
- fever;
- history of preceding infection;
- mental status changes; and
- electromyogram, cerebral spinal fluid or electroencephalogram abnormalities.

The clustering of cases that would occur with an attack would also help distinguish botulism from other conditions.

Treatment

For patients with food-borne botulism, physicians may try to remove contaminated food still in the gut by inducing vomiting or using enemas.

See ***Botulism,*** *page 7*

PLAGUE

Plague pandemics have been recorded as early as 541 A.D. and as recently as 1855 in China. Improved living conditions, enhanced public health measures and the advent of antibiotics have helped stem the incidence of plague, which typically spreads to humans from infected fleas.

But *Yersinia pestis*, the gram-negative coccobacillus that causes the plague, still persists in nature, primarily in rodent reservoirs. Fewer than 20 cases of plague are reported annually in the United States, with most occurring in southwestern states.

Y. pestis can cause three different plague syndromes. The most common, bubonic plague, occurs mainly from infected fleabites. A bite is followed by the development of regional necrotizing lymphadenitis or "buboes." Bubonic plague may then progress to secondary septicemia (septicemic plague) and pulmonary involvement (primary pneumonic plague). Person-to-person transmission is possible only by respiratory droplets from patients with pulmonary involvement.

Primary pneumonic plague from aerosol exposure is highly contagious, and it is the most likely exposure route for a bioterrorist attack. As part of their bioweapons programs, Soviet and U.S. scientists claim they developed aerosolized plague bacteria.

However, other exposure routes have been used in the past. In World War II, for instance, the Japanese army reportedly dropped plague-infected fleas over areas of China, causing outbreaks of the disease.

This article will focus on pneumonic plague. For information about other plague syndromes, go to www.acponline.org/bioterro/plague.htm or www.cdc.gov/ncidod/dvbid/plague/diagnosis.htm.

A number of clues would indicate a bioterrorist plague attack, including the following:

- Occurrence in areas where plague is not endemic to the rodent population.
- Absence of rodent deaths prior to the human outbreak.
- Sudden outbreak of severe pneumonia and sepsis in people with no risk factors. Fulminant pneumonia in otherwise healthy individuals suggests pneumonic plague or inhalation anthrax.

Clinical presentation and diagnosis

Patients with pneumonic plague present with fever, cough, dyspnea, cyanosis, hemoptysis and chest pain. Common gastrointestinal symptoms can include nausea, vomiting, abdominal pain and diarrhea.

To prevent a high risk of death, antibiotics should be given within 24 hours of the appearance of the first symptoms.

While chest radiograph findings vary, bilateral infiltrates or consolidation are common. Patients' pneumonia is fulminant and can cause respiratory failure, shock and death usually within two to six days.

Y. pestis is likely if sputum or blood samples reveal gram-negative bacilli or coccobacilli with bipolar (safety pin) staining on Wright, Giemsa or Wayson stains. Diagnosis is confirmed by culture and identification of the organism.

Under the best of circumstances, cultures are positive in 24 to 48 hours, but results may take as long as six days. Rapid tests—such as polymerase chain reaction, antigen detection and immunoassays—are available only at some state health departments, the CDC and military laboratories.

Given how rare plague infection is and the

See ***Plague,*** *next page*

Treating pneumonic plague

Adults: preferred choices

- Streptomycin 1 g IM BID
- Gentamicin 5 mg/kg IM or IV once daily or 2 mg/kg loading dose followed by 1.7 mg/kg IM or IV TID

Adults: alternative choices

- Doxycycline 100 mg IV BID or 200 mg IV once daily
- Ciprofloxacin 400 mg IV BID
- Chloramphenicol 25 mg/kg IV QID

Children: preferred choices

- Streptomycin 15 mg/kg IM BID, maximum dose 2 g
- Gentamicin 2.5 mg/kg IM or IV TID

Children: alternative choices

- Doxycycline: If ≥ 45 kg, give adult dose. If < 45 kg, give 2.2 mg/kg IV BID (maximum dose 200 mg/day)
- Ciprofloxacin 15 mg/kg IV BID
- Chloramphenicol 25 mg/kg IV QID

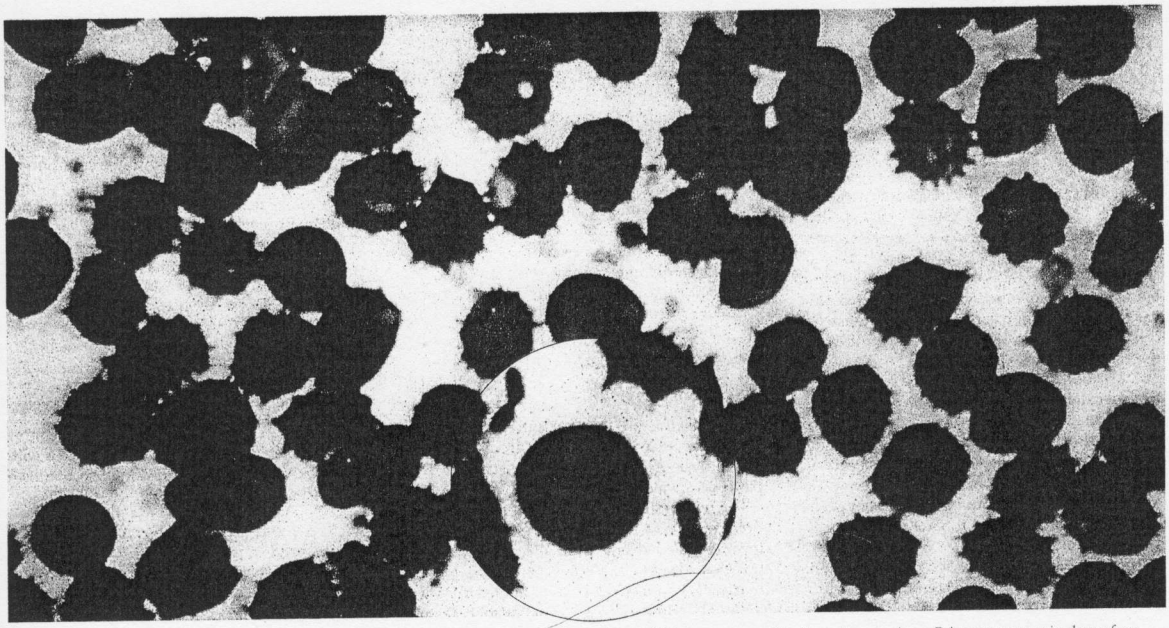
Pregnant women: preferred choice

- Gentamicin 5 mg/kg IM or IV once daily or 2 mg/kg loading dose followed by 1.7 mg/kg IM or IV TID

