CHAPTER 37

Biological Terrorism

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In the aftermath of the September 11, 2001 attacks and the subsequent mail-borne anthrax attack of October 2001, it has become clear that health care providers may be called upon to respond to victims of terrorism. Biological terrorism (BT), in particular, involves the use of virulent agents with the intent to cause mass casualties and/or induce fear, a scenario that if effected will severely strain the capacity of regional emergency medical services and pose unique management challenges to clinicians confronted with victimized children. Whether practicing as a pediatric emergency medicine specialist working in an urban children's hospital or as a general clinician in private office-based practice, pediatricians may be the first to suspect that a BT agent may have been utilized. Compared to adults, most caregivers have a relatively low threshold for having children and infants evaluated professionally when they become sick. Furthermore, pediatric patients may have a more rapid or severe response to a biological agent, potentially putting pediatricians and child care providers in the critical position of being the first to diagnose an exposure. The clinician's response to such a situation may determine whether the incident is controlled promptly or whether it evolves into a large-scale epidemiologic catastrophe.

Significant resources have become available in recent years if suspicion arises that a BT event has occurred. Involving in-hospital infectious disease specialists is an important first step. Local health departments can also provide guidance with information, testing, and response, and will typically be the liaison to any state and federal resources that may need to become involved.

Any patient suspected of having been exposed to a BT agent, regardless of whether it was intentional or accidental, will necessitate specific isolation, treatment, and personal protective needs for the staff who will likely require expert consultation if it is available. There are also mandatory and immediate reporting requirements for all of these agents discussed in this chapter.

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The evaluation of a pediatric patient exposed to an unknown terrorist agent benefits from an organized approach and a basic knowledge of the time frame of the various biological and chemical substance which may be involved. In general, chemical agents (e.g., nerve agents, cyanide) produce symptoms which evolve quickly, while BT agents typically take more time to affect their exposed patient. Challenging the clinician is the fact that many BT agents also share the common denominator of having a prodromal phase which mimics common illnesses such as influenza or pneumonia. As is true for the evaluation of any illness, a detailed history and physical examination will help guide the evaluation of the possibly exposed patient. Table 37-1 offers a diagnostic approach that emphasizes some of the classic findings of the major chemical and biological agents. It is like the astute clinician with an eye for the unusual epidemiologic characteristics of a BT incident that will first consider the diagnosis.

There are several methods used to categorize BT agents. They can be grouped and discussed by type (bacteria, virus, and toxin) as this chapter does, by the likelihood of their use due to availability, or by relative risk based on both availability and pathogenicity. The following sections focus on the biological agents that are considered "Category A" by the Centers for Disease Control and Prevention (CDC), meaning that they are thought to pose the highest risk to victims based on their relative ease of dissemination and their potential to cause extensive fatalities as well as social disruption.

ANTHRAX (*BACILLUS ANTHRACIS*)

Anthrax is caused by a gram-positive, encapsulated, aerobic, stable, spore-forming rod bacterium. In nature, it exists primarily as a zoonotic pathogen in herbivores, and cases are occasionally seen in humans who work in the outdoors or with animals. Most commonly this is seen as a cutaneous infection, although inhalational disease (Woolsorters' disease) can occur.

Anthrax is of considerable concern and represents one of the most likely agents of terror or warfare because of its stability. Anthrax spores to be used as a weapon would likely be dried for dispersion. Bioterrorism experts believe that its use as an effective BT agent would require sophisticated facilities for preparation. With the proper resources, anthrax can be engineered to be antibiotic-resistant. The source of the mail-borne anthrax used in the United States in the fall of 2001 has never been elucidated, although there is concern that it may have been stolen from an Army biodefense facility. This attack resulted in 22 cases, 11 cutaneous and 11 inhalational, resulting in 5 deaths from among the latter cohort.

Anthrax is a potent pathogen in its aerosolized form. In 1979, an inadvertent release of spores from a covert bioweapon facility in Sverdlovsk, USSR, caused nearly 100 infections downwind with a case fatality rate of up to 86%. The agent may pose an additional risk to infants and young children because of their proximity to the ground and because of their hand-to-mouth behavior, they may be at a higher risk of contacting, ingesting, or inhaling spores in a contaminated area.

Pathogenesis

The spores can be spread through direct contact, food contamination, and aerosolization. Anthrax can infect open skin at areas of broken integument and can be inhaled or ingested. Although human-to-human transmission is possible in its cutaneous form, it is otherwise not contagious.

Clinical Presentation

Cutaneous anthrax is the most common presentation in naturally occurring disease. The incubation period is approximately 1 week, at which point the source of infection develops into a painless vesicular lesion followed by a coal-black eschar. There is a possibility of a lethal systemic dissemination of the disease, although this is much less commonly seen.

The only known pediatric case of cutaneous anthrax from a biological attack was from the U.S. anthrax mail attacks in 2001. A 7-month-old infant who had been presumed to have a brown recluse spider bite with superimposed cellulitis tested positive for anthrax (Figure 37-1). Investigation revealed that the infant had been taken to visit his relative at a media outlet that was later confirmed to be contaminated by anthrax. Although the infant did display some evidence of a systemic illness with fever, hemolysis, thrombocytopenia, and renal insufficiency, he was subsequently discharged in stable condition after antibiotic treatment.

