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Diagnosis and Management of Suspected Cases of Bioterrorism: A Pediatric Perspective

Hanoch A. Patt, MD, and Ralph D. Feigin, MD

ABSTRACT. Since October 3, 2001, the Centers for Disease Control and Prevention and other organizations have been investigating potential bioterrorist-related anthrax cases. The pediatrician may be faced with complex issues related to diagnosis and treatment of illnesses caused by intentionally released biological agents. The agents that pose a major potential bioterrorist threat are reviewed by the clinical syndromes they produce: acute respiratory distress with fever, influenza-like illnesses, acute rash with fever, neurologic syndromes, and blistering syndromes. Specific and detailed diagnostic, treatment, and prophylaxis information is provided for anthrax, plague, tularemia, smallpox, botulism, viral hemorrhagic fevers, and other diseases. In cases of suspected bioterrorism, the pediatrician must be able to obtain diagnostic and treatment information efficiently and expeditiously. The system controlling the interaction between public and nonpublic health laboratories in suspected cases of bioterrorism is described. Finally, information regarding emergency contacts and links to educational resources is provided. *Pediatrics* 2002;109:685-692; *bioterrorism, biological agents, anthrax, plague, tularemia, smallpox, botulism, viral hemorrhagic fevers.*

ABBREVIATIONS. CDC, Centers for Disease Control and Prevention; ELISA, enzyme-linked immunosorbent assay; PCR, polymerase chain reaction; SEB, staphylococcal enterotoxin B; USAMRIID, United States Army Medical Research Institute of Infectious Diseases.

Since October 3, 2001, the Centers for Disease Control and Prevention (CDC) and other organizations have been investigating potential bioterrorist-related anthrax cases. The role of the pediatrician in responding to biological threats may include: 1) dealing with the consequences of an overt attack (ie, mass casualty incident); 2) diagnosing, treating, and reporting diseases associated with a covert attack (the current situation); and 3) responding to the concerns of worried parents regarding themselves and their children. Future roles may also include participation in vaccination programs designed to distribute vaccine that may protect children against biological agents deemed to be of suf-

ficient risk to health as to outweigh any potential risk of adverse reactions to the vaccine itself. As discussed in a March 2000 American Academy of Pediatrics policy statement regarding chemical and biological terrorism, children are particularly vulnerable to the threat of biological terrorism because of more rapid respiratory rate, higher skin-to-mass ratio, more permeable skin, less fluid reserve, and other physiologic and psychological reasons.¹ Rapid diagnosis in children sometimes is confounded by a child's inability to describe the symptoms of disease. This article focuses on a description of the major potential bioterrorist threats and clarification of diagnostic and treatment options for the pediatrician who encounters a patient with symptoms suggesting the possibility of illness attributable to biological agents.

A report in 2000 from the CDC divided biological agents into 3 categories based on the potential terrorist threat they may represent.² Category A (highest priority) agents include organisms that pose a risk to national security because they are either easy to disseminate or highly contagious, cause high mortality with a potentially major public health impact, cause public panic and social disruption, and require special action for public health preparedness. This category includes the causative agents of anthrax, smallpox, plague, tularemia, botulism, and viral hemorrhagic fevers (eg, Ebola, Marburg, Lassa, and others).

Category B (second highest priority) agents include those that are moderately easy to disseminate. These agents cause lower mortality but significant morbidity and require specific enhancements of CDC's diagnostic capacity and enhanced disease surveillance. They include the following: *Coxiella burnetii* (Q fever), *Brucella* species (brucellosis), *Burkholderia mallei* (glanders); alphaviruses (Venezuelan encephalomyelitis and similar diseases), ricin toxin from *Ricinus communis* (castor beans), ϵ toxin of *Clostridium perfringens*, and *Staphylococcus enterotoxin B*. Also included in this category are food or waterborne pathogens such as *Salmonella* species, *Shigella dysenteriae*, *Escherichia coli* O157:H7, *Vibrio cholerae*, and *Cryptosporidium parvum*.

Category C (third highest priority) agents could be engineered for mass dissemination in the future because of availability, ease of production and dissemination, and potential for high morbidity and mortality and major health impact. Some of these agents

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include Nipah virus, hantaviruses, tickborne hemorrhagic fever viruses, tickborne encephalitis viruses, yellow fever, and multidrug-resistant tuberculosis.

The major potential biological threats also can be categorized by the clinical syndromes they produce. Some cause acute respiratory distress with fever. Others are associated with influenza-like illnesses, acute rash with fever, neurologic syndromes, or blistering syndromes. The category A agents and some category B agents will be discussed within this framework. Except where noted, antibiotic treatment and prophylaxis information is compiled from the *2000 Red Book*³ and Houston Medical Response Task Force recommendations.