Pregnant women: alternative choices

- Doxycycline 100 mg IV BID or 200 mg IV once daily
- Ciprofloxacin 400 mg IV BID

All treatments should be given for 10 days. Based on recommendations of the Center for Civilian Biodefense Studies, Johns Hopkins University Schools of Medicine. ■



A blood smear containing Yersinia pestis *plague bacteria. Note the characteristic bipolar, "safety pin"-like appearance of the* Y. pestis *organisms. Primary pneumonic plague from aerosol exposure is highly contagious, and it is the most likely exposure route for a bioterrorist attack. Both Soviet and U.S. scientists claim they developed aerosolized plague bacteria.*

PLAGUE (CONTINUED)

Continued from previous page
importance of containing it, the first clinical or laboratory suspicion of plague should trigger immediate notification of the hospital epidemiologist or infection control practitioner, health department and local or state health laboratory. Public health officials can rapidly arrange definitive tests through state reference laboratories or the CDC.

Differential diagnosis

Severe and rapidly progressing pneumonia with sepsis suggests pneumonic plague or inhalation anthrax. However, these signs may be overlooked, given the clinical similarity to other bacterial or viral pneumonias.

The sudden appearance of a large number of cases of fulminate pneumonia in previously healthy people suggests the possibility of a bioterrorist attack with one of these two pathogens. The additional symptom of hemoptysis makes plague more likely.

Treatment

To prevent a high risk of death, antibiotics should be given within 24 hours of the appearance of the first symptoms. Do not delay treatment if plague is suspected.

There are no clinical trials to guide the treatment of pneumonic plague, although in vitro and animal studies (as well as anecdotal experience) suggest that a number of antibiotics can effectively treat plague, in addition to the few approved by the FDA.

Historically, the preferred treatment for plague has been the FDA-approved antibiotic streptomycin. But this drug is not as readily available as gentamicin, which studies suggest is as effective. Gentamicin is also inexpensive and can be given once daily.

Antibiotic resistance naturally occurs in some *Y. pestis* strains and may be genetically engineered into those used in a bioterrorist attack. Antibiotic susceptibility testing should be done, and results should be used to modify antibiotic prescribing. For detailed prescribing information, see "Treating pneumonic plague" on page 6.

Post-exposure containment

Studies suggest that aerosolized plague bacteria survive no longer than an hour on exposed surfaces, and that the risk of re-aerosolization of *Y. pestis* from the contaminated clothing of exposed persons is low. Contaminated clothing and linens should be disinfected according to hospital protocol.

Isolate patients for at least the first 48 hours of antibiotic therapy, and continue isolation until clinical improvement occurs. Contacts of pneumonic plague patients require droplet isolation—use a gown, gloves, eye protection and disposable surgical facial masks—for at least the first 48 hours of antibiotic therapy and until patients improve. Unnecessary contact with patients should be avoided during this time, and patients should wear surgical-type masks when they are being transported.

The typical incubation period for pneumonic plague is two to four days, although it can be as short as a day and as long as six days. Post-exposure prophylaxis is recommended for asymptomatic members of the household, hospital or other close contacts (within two meters) of patients with untreated pneumonic plague.

These contacts should receive oral doxycycline, 100 mg BID x 7 days if they are adults, including pregnant women. Children who weigh 45 kg or more should receive the same adult oral doxycycline dosage. Children less than 45 kg should receive oral doxycycline, 2.2 mg/kg BID x 7 days.

Alternatively, ciprofloxacin can be given 500 mg, twice daily to adults or 20-30 mg per kg of body mass daily. This should be divided into two doses for children.

Any patients receiving post-exposure prophylaxis who develop fever or cough should have their antibiotic therapy upgraded to that given to pneumonic plague patients. In a community experiencing a pneumonic plague outbreak, anyone who develops a fever greater that 38.5° C (101.3° F) or new cough, or infants with tachypnea, should also receive antibiotic treatment as described above for pneumonic plague. No pneumonic plague vaccine is currently available. ■

BOTULISM (CONTINUED)

Continued from page 5
Wounds should be debrided to remove devitalized tissue and the toxin-producing bacteria.

Treat botulism patients as soon as possible with equine serum trivalent botulism antitoxin, which can be obtained from the CDC through state and local health departments. The antitoxin contains antibodies that neutralize the most common types of botulinum toxins (A, B and E).

The CDC has a 24-hour network for physicians who need antitoxin or assistance with clinical management that can be accessed by calling: 404-639-2206, Monday through Friday, 8 a.m. to 4:30 p.m., or 404-639-2888 at any other time.

The U.S. Army has an investigational antitoxin that works for all types of botulinum toxins and would be considered in the event of an attack. However, the amount of time required for correct toxin typing would limit the effectiveness of this investigational antitoxin.

Timely administration of antitoxin minimizes subsequent nerve damage and disease severity. It will not, however, reverse existing paralysis, which typically takes months to subside.

Give botulinum antitoxin to patients with the tell-tale neurologic signs of botulism as soon as possible. Do not wait for diagnostic test results to begin treatment.

For patients exposed to unusually large amounts of toxin from a biological weapon, retest their serum for toxin after treatment with antitoxin to confirm that they've received an adequate amount.

Hypersensitivity reactions to the equine antitoxin can occur. To avoid reactions, give patients small challenge does of antitoxin. If no wheal occurs at the injection site, administer the full dose. Patients responding to the challenge with a substantial wheal may be desensitized over three to four hours before giving them the full dose.

There is no evidence that children, pregnant women or immunocompromised persons should not receive a standard dose of antitoxin. (This recommendation, however, is not universally held.) Infants have a much higher rate of anaphylaxis (2%) and hypersensitivity reactions (20%).