Inhalational disease as well as cutaneous anthrax would likely be seen after an offensive attack, as was appreciated in 2001 when spores were disseminated in the U.S. mail. The incubation time is typically 1 to 6 days but may be as long as 6 weeks in some cases. In its initial stages, it is difficult to differentiate from common illnesses. There is a gradual onset of fever, malaise, cough, fatigue, and occasionally chest pain. There is typically a lack of rhinorrhea, and the cough is nonproductive. After this prodromal illness, there may be a transient improvement for a few days followed by a sudden development of severe respiratory symptoms to include dyspnea, diaphoresis, cyanosis, and stridor. In approximately half of the cases, severe hemorrhagic meningitis may ensue. Inhalational anthrax has a high case fatality rate, as mentioned. Prompt

Table 37-1 Diagnostic Approach to the Pediatric Patient with Suspected BT Agent Exposure

History
- Epidemiologic factors: *epidemic* numbers of patients, *exposure* history, *exotic* disease presentations?
- Acuity of onset?
- Febrile prodrome?

Physical examination
- Vital signs
- Syndromic pattern: respiratory, neurologic, or dermatologic?

Laboratory assessment
- Chest radiograph
- Complete blood count
- Coagulation studies (for purpura, hemorrhagic diathesis)
- Further definitive tests, after consultation with infectious disease, toxicology experts; local health department, CDC (1-770-488-7100), Poison Control Center, etc.

Syndrome evaluation

Acute onset (seconds to minutes), afebrile: chemical agents
- Respiratory syndrome
  - Nerve agents (organophosphates): dyspnea, rhinorrhea, wheezing, rales, coma, seizures
  - Chlorine: eye, nose, throat irritation, progressing to wheezing
  - Phosgene: wheezing, pulmonary edema (onset over several hours)
- Neurologic syndrome
  - Nerve agents (organophosphates): cholinergic syndrome (miosis, rhinorrhea, lacrimation, dyspnea, wheezing, and rales) progressing to coma, seizures, paralysis, apnea
  - Cyanide: tachypnea, apnea, coma, seizures
- Dermatologic syndrome
  - Vesicants (mustard, arsenicals): erythema, vesicles, ocular inflammation after a few hours (with respiratory tract inflammation in severe cases)

Subacute onset (days), febrile: biological agents
- Respiratory syndrome
  - Anthrax, inhalational: febrile prodrome, chest pain; widened mediastinum ± infiltrates, pleural effusions, hilar adenopathy on chest radiograph; cyanosis, shock, meningitis
  - Plague, pneumonic: febrile prodrome, then fulminant pneumonia (typically with bloody sputum), bilateral infiltrates on chest radiograph; sepsis, DIC
  - Tularemia, pneumonic: abrupt onset fever, then fulminant pneumonia; hilar adenopathy; pleural effusions on chest radiograph
- Neurologic syndrome
  - Botulism: afebrile; bulbar dysfunction, progressive descending flaccid paralysis, intact sensation, and mental status; CSF negative
- Dermatologic syndrome
  - Anthrax, cutaneous: papule progressing to vesicle, then ulcer, then black, depressed eschar, with marked surrounding edema, typically relatively painless
  - Smallpox: febrile prodrome: centrifugal; synchronous vesiculopustular exanthem
  - Plague, septicemia: febrile prodrome, often with prominent gastrointestinal symptoms, then shock, petechiae, purpura, gangrene
  - Viral hemorrhagic fevers: febrile prodrome, with rapid progression to shock, purpura, bleeding diathesis

*Particularly regarding syndromes caused by aerosol exposure.
DIC, Disseminated intravascular coagulation, *CSF*, cerebrospinal fluid.
From Henretig FM, Cieslak TJ, Eitzen EM Jr: Biological and chemical terrorism. J Pediatr 2002;141:311-326, with permission.

and aggressive treatment and a high index of suspicion are necessary to maximize the patient's survivability.

Gastrointestinal (GI) anthrax also has an approximately 1-week incubation period before the development of GI symptoms such as nausea and anorexia, as well as fever. This may progress to abdominal pain, hematemesis, and bloody diarrhea.

Oropharyngeal anthrax is much less common and presents as unilateral or bilateral lymphadenopathy, which can be painful and impede the airway. There may also be symptoms including dysphagia and ulcerous lesions in the mouth and on the tongue.

Diagnosis and Laboratory Findings

In inhalational or GI disease, a Gram stain and routine blood culture may reveal bacteria in its desporulated form. Similarly, cerebrospinal fluid (CSF) may reveal *B. anthracis* in meningitis. A cutaneous swab of vesicular fluid of a lesion may demonstrate *B. anthracis*.

Anthrax toxin production occurs simultaneously to bacteremia and is detectable by specific test.

A chest film may show the classic *widened mediastinum* of anthrax as well as pleural effusion and/or infiltrate.