AGENTS ASSOCIATED WITH ACUTE RESPIRATORY DISTRESS AND FEVER

Anthrax

Before the current outbreak, anthrax had become an exceedingly rare disease in the United States. Much of the knowledge related to the clinical course of the disease is derived from information gathered after an accidental aerosol release in Sverdlovsk in the former Soviet Union in 1979. In that incident, there were 66 fatalities among the 77 patients identified. Cases occurred up to 6 weeks after exposure.⁴

Since October 2001, however, there have been 22 cases of anthrax reported (17 confirmed and 5 suspected).⁵ In addition, >10 000 people have been placed on antibiotic prophylaxis pending documentation of definitive exposure. In the future, anthrax could represent an even greater threat. A World Health Organization report in 1970 estimated that 50 kg of anthrax spores released upwind of a city with a population of 500 000 could cause 125 000 infections and 95 000 deaths.⁶ Thus, anthrax represents both a covert threat and a potential mass casualty incident.

The clinical syndromes associated with anthrax infection have been described in great detail elsewhere, but a brief description is appropriate here. Inhalation anthrax occurs after an incubation period of 1 to 6 days, but may occur as late as 60 days postexposure.⁷ The illness is biphasic, and the initial phase consists of an influenza-like syndrome with fever, myalgia, nonproductive cough, malaise or fussiness, and chest or abdominal pain. Importantly, the presence of rhinorrhea is very uncommon (<10% of cases) in anthrax infection and generally will help exclude anthrax as a diagnosis. After the prodrome, the patient will have worsening of fever and chest pain, and may develop dyspnea, diaphoresis, and cyanosis. At this stage, the illness progresses rapidly to shock and death within 24 to 36 hours. Inhalation anthrax often is complicated by meningitis (>50% of cases in adults). A chest radiograph early in the course of disease may be normal; later findings may include a widened mediastinum or pleural effusions.

Cutaneous anthrax occurs when spores are introduced on sites of broken skin. A painless, pruritic papule appears 1 to 7 days later. Over the next few days, vesicles containing clear or serosanguinous fluid develop around the initial papule, and the pa-

tient may develop low-grade fever. Vesicles rupture and become necrotic, eventually forming ulcers covered by black eschars. Patients usually will have marked edema around the vesicles and regional lymphadenopathy. Untreated, mortality in adults approaches 20%.

Gastrointestinal anthrax develops <1 week after spores are ingested in undercooked meat. Symptoms consist initially of fever, nausea, vomiting, and abdominal pain, and progress rapidly to bloody diarrhea or hematemesis. Oropharyngeal involvement is manifested by ulcerated lesions at the base of the tongue, dysphagia, and systemic symptoms. Untreated, mortality is approximately 50%.

Laboratory diagnosis of inhalation anthrax relies on blood cultures, as productive cough is not common with the disease and sputum samples are difficult to obtain reliably in children (sputum should be sent if available). Blood cultures generally will grow rapidly from patients with inhalation or gastrointestinal disease. When inoculated on a sheep blood agar plate, anthrax will grow, and in 15 to 24 hours 2 to 5 mm, tenacious, nonhemolytic colonies appear, often with comma-shaped projections (the so-called "Medusa head" appearance).⁸ Gram stain of skin lesions, cerebrospinal fluid, or blood will reveal broad, encapsulated gram-positive rods. The organism is non-motile and catalase-positive.

In cases of suspected cutaneous anthrax, specimens for Gram stain and culture may be obtained from previously unopened vesicles or from beneath an eschar by lifting the outer edge, inserting a swab, and rotating for several seconds without removing the eschar. Rectal swabs or stool samples may be sent for culture if gastrointestinal anthrax is considered. Confirmatory tests are available through the Laboratory Response Network (whose structure will be discussed below) Level B and/or C labs and include culture on nutrient agar in 5% carbon dioxide and staining with India ink and direct fluorescent antibody staining of cell-wall polysaccharide antigen.⁹ Rapid tests such as enzyme-linked immunosorbent assay (ELISA) or polymerase chain reaction (PCR) from nasal swabs can be performed in some hospital laboratories or by municipal and state public health laboratories. Nasal swabs are not indicated in the evaluation of the symptomatic individual and are only useful as an adjunctive tool in epidemiologic investigation by members of the public health system.

Postexposure prophylaxis is indicated only after a confirmed or suspected aerosol exposure to anthrax spores and should be initiated in coordination with the local or state public health system. For children, the CDC recommends ciprofloxacin 10 to 15 mg/kg/dose orally every 12 hours (not >500 mg/dose) as an initial therapy.⁵ Alternatively, doxycycline at 2.2 mg/kg/dose orally twice daily may be used (up to 100 mg twice each day). If the responsible organism is found to be susceptible to penicillin, prophylaxis should be changed to amoxicillin 80 mg/kg/d in 3 divided doses (not >500 mg/dose). Antibiotic prophylaxis should be continued for 60 days.

For initial therapy in inhalation or gastrointestinal

anthrax, the CDC recommends intravenous ciprofloxacin or doxycycline at the doses noted previously plus 1 or 2 additional antibiotics (many options are available). We would recommend clindamycin (30 mg/kg/d intravenously) because its inhibition of DNA synthesis may be useful in neutralizing the elaboration of toxins (lethal factor, edema factor, and protective antigen) associated with the infection.⁹ Therapy may be switched to the oral route when clinically appropriate and should be continued for 60 days of total therapy.