Botulism patients often need extensive supportive care, including feeding by enteral tube or parenteral nutrition, mechanical ventilation and treatment of secondary infections. Patients must be closely monitored for airway obstruction and impending respiratory failure, and they must often be placed in intensive care units.

Post-exposure containment

Medical personnel treating botulism patients need to take standard precautions. The incubation period lasts between two hours and eight days for food-borne botulism, with most cases developing within 12 to 72 hours after ingesting contaminated food. The incubation period for inhalation botulism is unknown.

Any suspicion of even a single case of botulism should immediately raise concerns of an outbreak potentially associated with shared, contaminated food. Work with the CDC and local or state health departments to try to locate the contaminated food source, which should be promptly removed from potential consumers and submitted to public health authorities for testing. Physicians should also identify other persons who may have been exposed to contaminated food, and should monitor them for symptoms.

There is evidence that treating exposed individuals with antitoxin can prevent both food-borne and inhalation botulism. But the antitoxin's scarcity and reactogenicity will limit its use in post-exposure prophylaxis.

The current standard practice for food-borne botulism is to closely monitor people who may have been exposed to botulinum toxin. These patients should be treated promptly with antitoxin if they develop signs of botulism.

An investigational botulinum toxoid that protects against types A, B, C, D and E toxins is distributed by the CDC to laboratory workers at high risk of exposure to botulinum toxin, and by the military to protect troops against attack. The toxoid induces immunity over several months and thus is ineffective as post-exposure prophylaxis. Mass immunization with the toxoid is currently not recommended, nor is the toxoid routinely given to health care workers. ■

SMALLPOX

While the world was officially declared free of smallpox in 1980, the United States, Russia and possibly other countries or groups have access to smallpox cultures. As a result, bioterrorism through the release of smallpox is possible.

Former Soviet Union officials, for example, have testified that their government successfully produced large quantities of smallpox virus that was adapted for use in bombs and missiles. Even more chilling, aerosol release of the smallpox virus would disseminate the disease widely. The virus is very stable in an aerosol form, and only a relatively small dose is needed to infect large numbers of people.

Smallpox would pose a significant threat to civilian populations because of its case-fatality rate of 30% and up. In addition, there is no effective treatment for the viral disease.

The U.S. population would be particularly susceptible to smallpox because people under age 30 have not been routinely vaccinated for the disease. Older individuals might also lack protection even if they had been vaccinated, because immunity to smallpox wanes over time.

Clinical presentation and diagnosis

Smallpox is diagnosed based on clinical grounds and then confirmed by laboratory tests conducted at the CDC or other high-containment laboratories.

A single suspected case of smallpox constitutes an international health emergency. National officials and local and state health authorities must be notified immediately.

There are four principal presentations of smallpox based upon the nature and evolution of the lesions: ordinary, modified, flat and hemorrhagic. In addition, variola sine eruptione (smallpox without rash) is a febrile syndrome occurring during the incubation period in vaccinated individuals exposed to smallpox.

Ordinary smallpox occurs in over 90% of unvaccinated individuals exposed to smallpox. It initially presents with a febrile prodrome characterized by severe headache and backache, and sometimes vomiting. The fever is usually high, from 101° F (38.3° C) to 104° F (40° C), lasts two to four days, and is often associated with prostration.

The ordinary smallpox rash first appears as an oral enanthem characterized as minute red spots in the mouth and pharynx that enlarge and then quickly erode.

These lesions release large amounts of virus into the saliva at about the time the skin rash appears. The exanthem first appears as a few macules on the face (especially the forehead), followed by the proximal extremities, distal extremities and then the trunk.

The macules evolve into vesicles by the second or third day. The vesicles become distended with fluid that first appears opalescent then becoming opaque and turbid. The distended vesicles often have a central depression or dimple that may persist into the pustular stage. Umbilication is seldom seen in other vesicular or pustular illness and is an important distinguishing feature of smallpox. By the sixth or seventh day all the vesicles become pustules and each individual lesion reaches it maximum size during this stage.

The smallpox rash starts on the face, spreads to the extremities and often is less intense on the trunk.

The pustules are sharply raised, round, very firm and deeply embedded into the skin. On palpating the skin, these lesions feel like a bead or a hard pea. By the end of the second week the pustules crust over, and by the third week the crusts fall off, leaving characteristic pitted scars.

Smallpox lesions occur in crops on each body area. As a result, on any one part of the body, the smallpox lesions are all in the same stage of development: macules, papules or vesicles, pustules, or scabs.

The distribution of the rash is centrifugal; it is most dense on the face; more dense on the extremities than on the trunk; and more dense on the proximal than the distal extremities. The palms and soles are involved in most cases.

In general, the extent of the rash parallels the clinical severity. In some cases the concentration of the lesions on the face or extremities can be so dense that the rash becomes confluent. These individuals tend to have a higher mortality rate as compared to those with a sparse exanthem.

Modified smallpox occurs in previously vaccinated individuals. The prodrome is usually less severe as compared to ordinary smallpox and the skin lesions tend to evolve more rapidly, may be more superficial, and may not develop at the same rate and thus fail to show the uniformity of skin lesions typical of ordinary smallpox. Modified smallpox can easily be confused with chickenpox.

Flat (malignant) smallpox is characterized by lesions that remain flat and fail to form raised vesicles or pustules. The prodrome is very severe, the lesions evolve very slowly, are soft and velvety to touch, and do not umbilicate. In a large series of smallpox cases in India, the vast majority of flat smallpox occurred in children and was almost universally fatal.

Hemorrhagic smallpox is a rare, severe form that is accompanied by extensive bleeding into the

See ***Smallpox,*** *next page*

CDC criteria for assessing smallpox risk

The CDC has developed criteria that can be used to evaluate suspected smallpox cases and to categorize them into high, moderate or low risk using major and minor smallpox criteria.

Major smallpox criteria

1. Febrile prodrome (fever > 101° F, 38.3° C) 1-4 days before rash onset and at least one of the following systemic complaints: prostration, headache, backache, chills, vomiting or abdominal pain.
2. Rash lesions are deep in the skin, firm or hard to the touch, round and well circumscribed, and may become umbilicated or confluent.
3. On any one part of the body, all the lesions are in the same stage of development.