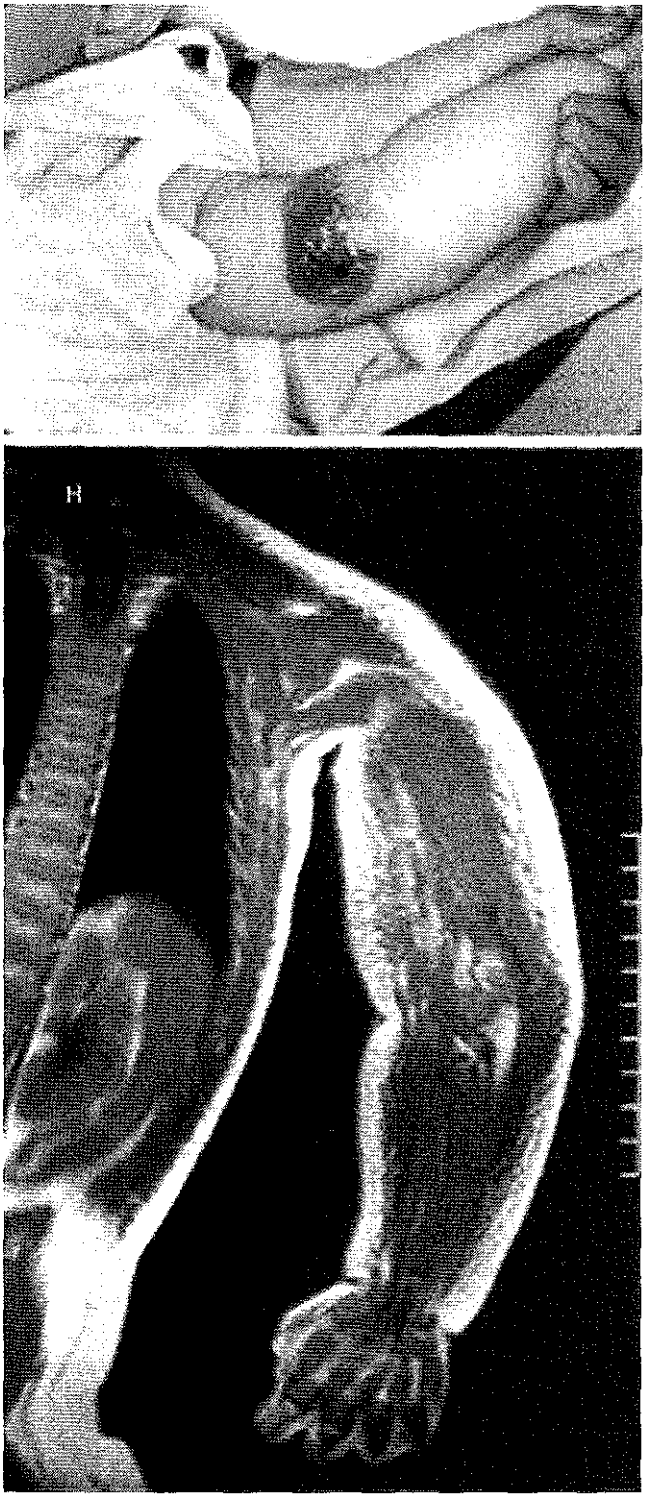

Figure 37-1 Seven-month-old infant diagnosed with cutaneous anthrax after the 2001 U.S. mail attack. Note the dark eschar in the top figure, classic for this disease. From Roche et al. Cutaneous anthrax infection. NEJM 2001;345(22):1611.

Nasal swabs may be used for epidemiologic data collection, but not for the diagnosis of suspect cases.

Differential Diagnosis

Cutaneous anthrax is important to differentiate from tularemia, staphylococcal or streptococcal skin infection, and the brown recluse spider bite. Any painless coal-black lesion should prompt the consideration of a test for anthrax.

Inhalational anthrax patients are typically not diagnosed until the disease has progressed to life-threatening stages, because its initial symptoms are so similar to many common respiratory illnesses. Advanced disease may mimic a dissecting/ruptured aortic aneurysm or the superior vena cava syndrome.

Gastrointestinal anthrax is commonly mistaken for gastroenteritis, an acute abdomen, or food poisoning.

Management

Therapy

In *active disease*, ciprofloxacin 10 mg/kg/dose IV q12h (max 400 mg/dose) or doxycycline 2.2 mg/kg/dose IV q12h (max 100 mg/dose) are considered first line therapy for anthrax. Expert consultation is advised, as the use of additional antibiotics may be recommended. Although both ciprofloxacin and doxycycline are relatively contraindicated in the pediatric patient, their use is warranted if anthrax is suspected. Treatment is continued with such multiple antibiotics by the parenteral route until the patient's condition has stabilized, and then oral antibiotics are continued for 2 months. Therapy must be aggressive and broad spectrum until susceptibilities are obtained in the appropriate laboratory facility.

Postexposure prophylaxis against anthrax can also be accomplished with ciprofloxacin or doxycycline. If the organism proves susceptible, amoxicillin may be substituted (Table 37-2).

Aggressive treatment should be instituted as soon as disease is suspected. Most inhalational cases are fatal, despite treatment. Cutaneous anthrax has a 20% mortality rate if untreated, and the GI case fatality rate is approximately 50%.

Vaccination is possible for adults at high risk of exposure such as soldiers or animal workers.

PLAGUE (*YERSINIA PESTIS*)

Plague is a gram-negative, rod-shaped, nonsporulating bacterium existing as a zoonotic pathogen in rodents, with fleas as the primary vector infecting humans. Infected cats may also transmit the disease.

to humans. Plague is enzootic in the southwestern United States, where naturally-occuring cases are periodically seen.

Plague is one of the original biological agents used in aggression. As early as the 13th and 14th centuries, diseased corpses were used as projectiles with the intent to spread diseases. Plague, or the "Black Death," was notably among them. It is a highly contagious and lethal disease that killed approximately one fourth of the European population in the 14th century. Hundreds of years later, ceramic "flea bombs" were reportedly dropped by the Japanese on the Chinese by air in the early 1940s with the intent of spreading plague.