Minor smallpox criteria

1. The distribution of the rash is centrifugal (i.e., greatest concentration of the lesions on the face and distal extremities with relative sparing of the trunk.
2. The first lesions of the rash appear on the oral mucosa or palate, or on the face or forearms.
3. The patient appears toxic or moribund.
4. Lesions progress slowly (i.e., individual lesions evolved from macules to papules to pustules; each stage lasting 1-2 days).
5. Lesions on the palms or soles.

A person is considered high risk for smallpox if he or she fulfills all three major criteria. Persons are considered at moderate risk if they have a febrile prodrome and either one other major criterion or > 4 minor criteria. Any person who does not have a febrile prodrome is considered low risk, as are persons who have a febrile prodrome and less than 4 minor criteria.

All high risk patients require contact precautions and respiratory isolation. These patients should be immediately reported to the local and/or state health authorities. Consultation with infectious disease or dermatology specialists is strongly recommended. If high risk status is confirmed, the case must be reported to the CDC and arrangements will be made for laboratory testing for smallpox virus.

Moderate risk patients should be isolated and urgently evaluated with help from infectious disease or dermatology specialists. The most important laboratory procedure for moderate risk patients is rapid diagnostic testing for varicella zoster virus. Low risk patients can be clinically managed as indicated. Smallpox testing is not indicated for individuals who do not meet the CDC case definition.

Smallpox infection can be rapidly confirmed in high-containment laboratories by electron microscopic examination of vesicular or pustular fluid or scabs.

Specimens should be collected by someone who has recently been vaccinated and is wearing gloves, a gown, protective eyewear and an N95 mask or HEPA-filtered respirator.

Proper precautions must be taken with specimens. They should be put in a vacutainer tube that is sealed with adhesive tape at the juncture of the stopper and tube. This tube must be enclosed in a second durable, watertight container.

A case investigation worksheet and a poster that includes the rash illness algorithm and information on differential diagnosis are available from the CDC Web site at http://www.cdc. gov/smallpox. ■

Continued from previous page

skin, mucous membranes and gastrointestinal tract. In India, the majority of cases were found in adults, with pregnant women at highest risk.

Differential diagnosis

Absence of a high, incapacitating fever prior to the rash makes smallpox very unlikely.

For most physicians, the diagnostic task will be to distinguish chickenpox from smallpox. Although the chickenpox rash resembles that of smallpox, the former is more superficial, more delicate in appearance and less sharply circumscribed.

The distribution of the lesions also differs. Chickenpox lesions rarely develop on the palms and soles, as is the case with smallpox. Chickenpox lesions begin on the trunk and then spread to the face and extremities, with most lesions concentrated on the trunk or equally distributed between trunk and extremities. In contrast, the smallpox rash starts on the face, spreads to the extremities and often spares or is less intense on the trunk.

In addition, the lesions of smallpox rash evolve at the same rate and are at the same stage of development on any given part of the body. New varicella lesions, by contrast, appear in crops every few days, and lesions at different stages of maturation (i.e., vesicles, pustules and scabs) appear at the same time on the same part of the body. Varicella lesions also rapidly evolve, often developing from macules to crusting vesicles within 24 hours, whereas each stage of the smallpox rash persists for two to three days.

The ACP Bioterrorism Resource Center has descriptions and clinical images of smallpox and its mimics at www.acponline.org/bioterro/smallpox_mimics.htm.

Treatment

Because smallpox is caused by the variola virus, there are no known antiviral drugs that can effectively treat it.

Vaccinia immune globulin does not effectively treat active smallpox infection. Routine care is supportive and includes nutritional, hemodynamic and volume support, as well as prevention and treatment of secondary bacterial infections with antibiotics.

Post-exposure containment

The incubation period for smallpox is between seven and 17 days. Patients are most infectious with the onset of oral lesions because the main means of transmission is via saliva droplets.

Prolonged and direct face-to-face contact is usually required to spread smallpox from one person to another. Smallpox can also be spread through direct contact with infected bodily fluids or contaminated objects such as bedding or pieces of clothing.

Smallpox is infrequently spread by virus carried in the air in enclosed settings such as buildings, buses and trains. An infected person is contagious until the last smallpox scab falls off. Humans are the only natural hosts of variola.

Immediately isolate all patients that are at high or moderate risk for smallpox. Because of the potential for widespread aerosol dissemination of smallpox virus, patients should be isolated in the home or other nonhospital facility whenever possible. Primary and secondary contacts of smallpox patients do not need to be isolated unless they develop symptoms of the disease.

Vaccination and close monitoring of primary and secondary contacts of patients are effective containment measures and should be implemented by public health officials. The vaccinia vaccine lessens the severity of smallpox or prevents it altogether if it is administered within seven days of exposure.

The vaccinia vaccine should be considered for people who have previously been vaccinated, because immunity begins to wane three to five years after the vaccine is given. People who have been directly exposed to the smallpox virus should get the vaccine regardless of their health status.

For more information on the smallpox vaccine, which is currently not advised for the general public, read "Smallpox vaccine," above. ■

Smallpox vaccine

To facilitate preparedness and response, the Advisory Committee on Immunization Practices (ACIP) recommends vaccination only for persons designated by public health authorities as necessary to conduct investigation and follow-up of initial smallpox cases who would have direct patient contact.

ACIP recommends that each state and territory establish and maintain >1 smallpox response team. ACIP and the Healthcare Infection Control Practices Advisory Committee (HICPAC) recommend that each acute-care hospital identify health care workers who can be vaccinated and trained to provide direct medical care for the first smallpox patients requiring hospital admission and to evaluate and manage patients who are suspected of having smallpox.

When feasible, the first-stage vaccination program should include previously vaccinated health care personnel to decrease the potential for adverse events. Additionally, persons administering smallpox vaccine in this pre-event vaccination program should be vaccinated.