Pathogenesis

Plague is known in two forms: bubonic and pneumonic. *Bubonic* plague is typically caused by fleas that have fed on infected animals. It may progress to *secondary* pneumonic or *septicemic* plague. Bubonic plague is the form of disease that is most often seen in naturally acquired illness.

Pneumonic plague in its *primary* form (not preceded by bubonic disease) would be seen if *Y. pestis* was used as an aerosolized weapon. In contrast to anthrax, plague is highly contagious, making it an especially dangerous BT agent that can cause a widespread outbreak from human to human transmission. No cases of pneumonic plague have been recognized in the United States in 80 years.

Clinical Presentation

Bubonic plague has an incubation period of 2 to 10 days before the acute onset of nonspecific symptoms such as high temperature, malaise, myalgias, headache, and nausea and vomiting. Painful lymphadenopathy (the "bubo") develops concurrently or shortly thereafter in the extremity that has been bitten. The patient may have a palpable or painful liver and/or spleen, and may develop various skin lesions in lymphatic drainage area of the bubo.

Septicemic plague represents a secondary infection in some of those who develop bubonic or pneumonic plague. It presents in a fashion similar to gram-negative sepsis with hypotension, high temperature, chills, nausea, vomiting, and diarrhea. Patients may also develop acral thromboses, necrosis, gangrene, and disseminated intravascular coagulopathy (DIC) as part of endotoxin release. About 1 in 20 persons with septicemic plague will develop subsequent plague meningitis.

Pneumonic plague presents after an incubation period of 1 to 6 days in primary disease, longer in secondary. There is typically a rapid onset of severe respiratory symptoms such as high temperature, chills, malaise, myalgias, and headache. This is followed a day later by the telltale *bloody sputum* and cough, as well as nausea, vomiting, and diarrhea. The sputum findings are classic for this disease.

Diagnosis and Laboratory Findings

The initial diagnosis of plague is guided by clinical impression. *Bubonic* plague should be suspected based on the cutaneous findings and history. Lymph node aspirate reveals a "safety pin" stained bipolar bacillus. In *pneumonic* plague, chest x-ray study typically shows bilateral infiltrates. Laboratory findings typically include leukocytosis and a bandemia with greater than 80% polymorphonuclear leukocytes (PMNs). DIC and laboratory results suggestive of organ failure may be present in progressive disease. Have a high index of suspicion for pneumonic plague when presented with multiple patients with *pneumonia and hemoptysis*.

The organism grows slowly in routine culture medium, which may hinder diagnosis. Immunofluorescent *Y. pestis* F1 antigen titers are necessary to confirm the diagnosis.

Differential Diagnosis

Cutaneous disease presents with a unique presentation of lymph node findings. Because of the incubation period, a travel history is important, even in areas where enzootic disease is not present. There have been two recent cases of bubonic plague diagnosed in New York City from travelers who had been in the U.S. Southwest on vacation.

Pneumonic plague can be mistaken for any of the more common diseases of respiratory distress and fever, such as community-acquired pneumonia, hantavirus pulmonary syndrome, meningococcemia, rickettsiosis, ricin, or staphylococcal enterotoxin B (SEB) exposure.

Management

In *active cases*, promptly initiated therapy is essential, especially for pneumonic plague, for which the mortality rate is nearly 100% in untreated disease. Gentamicin therapy should be initiated at 2.5 mg/kg/dose IV/IM q8h (not to exceed 300 mg/day) *OR* doxycycline 2.2 mg/kg/dose IV q12h (not to exceed a 100-mg dose) *OR* streptomycin 15 mg/kg IM twice daily.

For postexposure *prophylaxis*, doxycycline 2.2 mg/kg PO twice daily (max dose 100 mg) for 1 week is recommended, or consider ciprofloxacin, tetracycline, or chloramphenicol.

Vaccination is not available in the United States for plague.

Table 37-2 Major Biological Agents of Terrorism

Disease	Etiology	Clinical Findings*	Incubation Period	Diagnostic Samples	Diagnostic Assay	Isolation Precautions	Initial Treatment†	Prophylaxis
Anthrax	*Bacillus anthracis*	*Inhalational:* febrile prodrome with rapid progression to mediastinal lymphadenitis, medastinitis (chest x-ray: ± infiltrates, widened mediastinum, pleural effusions); sepsis; shock; meningitis *Cutaneous:* papule progressing to vesicle, to ulcer, then to depressed black eschar, with marked edema	1 to 5 days (up to 6 wk?)	Blood CSF Pleural fluid Skin biopsy	Culture Gram stain ELISA PCR Immunohistochemical assay	Standard	Ciprofloxacin: 10 mg/kg (max 400 mg) IV q12h *OR* Doxycycline: 2.2 mg/kg (max 100 mg) IV q12h†	Ciprofloxacin: 15 mg/kg (max 500 mg) PO BID × 60 days *OR* Doxycycline: 2.2 mg/kg (max 100 mg) PO BID × 60 days‡
Plague	*Yersinia pestis*	Febrile prodrome with rapid progression to *fulminant* pneumonia with bloody sputum, sepsis, DIC	2 to 3 days	Blood Sputum Lymph node aspirate	Culture Gram stain Wright stain Giemsa stain ELISA IFA Ag-ELISA	Pneumonic: droplet until patient is treated for 3 days	Gentamicin: 2.5 mg/kg IV q8h *OR* Doxycycline: 2.2 mg/kg IV (max 100 mg) IV q12h *OR* Streptomycin 15mg/kg IM q12h	Doxycycline: 2.2 mg/kg (max 100 mg) PO BID × 7 days *OR* Ciprofloxacin: 20 mg/kg (max 500 mg) PO BID × 7 days *OR* Chloramphenicol: 25 mg/kg (max 1 g) PO BID × 7 days
Smallpox	*Variola* virus	Febrile prodrome Synchronous vesicopustular eruption, predominately on face and extremities	7 to 17 days	Pharyngeal swab Scab material	ELISA PCR Virus isolation	Airborne, droplet, contact		Vaccination within 4 days (consider vaccinia immune globulin: 0.6 mL/kg IM within 3 days of exposure for vaccine complications, immunocompromised persons)

Tularemia	*Francisella tularensis*	*Pneumonic*: abrupt-onset fever, fulminant pneumonia (chest x-ray: prominent hilar adenopathy) *Typhoidal*: fever, malaise, abdominal pain	2 to 10 days	Blood, Sputum Serum Tissue	Culture Serology: agglutination EM	Standard	Gentamicin: 2.5 mg/kg IV q8h *OR* Doxycycline: 2.2 mg/kg (max 100 mg) IV q12h *OR* Ciprofloxacin: 15 mg/kg (max 500 mg) IV q12h *OR* Chloramphenicol 15 mg/kg (max 1 g) IV q6h	Doxycycline: 2.2 mg/kg (max 100 mg) PO BID *OR* Ciprofloxacin: 15 mg/kg (max 500 mg) PO BID
Botulism	*Clostridium botulinum* toxin	Afebrile Descending flaccid paralysis Cranial nerve palsies Sensation and mentation intact	1 to 5 days	Nasal swab?	Mouse bioassay Ag-ELISA	Standard	CDC trivalent antitoxin (serotypes A, B, E) DOD heptavalent antitoxin (serotypes A-G) (IND) California Department of Health immune globulin (IND)	None
Viral hemorrhagic fevers	Arenaviridae (e.g., Lassa fever) Filoviridae (e.g., Ebola, Marburg)	Febrile prodrome; rapid progression to shock, purpura, bleeding diathesis	4 to 21 days	Blood Serum	Viral isolation Ag-ELISA RT-PCR Serology: Ab-ELISA	Contact, droplet; consider airborne if massive hemorrhage	Supportive care Ribavirin (arenaviruses): 30 mg/kg IV initially 16 mg/kg IV q6h × 4 days, then 8 mg/kg IV q8h × 6 days (IND)	None

*Syndrome expected after aerosol exposure.

†CDC recommended one or two additional antibiotics for inhalational anthrax in fall 2001 outbreak: rifampin, vancomycin, penicillin or ampicillin, clindamycin, imipenem, or clarithromycin. Recommendations in future outbreaks may evolve rapidly, and frequent consultation with local health departments and CDC (1-770-488-7100; www.bt.cdc.gov) is encouraged.

‡Amoxicillin 80 mg/kg/day divided q8h can be substituted if strain proves susceptible.

CSF, cerebrospinal fluid; DIC, disseminated intravascular coagulation; ELISA, enzyme-linked immunosorbent assay; IFA, immunofluorescent assay; IND, investigational new drug status; PCR, polymerase chain reaction; RT-PCR, reverse transcriptase polymerase chain reaction.

Adapted from Henretig FM, Cieslak TJ, Eitzen EM Jr: Biological and chemical terrorism. J Pediatr 2002;141:311-326.

TULAREMIA (*FRANCISELLA TULARENSIS*)

A gram-negative coccobacillus, tularemia is a primarily zoonotic disease, but it can infect humans via skin, inhalation, or mucous membrane contact. Because of its association with animal workers, trappers, and insects under natural conditions, it has been termed "rabbit fever" or "deer fly fever."

Tularemia was one of the first bacteria weaponized by the United States offensive program in the 1950s, and it is thought to be an agent widely researched and developed by the former USSR, among others. This disease may be seen in the form of an ulceroglandular disease or typhoidal infection. Naturally occurring cases have occurred in all of the contiguous United States, with an incidence of approximately 200 cases a year.

Pathogenesis

Infection can be via the GI tract, mucous membrane, ocular or broken skin exposure, or via inhalation of aerosolized bacteria. The latter would be unlikely except in the intentional dissemination of the bacteria as a weapon. Although tularemia is highly infectious, it is not contagious between humans.

Clinical Presentation

Primary *typhoidal* disease would be the most likely manifestation after an intentional dissemination of tularemia via inhalation or ingestion. After an unpredictable incubation phase that ranges from 3 to 21 days, there is commonly an acute onset of constitutional symptoms such as high temperature, malaise, myalgias, and weight loss. Lymphadenopathy is not commonly seen. Typhoidal disease may progress to *pneumonic* tularemia in as many as 80% of cases. Severe symptoms of chest pain, cough, dyspnea, and signs of pneumonia develop. The case fatality rate is approximately 35% in untreated patients.

Ulceroglandular disease represents the majority of naturally occurring cases, typically in animal handlers, hunters, veterinarians, or those exposed to fly bites in the outdoors. Symptoms include fever, chills, headache, and marked lymphadenopathy in the drainage area of the exposure. An ulcerated skin lesion typically occurs at the site of exposure.

About 30% of ulceroglandular disease may progress to typhoidal disease.