To avoid serious adverse reactions to the smallpox vaccine, which contains a live vaccinia virus that can be spread to others, persons who have the following conditions, or who live with persons who have the following conditions, should not receive the smallpox vaccine except in an epidemic setting:

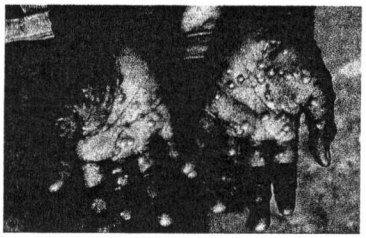
- Persons with current or past diagnosis of eczema or atopic dermatitis.
- Persons with active acute or chronic disruptive skin conditions including burns, impetigo, chickenpox, contact dermatitis, shingles, herpes, severe acne or psoriasis.
- Persons who are immunosuppressed because of conditions such as HIV/AIDS, solid organ or stem cell transplants, malignancy, leukemia, lymphoma, agammaglobulinemia, autoimmune disease or receiving immunosuppressant drugs (including inhaled steroids).
- Persons allergic to the vaccine or any of its ingredients (it may contain polymyxin B sulfate, streptomycin sulfate, chlortetracycline hydrochloride, neomycin sulfate).
- Persons with conjunctival inflammation.
- Infants younger than 12 months.
- Women who are pregnant or plan to get pregnant.
- Women who are breastfeeding.
- Persons with a moderate to severe short-term illness.
- Persons with known cardiac disease such as previous myocardial infarction, angina, congestive heart failure, or cardiomyopathy.

This last recommendation follows reports of cardiac events following smallpox vaccinations, including myocardial infarctions and angina without myocardial infarction. It is unclear if there is any association between smallpox vaccination and these cardiac events. Experts are exploring these issues in depth, and this exclusion may be removed as more information becomes available.

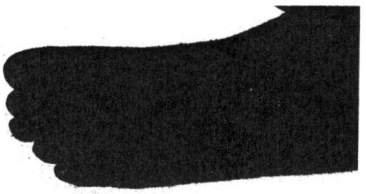
To prevent the spread of vaccinia from vaccinated patients, advise vaccinees and/or guardians to do the following until a scab has formed:

- Keep the vaccination site covered.
- Do not touch, scratch or rub the vaccination site.
- Avoid person-to-person contact with susceptible persons.
- Avoid touching, rubbing or otherwise performing any maneuvers that might transfer the vaccinia virus to the eye or surrounding skin.
- Discard the vaccination site covering carefully and enclose it in a sealed plastic bag.
- After handling the vaccination site covering, thoroughly wash hands.

For information on normal and adverse reactions to the smallpox vaccine and how to manage them, go to www.bt.cdc.gov/agent/smallpox/vaccination/clinicians.asp. ■



Smallpox lesions appear on the palms of the hand and the soles of the feet – a key difference from lesions caused by chickenpox.



TULAREMIA

Tularemia is caused by *Francisella tularensis*, one of the most infectious pathogenic bacteria known. Inoculation with or inhalation of just 10 organisms can cause disease.

The microbe is an aerobic, gram-negative coccobacillus that can survive for weeks at low temperatures in water, moist soil, vegetation and decaying animal carcasses. Natural reservoirs of infection include rodents, squirrels, rabbits and hares.

Tularemia cases have been reported in every state except Hawaii, with the majority occurring in south-central and western states. Most U.S. cases are reported between June and September, when arthropod-borne transmission is most common. Winter cases do occur, usually among hunters and trappers who handle infected animal carcasses.

Humans can also become infected through direct contact with or ingestion of contaminated food, water or soil, and by inhalation of infective aerosols. Person-to-person transmission does not occur. Natural cases of tularemia are relatively rare, with less than 200 cases reported every year in the United States.

Tularemia has several forms, depending on the exposure route. Most naturally-occurring cases are ulceroglandular, although oculoglandular, glandular, oropharyngeal, pneumonic, typhoidal or septic forms also occur.

While *F. tularensis* could be used in a number of ways as a bioweapon, an aerosol release is most likely. Airborne *F. tularensis* would be expected to principally cause pneumonic tularemia or oropharyngeal disease with cervical lymphadenitis.

Some aerosol exposures, however, might contaminate the eye (resulting in ocular tularemia) or penetrate broken skin, causing ulceroglandular or glandular disease. Pneumonic tularemia is rare, and you should suspect bioterrorism if you encounter the pneumonic form.

Clinical presentation and diagnosis

General symptoms of tularemia include abrupt onset of fever (38° C to 40° C; 100.4° F to 104° F), headache, chills, rigors, myalgias, coryza and sore throat. Nearly half of all patients demonstrate a pulse-temperature dissociation.

A dry or slightly productive cough and substernal chest pain are common, even in the absence of pneumonia. Nausea, vomiting and diarrhea sometimes occur.

With ulceroglandular tularemia, a papule appears at the inoculation site with the onset of generalized symptoms. It quickly becomes pustular, ulcerates and may develop an eschar. Regional lymphadenopathy also develops and may suppurate and rupture.

With oculoglandular tularemia, ulceration occurs on the conjunctiva, accompanied by chemosis, vasculitis and regional lymphadenitis. Glandular tularemia is typified by lymphadenopathy and generalized symptoms, without an ulcer.

With oropharyngeal tularemia, the patient may develop stomatitis, but exudative pharangitis or tonsillitis with ulceration is more common. Cervical or retropharyngeal lymphadenopathy may also occur.

The signs of pneumonic tularemia include one or more of the following: pharyngitis, bronchiolitis, pleuritis with adhesions and effusion, hemorrhagic inflammation of the airways, or hilar lymphadenitis.

In the clinical setting, the presence of nodular infiltrates with a pleural effusion suggests either tularemia or plague pneumonia. A substantial number of patients may have minimal or absent pulmonary signs, and generalized constitutional symptoms may predominate. Report any suspicion of pneumonic tularemia immediately to state or local public health officials.

Typhoidal tularemia is a systemic illness in the absence of signs that indicate either an inoculation site or anatomic localization of infection. Patients may also present with gastrointestinal manifestations, including abdominal pain and diarrhea.

Early symptoms of tularemia sepsis are nonspecific and include fever, abdominal pain, diarrhea and vomiting. Patients may progress to septic shock with complications of the systemic inflammatory response, including disseminated intravascular coagulation, adult respiratory distress syndrome and multiple organ failure.

The diagnosis of tularemia is supported when microscopic examination of respiratory secretions or blood reveals a characteristically small, pleomorphic and faint staining, gram-negative coccobacillus. It does not show the bipolar staining characteristic of *Yersinia pestis*, the agent of plague, and it is distinguishable from the large gram-positive rods characteristic of *Bacillus anthracis*.

Diagnosis of tularemia is usually confirmed by growth of *F. tularensis* on cysteine-enriched culture media at a biological safety level two or three facility, or by acute and convalescent serologic studies. Examination of cultures in which *F. tularensis* is suspected should be done in a biological safety cabinet.

Any testing that might produce aerosols or droplets should be conducted under biological safety level 3 conditions. Laboratory personnel should be alerted when tularemia is suspected.

Positive blood cultures are rare. Rapid diagnostic tests, such as polymerase chain reaction or fluorescent-labeled antibody assays, are not widely available. However, they can be performed in some research or reference laboratories on sputum, secretions, exudates or biopsy specimens. If alerted and prepared, laboratories can have test results available within several hours of receiving the specimens.

Differential diagnosis

Tularemia becomes more likely as a cause of pneumonia (as opposed to more common forms of pneumonia) if patients have a severe, atypical pneumonia with pleuritis, hilar lymphadenopathy and negative blood cultures that do not respond to beta-lactam antibiotics.

You should also suspect tularemia if there is a clustering of acute, severe respiratory illness in previously healthy persons. Tularemia would be expected to progress more slowly and cause fewer fatalities than either inhalation plague or anthrax.

Treatment

The standard treatments for tularemia are streptomycin or gentamicin. Tetracycline and chloramphenicol are also effective.

Fluoroquinolones have been shown to be effective in vitro and in animal studies, but they are not approved by the FDA for treating tularemia. For more specific prescribing information, see "Tularemia: treatment and post-exposure prophylaxis" on this page.

Drug-resistant strains might be used in a bioterrorist attack. Consequently, you should conduct antimicrobial susceptibility testing of isolates and adjust your choice of antibiotic accordingly. The case fatality rate is 30% to 60% for untreated patients and less than 2% for those patients receiving treatment.

Post-exposure containment

The incubation period for tularemia ranges from one to 14 days. The recommended post-exposure prophylaxis is doxycycline or ciprofloxacin for 14 days.

Close contacts of patients with documented tularemia do not require prophylaxis, as person-to-person transmission has not been reported. You do not need to isolate patients with tularemia, although standard hospital precautions should be taken.

A live, attenuated vaccine derived from an avirulent strain is available as an investigational new drug. The vaccine has been used to protect laboratory workers who routinely handle the bacteria. Immunity develops over two weeks but does not completely protect against inhalational exposure, making the vaccine inappropriate for post-exposure prophylaxis. ■

Tularemia: treatment and post-exposure prophhylaxis

This information is based upon the recommendations of the Center for Civilian Biodefense Studies, Johns Hopkins University Schools of Medicine.

Treatment

Adults: preferred choices
- Streptomycin 1 g IM BID x 10 days
- Gentamicin 5 mg/kg IM or IV once daily x 10 days

Adults: alternative choices
- Doxycycline 100 mg IV BID or 200 mg IV. once daily x 14-21 days
- Ciprofloxacin 400 mg IV BID x 10 days
- Chloramphenicol 15 mg/kg IV QID x 14-21 days

Children: preferred choices
- Streptomycin 15 mg/kg IM BID, maximum dose 2 g x 10 days
- Gentamicin 2.5 mg/kg IM or IV TID x 10 days

Children: alternative choices
- Doxycycline: If ≥ 45 kg, give adult dose. If < 45 kg, give 2.2 mg/kg IV BID (maximum dose 200 mg/day) x 14-21 days
- Ciprofloxacin 15 mg/kg IV BID not to exceed 1g/d x 10 days
- Chloramphenicol 25 mg/kg IV QID x 14-21 days

Pregnant women: preferred choice
- Gentamicin 5 mg/kg IM or IV once daily x 10 days

Pregnant women: alternative choices
- Doxycycline 100 mg IV BID x 14-21 days
- Ciprofloxacin 400 mg IV BID x 10 days

Post-exposure prophylaxis for asymptomatic persons (during early incubation period)
- Adults: oral doxycycline 100 mg BID x 14 days
- Children: If ≥ 45 kg, give adult oral doxycycline dosage. If < 45 kg, give oral doxycycline 2.2 mg/kg BID x 14 days
- Pregnant women: oral doxycycline 100 mg BID x 14 days OR ciprofloxacin 500 mg orally x 14 day.s ■

Ebola virus

As the name implies, viral hemorrhagic fevers target the vascular bed, causing microvascular damage and changes in vascular permeability that result in a bleeding diathesis.

Viral hemorrhagic fevers (VHFs) are caused by four viral families. For more detailed information on these families and the viruses they include, see "Hemorrhagic fever viruses," below.

All the viruses that cause VHF are zoonotic RNA viruses. Most are hosted primarily by rodents and arthropods, although the reservoir and vector for Ebola and Marburg viruses are unknown.

Humans are incidentally infected when they make contact with excreta of infected rodents or vector-infected livestock, or are bitten by infected mosquitoes or ticks. Some VHFs can also be transmitted from person to person.

Each VHF is restricted mainly to the habitat of its primary host, although travelers can spread the disease to outlying areas.

Scientists in both the former Soviet Union and the United States developed several hemorrhagic viruses as bioweapons, including Marburg, Ebola, Lassa, Junin, yellow fever and Rift Valley fever. Consider the possibility of a bioterrorist attack if you see VHF in a patient not known to have traveled to an endemic area.

Clinical presentation and diagnosis

All VHFs are characterized by high fever, headache, arthralgias, myalgias, abdominal pain and fatigue. Signs of bleeding range from only conjunctival hemorrhage, mild hypotension, flushing and petechiae, to shock and generalized mucous membrane hemorrhage and evidence of pulmonary, hematopoietic and neurologic dysfunction.

Renal insufficiency is proportional to cardiovascular compromise, except in hemorrhagic fever with renal syndrome, in which it is an integral part of the disease. Patients often die from multi-organ failure.