In some cases, an ulcerous lesion is not seen; this is termed *glandular* tularemia.

Less commonly, local inoculation of the eyes and mouth may lead to *oculoglandular* or *oropharyngeal* tularemia, with signs and symptoms consistent with ulceroglandular disease.

Diagnosis and Laboratory Findings

As with most biological attacks, maintain a high index of suspicion for tularemia if epidemiologic analysis reveals *an abnormal clustering of atypical pneumonia with systemic illness.* A chest x-ray study may demonstrate typical or interstitial pneumonia, possibly with pleural effusion. Laboratory studies typically demonstrate low to moderate leukocytosis (<22,000/μL) with a normal differential. Bacteria may be cultured and isolated from blood, lesion swabbing, sputum, and aspirates, but may require specific media and precautions if tularemia is suspected. Enzyme-linked immunosorbent assay (ELISA) serum antibody titers are used to establish diagnosis.

Differential Diagnosis

Typhoidal tularemia may be difficult to distinguish from other severe pulmonary infections such as mycoplasma and plague. It may mimic the symptoms of other typhoidal illnesses such as malaria, salmonella, and rickettsial infections as well as influenzal illnesses. The ulceroglandular lesion could be confused with an insect bite or noninfectious ulcerous lesion.

Management

Gentamicin 2.5 mg/kg IV/IM q8h or streptomycin 15 mg/kg IM q12h (max dose of 2g) are the first line treatments for pediatric tularemia. Alternatively, doxycycline, ciprofloxacin, or chloramphenicol can be used (see Table 37-2). Doxycycline 2.2 mg/kg/dose IV q12h (<100 mg dose) or ciprofloxacin 15 mg/kg (max 500 mg) IV q12h *OR* chloramphenicol 25 mg/kg (max 1 g) q6h IV are acceptable substitutes.

Doxycycline 2.2 mg/kg PO twice daily (<100 mg dose) for 2 weeks is used for *prophylaxis* of tularemia. Alternatively, ciprofloxacin 15 mg/kg PO BID (max dose of 1g) for 2 weeks can be used.

A live attenuated product is available as a *vaccination* for laboratory workers or those at high risk for tularemia.

SMALLPOX (*VARIOLA MAJOR* AND *VARIOLA MINOR*)

The causative agent of smallpox is the Orthodox virus *Variola*, which takes two forms, *major* and *minor*. *Variola major* causes the more serious illness. Smallpox outbreaks have occurred for thousands of years in world history, most recently in Africa in the mid-1970s in Somalia. It is a highly contagious disease that has a case fatality rate of approximately 30%.

Endemic disease was eliminated by 1980 through monumental vaccination efforts by the World Health Organization, among others. After eradication, the public was told that the only world samples that remained were secure in the United States and Russia. Unfortunately, accountability of the samples is suspect, and the integrity of the few remaining research stockpiles of the virus is unknown. It is known to be a studied agent by other countries, including the former Soviet Union, where it was allegedly heavily studied and mass produced as a biological weapon. As much as 20 tons of weaponized smallpox, in violation of the 1972 International Biological Weapons Convention, may have been produced. This covert facility reportedly studied and weaponized many other biological agents, including most of those discussed in this chapter.

Smallpox represents a potent BT agent because of its virulence and its contagiousness. The pediatric and adolescent population would be entirely disease-naive, now that routine vaccination has been stopped for decades. It is uncertain what level of protection of the previously immunized adult population would experience, if any.

Pathogenesis

Smallpox infection occurs via the inhalation of aerosolized virus, or possibly by indirect contact with contaminated fomites.

Clinical Presentation

The incubation period of *smallpox (Variola major)* is 7 to 19 days, after which entirely nonspecific flulike symptoms develop, including fever, headache, myalgias, vomiting, fatigue, and an erythematous rash. This is reliably followed 2 to 3 days later with a rash to the face, hands, and forearm consisting of macular lesions. The mucosal surfaces may be affected. Over the next week the lesions become deep-seated and pustular, typically in a *centrifugal* pattern that spares the trunk. Up to 2 weeks after symptoms develop the pustules develop into scabs, which then slough to reveal a depressed scar similar to the one seen at the site of vaccination in adults who were immunized.

Patients are considered contagious until all scabs have separated naturally.

Other presentations of smallpox besides the one described herein can occur. *Hemorrhagic smallpox* is generally fatal within a week and rapidly progresses through symptoms of fever, headache, and abdominal pain. A petechial rash then develops involving the skin and mucous membranes. This disease may resemble the presentation of a viral hemorrhagic fever. *Malignant smallpox* may involve flat, nonpustular lesions that develop after the prodromal phase of the illness.

Variola minor infections have approximately the same timetable but may have more subdued lesions, milder syndromic symptoms, and a lower case fatality rate. The illness may be variably subdued in previously immunized individuals.

Diagnosis and Laboratory Findings

The presentation of any illness with *synchronous development of pustular lesions* should raise a high index of suspicion, as should any unusual cluster of diseases involving skin lesions. Prompt evaluation and identification of suspected cases is vital due to the threat of continued exposures from infected persons. Diagnosis is typically by electron microscopy of vesicular scrapings, although silver staining may also be utilized. Identification may also be via polymerase chain reaction. Specimens should be handled at one of a small number of federal laboratories with the highest biosafety precautions.

Differential Diagnosis

Smallpox can be difficult to differentiate from other vesicular illnesses such as *varicella* (chickenpox), which typically does not present with a centrifugal distribution of lesions or synchronous lesion development. Monkeypox (a milder relative of *variola*), cowpox, and other skin diseases such as erythema multiforme or contact dermatitis can also appear in a similar fashion. Interestingly, the United States experienced its first monkeypox cases in 2003 in the U.S. Midwest, which initially caused significant alarm in the medical community, which appropriately initially considered smallpox as the causative agent.

Management

A case of smallpox would represent a public health emergency of the highest order. Because the disease is not treatable, case control would focus on the isolation of symptomatic patients, the quarantine of exposed or possibly exposed individuals, and the widespread vaccination of any potential contacts to reduce the possibility of secondary transmission. Vaccination may prevent the development of diseases up to 3 to 4 days after inoculation. The use of antiviral medications such as cidofovir is being investigated for use in smallpox.

Preexposure or postexposure prophylaxis is possible for smallpox. Specific populations at risk may be vaccinated (military, some high-risk health care workers), although this practice is not currently widespread. Live *vaccinia* virus is used at this time for vaccination (hence the origin of the word); however, there are tissue cell culture vaccines in development. There are many rare but serious complications to vaccination, including the possibility of cardiac disease and death, which led to the

cessation of the initiative to broadly vaccinate first responders in 2003. If smallpox exposure is suspected, however, there are few if any contraindications to the use of the vaccine. *Passive immunoprophylaxis* consisting of *vaccinia* immune globulin is used to treat severe side effects of the vaccination process. As mentioned earlier, a vaccine is prepared, but it is not available for civilian use at this time. It is stockpiled in the Strategic National Stockpile (SNS) for emergency use by the CDC.

VIRAL HEMORRHAGIC FEVERS

Many RNA viruses can cause a febrile hemorrhagic illness that affects the microvascular system. These include *Ebola*, *Marburg*, *yellow fever*, *dengue*, and *Lassa* virus. All can be rapidly progressive and lethal, and all have been suspected as potential BT agents.

Most viral hemorrhagic fever (VHF) viruses are endemic in certain equatorial regions, although it is not known what the nonhuman animal reservoir is in all cases. VHF viruses are not highly contagious because they are not transmitted by air through respiratory secretions. There is significant concern that either engineering or spontaneous mutation could lead to a strain of VHF that is airborne. An outbreak of *Ebola* species *reston* occurred in the United States in 1989 in imported primates in Reston, Virginia. This particular strain was fortunately not pathogenic in humans, but frighteningly this strain was likely transmitted by airborne means. This incident inspired the book *The Hot Zone* by Richard Preston.

Four families of VHF exist and can cause a variety of illnesses:

- *Arenavirus*: Machupo, Lassa, Argentine hemorrhagic fever
- *Bunyavirus*: hantavirus, Congo-Crimean fever, Rift Valley fever
- *Filovirus*: Ebola, Marburg
- *Flavivirus*: yellow fever, dengue

Pathogenesis

There are a variety of infectious route and animal reservoirs specific to each virus family (Table 37-3).

The common pathophysiology is a degradation of the vascular system and coagulopathy, which is described below and is highly lethal.

Clinical Presentation

The general syndrome of VHF includes some or all of the following symptoms: microvascular degradation, coagulopathy, complement system activation, fever, myalgias, weakness, conjunctival injection, hypotension, flushing, petechial lesions, and edema. These may progress to shock, systemic hemorrhage, DIC, and renal or multisystem organ failure. Specific VHF viruses may emphasize one or more of these signs and symptoms.

Diagnosis and Laboratory Findings

A high index of suspicion would be required to identify a VHF BT attack in its early phases. *Clusters of unusual diseases* will likely be the first signs. Not all cases of VHF will be a BT attack, because these diseases are endemic in some locations. A thorough travel and exposure risk history is an important component of the initial history and physical examination. *Thrombocytopenia* and *leukopenia* are typical, with some exceptions. Elevated liver function tests, proteinuria, and hematuria may be seen. ELISAs may provide rapid diagnosis of the viremia in some cases. Viral culture may also diagnose a suspected VHF virus.

Differential Diagnosis

The differential diagnosis includes parasitemia (e.g., malaria), typhoid fever, salmonellosis, leptospirosis, rickettsiosis, shigellosis, gram-negative sepsis, leukemia, systemic

Table 37-3

Type of Viral Hemorrhagic Fever	Animal Carriers	Route of Infection	Endemic Area
Arenavirus	Rodents	Inhaled dust contaminated with rodent waste	Central America, West Africa
Bunyavirus	Ticks, rodents, mosquitoes	Inhaled dust contaminated with rodent waste, bite from vector	Africa, Europe, Asia
Filovirus	Unknown	Infectious body fluids, respiratory route	Africa (periodically emerges)
Flavivirus	Mosquitoes, ticks	Bite from vector	

lupus erythematosus (SLE), idiopathic thrombocytopenic purpura (ITP), and others.

Management

Acute Disease

Because there is no cure for VHF, isolation and intensive care management are the mainstays of treatment. Intravenous fluids, blood products, pressor agents, and invasive monitoring will likely be necessary. Case control is focused on the isolation of symptomatic patients and their infectious byproducts. Negative pressure isolation is required.

Some VHF virus patients may benefit from ribavirin use. Argentine hemorrhagic fever patients may benefit from convalescent serum use.

Prophylaxis

None is available. Exposure prevention is essential.