It can be difficult to distinguish one VHF from another, although some viral hemorrhagic fevers do present with suggestive clinical syndromes:

- Jaundice and hepatitis dominate the clinical presentation in some cases of Rift Valley, Congo-Crimean, Marburg and Ebola hemorrhagic fevers, and yellow fever.
- Biphasic illnesses with pulmonary symptoms followed by central nervous system manifestations are characteristics of Kyasanur Forest disease and Omsk hemorrhagic fever.
- Severe peripheral edema without significant hemorrhage suggests Lassa fever.
- Severe hemorrhage and nosocomial transmission suggest Congo-Crimean hemorrhagic fever.
- Fever, hemorrhage, shock, renal failure and polyuria mark the classic presentation of hemorrhagic fever with renal syndrome.

A number of laboratory findings indicate VHFs. Thrombocytopenia is common to most viral hemorrhagic fever infections, with the exception of Lassa fever. Leukopenia is common to most viral hemorrhagic fever infections except Lassa, Hantaan and some cases of Congo-Crimean hemorrhagic fevers.

Rapid enzyme immunoassays and viral cultures are available for VHFs, but only at the CDC and the U.S. Army Medical Research Institute of Infectious Diseases in Maryland. Because no viral hemorrhagic fevers are endemic in North America, any suspected cases should immediately be reported to local public health officials and the CDC.

To contain the spread of VHFs, barrier and contact precautions must be meticulous.

Differential diagnosis

Malaria is the major entity in the differential diagnosis. Other entities that mimic viral hemorrhagic fevers include typhoid fever, leptospirosis, shigellosis, relapsing fever, fulminant hepatitis and meningococcemia.

Noninfectious mimics include acute leukemia, systemic lupus erythematosus, immune thrombocytopenic purpura, thrombotic thrombocytopenic purpura and hemolytic uremic syndrome.

In naturally occurring VHF cases, patients are likely to have risk factors such as travel to an endemic area and handling of animal carcasses, exposure to sick people or arthropod bites within 21 days of the illness. In a bioterrorist attack, a high index of suspicion is required to make the correct diagnosis and distinguish VHF from its many mimics.

Suggestive clues that warrant immediate notification of local and state public health agencies include an outbreak of a severe disease characterized by a fever > 38.3° C (101° F) and any two of the following: hemorrhagic or purpuric rash, epistaxis, hematemesis, hemoptysis, blood in the stool or any other hemorrhagic symptom.

Treatment

Ribavirin reduces morbidity in hemorrhagic fever with renal syndrome. It also reduces morbidity and mortality in Lassa fever. There is some evidence ribavirin may be effective in Argentine hemorrhagic fever when given within seven days of onset.

Physicians also use convalescent plasma experimentally to treat Argentine hemorrhagic fever. But for most viral hemorrhagic fevers, there is no proven effective treatment.

Avoid intramuscular injections, antiplatelet drugs and anticoagulant agents when treating patients with VHFs. Corticosteroids are not beneficial, and fatality rates—which vary by virus—can be as high as 90%.

Post-exposure containment

The incubation period varies according to virus, but it ranges from two to 21 days. Viral hemorrhagic fever patients often have significant infectious virus in their blood and body secretions.

Barrier and contact precautions must be meticulous. While aerosol transmission of hemorrhagic fever viruses is infrequent, respiratory isolation should be used for all patients.

Isolate patients in negative-pressure rooms and use gowns, gloves, eye protection and N95 masks when treating them. Note that for some VHFs, secondary transmission occurs by contact with objects contaminated with infected body fluids.

The risk of person-to-person transmission of VHFs is highest during the later stages of illness, which are characterized by vomiting, diarrhea, shock and often hemorrhage. VHF infections have not been reported in persons whose contact with an infected patient occurred only during the incubation period, or before the patient became febrile.

Prophylaxis following exposure to arenavirus may be attempted with ribavirin, although the effectiveness of this measure is not known. Individuals with potential exposure should be instructed to check their temperature twice a day and monitor themselves for any symptoms.

A licensed vaccine is available only for yellow fever. In addition, an experimental vaccine for Argentine hemorrhagic fever is currently under investigation. ■

Hemorrhagic fever viruses

Arenaviruses

- Argentine hemorrhagic fever
- Bolivian hemorrhagic fever
- Sabia-associated hemorrhagic fever
- Lassa fever
- Lymphocyctic choriomeningitis
- Venezuelan hemorrhagic fever

Filoviruses

- Ebola hemorrhagic fever
- Marburg hemorrhagic fever

Bunyaviruses

- Crimean-Congo hemorrhagic fever
- Rift Valley fever (Hantaan fever)
- Hemorrhagic fever with renal syndrome

Flaviviruses

- Tick-borne encephalitis
- Kyasanur Forest disease
- Omsk hemorrhagic fever ■

CDC Emergency Response Hotline

770-488-7100

SELF-ASSESSMENT

Questions

1. A 23-year-old groundskeeper for a university in Michigan is evaluated because of a series of ulcerating nodules on his right forearm.

The first nodule appeared five days ago, and since that time two more nodules just proximal to the first nodule have appeared. Yesterday, the first second nodule developed small ulcers.

The ulcers and nodules are mildly painful. The patient reports having a low-grade fever, but otherwise is in good health. He has not traveled outside of the Midwest.

On physical examination, his temperature is 99° F (37.2° C). There are a series of nodules arranged in a linear pattern extending proximally from the mid-volar aspect of the right forearm to the elbow.

The distal nodule is the largest, measuring 3x2 cm, and it and the subsequent nodule are ulcerated, showing a red granular base. There are tender, enlarged lymph nodes in the right axilla.

Which of the following is the most likely diagnosis?

A. Cutaneous anthrax
B. Sporotrichosis
C. Cutaneous leshmaniasis
D. Tularemia

2. A 37-year old, previously healthy postal worker in New Jersey is evaluated because of an enlarging sore on his right arm for 10 days. He denies trauma to the arm.