Vaccination

Vaccination is limited to the yellow fever vaccine. See the CDC's recommendations at www.cdc.gov for current guidelines regarding dosage and usage for international travel.

TOXINS (*BOTULINUM*, *STAPHYLOCOCCUS* ENTEROTOXIN B, RICIN, MYCOTOXINS)

Departing from the live agents described above, toxins are nonliving, noninfectious but highly poisonous biological substances that can incapacitate or kill in minute quantities.

Toxins hold the potential to be highly effective weapons if efficiently disseminated. They are limited by their stability in the environment. Some of them can be made from common pathogens and substances. The toxins thought to pose the highest risk are discussed here.

Botulinum Toxin

This is one of the most potent neurotoxins formed by the spore-forming bacteria *Clostridium botulinum*. It is thought to have been produced in massive quantities by several nations and terrorist groups. Inhaled or ingested toxin produces symptoms identical to food-borne botulism. A Category A agent, the toxin blocks neuromuscular transmission by inhibiting acetylcholine release (presynaptic inhibition). It can be inhaled or ingested. Clinical presentation may consist of cranial nerve palsies (diplopia, ptosis, dysphagia, dysphonia) followed by symmetrical descending flaccid muscle paralysis. Respiratory failure may take place. Autonomic effects (mydriasis, ileus, constipation, dry mouth) may manifest. Victims may have a transiently positive edrophonium (Tensilon) test, and their CSF examination is typically normal. The differential diagnosis includes Guillain-Barré syndrome, tick paralysis, myasthenia gravis, nerve agent, and atropine poisoning. Naturally occurring food-borne botulism is common, so not all cases will be acts of terrorism. Inhaled *Botulinum* poisoning may also be seen in infants in certain geographic areas. Respiratory support and dependent care may be required for up to several months. Antitoxin (BAT) is available and neutralizes circulating toxin but will not reverse symptoms. A vaccine is available but not to the general public. Prophylactic treatment with BAT is not recommended.

Staphylococcus aureus Enterotoxin B (SEB)

SEB is a bacterially produced toxin that is commonly encountered as a food-borne illness. As a weapon, the toxin was produced by the U.S. offensive program (and likely others) before 1969. This bacterial "superantigen" can cause an intense systemic inflammatory response via direct T-cell stimulation, typically after ingestion or possibly inhalation. A febrile respiratory syndrome and/or pulmonary edema would be expected after inhalation of the toxin. In food poisoning or GI toxicity, the pulmonary symptoms would likely be absent, and a high temperature would be expected. The differential diagnosis includes anthrax, tularemia, Q fever, plague, hantavirus, chlamydial pneumonia, and mustard or phosgene gas. Treatment focuses on supportive care through the acute phase of the disease. There is no vaccine or antitoxin at this time.

T2 Mycotoxins

These are toxic compounds produced by *Fusarium*, a grain mold, and are suspected as the active agent in "yellow rain." Effects are similar to those of radiation exposure; consequently, *Fusarium* is considered a "radiomimetic agent." If skin is contacted, burning, redness, lesions, and subsequent necrosis may occur. Respiratory symptoms include pain, sneezing, epistaxis, wheezing, cough, and hemoptysis. Common GI symptoms are vomiting and diarrhea. The agent likely inhibits protein and nucleic acid synthesis and inhibits mitochondrial function. These agents can be inhaled, ingested, or absorbed transdermally. Any exposure may lead to weakness and ataxia progressing to shock and death in minutes to days. A differential diagnosis should include mustard gas or other vesicant agents, SEB, and ricin. An exposure history may include a reported contact with an oily aerosolized liquid. Mass spectrometry may be useful in confirming diagnosis. Supportive treatment is the focus, and GI decontamination may be used if the agent is ingested. There is no vaccine or antitoxin is available. Prompt skin decontamination is essential if suspected.

Ricin

Ricin is a cytotoxin extracted from castor beans, which are available worldwide. It works by inhibiting protein synthesis, leading to necrosis of the epithelial lining of the stomach and lungs. It may cause DIC and microvascular injury. Fever, chest tightness, cough, dyspnea, nausea, joint pain, lung inflammation, cyanosis, cough, and respiratory failure from acute respiratory distress syndrome (ARDS) would be expected. Symptoms may be dose-related. The disease should be suspected in cases of an onset of pulmonary symptoms in a geographic cluster of patients. Symptoms would not improve with antibiotics. A widened mediastinum would likely be absent, which may help differentiate ricin from anthrax. Chest x-ray study may show bilateral infiltrates, and laboratory results may indicate a leukocytosis with a left shift. ELISA may confirm a diagnosis when used on respiratory secretions. Ricin is difficult to separate from some of the other agents with similar presentation, such as SEB toxin, Q fever, tularemia, plague, anthrax, phosgene gas, or any pulmonary irritant (e.g., chlorine gas). Care is focused on supportive measures, especially of the respiratory system. GI decontamination should be considered. No antitoxin or vaccine is available.

MAJOR POINTS

- In-hospital Infectious Disease specialists and local health departments can provide guidance on initial isolation, management, testing, and response to a suspected or confirmed biological threat.
- Major potential agents of biological terrorism include anthrax, plague, smallpox, tularemia, botulism, and viral hemorrhagic fevers.
- Many BT agents will present with common symptoms, making them difficult to diagnose at first. A thorough history and physical exam as well as an awareness of the characteristic signs and symptoms of each of these agents will be helpful in making a diagnosis.

SUGGESTED READINGS

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