The sore began as a painless, itchy papule that enlarged over one to two days, with small blisters forming on top of the papule that filled with clear fluid. As the blisters enlarged, extensive swelling developed around the sore. The blister broke down, forming a painless ulcer covered by a black scab. His symptoms include low-grade fever and malaise. He has not traveled outside of the mid Atlantic area.

On physical examination the patient is not in any obvious distress. Temperature is 99° F (37.2° C). There is a 3 cm ulcer located on the upper, outer aspect of the right arm. A black, adherent eschar covers the ulcer. The ulcer and eschar are surrounded by extensive non-pitting edema. Lymphadenopathy is present in the right axilla.

Which of the following is the most likely diagnosis?

A. Cutaneous anthrax
B. Cat-scratch disease
C. Tularemia
D. Herpes simplex infection

3. A previously healthy 16-year-old boy is evaluated in the office for dysphagia.

Starting this morning he had difficulty swallowing, with fluid regurgitating out of his nose when he tried to swallow milk. He also reported having "double-vision" while reading the morning newspaper.

On physical examination, he is afebrile, his blood pressure is 120/70 mm Hg, and pulse is 70/min. He has bilateral ptosis and enlarged, sluggishly reactive pupils. The mouth is dry and the pharynx is injected. Muscle strength is good with normal deep tendon reflexes, and there are no sensory changes. The mental status examination is unremarkable.

A patient with similar symptoms was evaluated yesterday. This patient was found to have diplopia, dysarthria, dysphonia and dysphagia as well as hypotonia of the neck muscles.

Which of the following is the most likely diagnosis?

A. Botulism
B. Guillain-Barré polyradiculopathy
C. Myasthenia gravis
D. Poliomyelitis

4. A previously healthy 23-year-old woman residing in Washington is admitted to the hospital with a 2-day history of cough, substernal chest pain, fever (40° C), headache, chills, rigors, myalgias, coryza and sore throat.

On chest X-ray, she has patchy, nodular infiltrates and a pleural effusion. The sputum reveals numerous gram-negative coccobacilli. Despite empiric treatment with a beta-lactam antibiotic, she continues to deteriorate over the next 48 hours.

On the second hospital day, three of her coworkers are admitted to the hospital with similar symptoms. The possibility of a deliberate epidemic is considered, and the differential diagnosis is broadened to include inhalational anthrax, pneumonic plague and inhalation tularemia.

Which of the following communications to the public health system is most appropriate?

A. Immediately inform the CDC
B. Confirm the diagnosis and inform the CDC
C. Immediately inform the local or state public health organization
D. Confirm the diagnosis and inform the local or state public health organization

5. A 37-year-old woman from New Mexico is admitted to the hospital with a rapidly progressive bronchopneumonia.

She was feeling well until two days ago when she developed fever, cough, hemoptysis, dyspnea and chest pain. Within hours of admission to the hospital, gram-negative bacilli are identified in a sputum sample. Two days after admission she is placed on a ventilator to manage respiratory failure.

Which of the following most strongly suggests the possibility that this patient's illness is the result of a bioterrorist attack?

A. Isolation of **Yersina pestis** *from the sputum and blood*
B. The presence of inguinal buboes
C. A cluster of similar cases in previously healthy people
D. Respiratory failure

6. A 37-year-old man who is HIV positive is evaluated because of fever and a generalized rash.

He has been in his usual state of health until five days ago when he suddenly developed a fever, headache, myalgias, and a painful, generalized eruption. The patient has been HIV positive for one year, and because he was asymptomatic, elected to postpone antiretroviral medications.

On physical examination, his temperature is 104° F (40° C), blood pressure is 140/86 mm Hg and pulse rate is 100/min. There is a generalized vesicular-pustular eruption that is most prominent over his right shoulder, right arm and right upper back, but several lesions are also evident over the rest of his thorax, face, and extremities.

On any one part of this body, papules, vesicles, pustules, and scabs are present. Six weeks ago his CD4 lymphocyte count was 300 /μL, and his most recent plasma viral load was 200,000 copies/mL.

Which of the following is the most likely diagnosis?

A. Disseminated herpes zoster
B. Erythema multiforme
C. Molluscum contagiosum
D. Smallpox

7. Twelve patients with fever and a generalized vesicular or pustular eruption were admitted to the hospital over the previous two days. After an initial investigation, it is deemed that the cases are highly suspicious for smallpox.

Which of the following smallpox vaccination strategies is most likely to have the best risk/benefit ratio?

A. National mass vaccination program
B. Ring vaccination and containment
C. Vaccination of immediate family only
D. Vaccination of the index cases

8. A 38-year-old woman is evaluated in the emergency department because of fever and a generalized rash. She was in her usual state of good health until seven days ago.

At that time, she rapidly developed a high fever, headache, backache, chills and abdominal pain with occasional vomiting. Four days ago she developed a rash. It started as a red, flat rash, then evolved into small papules, and now consists entirely of vesicles. She takes no medications. She recalls having chickenpox as a child.

On physical examination, her temperature is 104° F (40° C), blood pressure is 148/90 mm Hg and pulse is 112/minute. She appears acutely ill and is possibly confused. She has a generalized vesicular eruption on her face, extremities (including the palms and soles), thorax and abdomen. The vesicles are well circumscribed, round and firm to palpation.

Which of the following management options should be done next?

A. Collect fluid from the vesicles for culture
B. Have the patient wear a mask at all times
C. Institute airborne and contact precautions
D. Report the case to the CDC

9. Over a four-day period, five men, four women and six children are admitted to Philadelphia metropolitan hospitals with fever, prostration, hypotension and various degrees of mucosal bleeding. All patients have thrombocytopenia, leukopenia, and elevated liver and renal function tests. None of the patients have traveled outside the mid-Atlantic area in the past three months. A viral hemorrhagic fever is suspected.

Which one of the following epidemiological clues most strongly suggests that the outbreak is the result of a deliberate epidemic?

A. Multiple simultaneous epidemics of different diseases
B. Unusual age distribution of a common disease
C. Unusual antibiotic resistance pattern
D. Unusual geographic clustering of disease
E. Unusual route of exposure

Answers

1. B 2. A 3. A 4. C 5. C 6. A 7. B 8. C 9. D

For a discussion of each answer, visit www.acponline.org/bioterro/self_assessment.htm.