Plague

Plague, caused by the bacterium *Yersinia pestis*, has been used as a biological weapon for at least 600 years. In 1346, the attacking Tartar army hurled the corpses of plague victims over the walls of Kaffa, and the ensuing epidemic resulted in the city's surrender.⁴ Plague continues to be a major potential biological terrorist threat because of its contagiousness.

The clinical syndromes associated with plague are pneumonic, bubonic, and septicemic. In children, bubonic plague is much more common in naturally occurring cases. Pneumonic plague presents 2 to 3 days after inhalation of the organism (exact timing is probably dose-dependent), with high fever, chills, headache, malaise, and myalgia. These symptoms quickly progress to a cough, often with hemoptysis and cyanosis. Other symptoms such as nausea, vomiting, diarrhea, and abdominal pain are common. The disease is rapidly progressive and, untreated, results in respiratory failure and shock. Untreated, mortality approaches 100%.¹⁰ A chest radiograph may show bilateral infiltrates of many types. Non-specific laboratory findings are consistent with a severe bacterial infection with disseminated intravascular coagulation. Other diseases on the differential diagnosis of pneumonic plague include hantaviral infection and community-acquired pneumonia.

Bubonic plague has a slightly longer incubation of 2 to 10 days and then presents with malaise and fever followed by or concurrent with the formation of the bubo (a swollen, painful, infected lymph node). The septicemic form of plague may occur with or without lymphadenopathy or pulmonary symptoms and resembles a severe gram-negative septicemia. Meningitis complicates approximately 6% of septicemic and pneumonic plague cases. Untreated, mortality from bubonic plague approaches 60% but is reduced substantially by prompt treatment.

Diagnosis of plague in the setting of a bioterrorist attack likely will be based on clinical suspicion, suggested by the presentation of many previously healthy patients with rapidly progressive pneumonia with hemoptysis. Sputum, blood, lymph nodes, and cerebrospinal fluid (if indicated) should be obtained for Gram, Wright, Wayson, or Giemsa stain and culture. The organism appears as a sometimes bipolar gram-negative bacillus or coccobacillus with a safety-pin appearance. The organism is slow-growing but may be cultured on blood agar, MacConkey agar, or infusion broth. The laboratory should be notified that plague is suspected so specimens can be incubated both at 28°C for rapid growth and 37°C for

identification of the capsular antigen. Colonies may show a "hammered copper" or "fried egg" morphology. Blood in a red top tube also should be drawn for F1-antigen immunoassay, and any specimen can be sent for direct fluorescent antibody.⁴ These tests should be ordered in coordination with the public health service to transport the specimen to the appropriate specialized hospital, state health department, CDC, or military laboratory.

Options for postexposure prophylaxis include doxycycline 2.2 mg/kg twice daily (up to 100 mg every 12 hours), trimethoprim-sulfamethoxazole 8 to 12 mg/kg (of trimethoprim) divided twice daily, or ciprofloxacin 15 to 20 mg/kg twice daily for 7 days.

For symptomatic cases, initial antibiotic choices for plague in children include streptomycin 30 mg/kg/d intramuscularly in 2 divided doses or gentamicin 2.5 mg/kg intramuscularly or intravenously every 8 hours. Other options include doxycycline or chloramphenicol. Chloramphenicol (25 mg/kg as an initial intravenous dose, followed by 50–100 mg/kg/d intravenously given in 4 divided doses every 6 hours) with or without streptomycin should be used to treat plague meningitis. Duration of therapy is 10 days. Patients should be in droplet isolation until plague pneumonia is excluded. If plague pneumonia is the ultimate diagnosis, patients should be isolated for 72 hours after the initiation of appropriate antibiotic therapy.

Other Agents Causing Respiratory Distress With Fever

There are other potential bioterrorist agents that cause respiratory distress and fever. Two toxins, considered category B agents by the CDC, are ricin and staphylococcal enterotoxin B (SEB). Ricin is a potent protein toxin derived from the beans of the castor plant, and therefore is potentially widely available. Approximately 4 to 8 hours postexposure, patients develop acute onset of fever, chest pain, cough, dyspnea, nausea, and arthralgia. Pulmonary capillary leak with acute respiratory distress syndrome develops within 18 to 24 hours, and death occurs 36 to 72 hours postinhalation exposure.⁴

Serum and/or respiratory secretions should be sent for ELISA testing, and PCR can detect castor bean DNA. The local health department should be informed immediately of suspected cases. Ricin should be suspected in the appropriate clinical and epidemiologic setting (ie, multiple geographically clustered patients presenting with acute lung injury). Treatment is supportive, although gastric lavage and cathartics can be used if the toxin is ingested. No prophylaxis except for protective mask is available.

The symptoms of SEB intoxication depend on the route of exposure. Oral ingestion results in symptoms such as nausea, vomiting, and diarrhea. Respiratory symptoms appear 3 to 12 hours after aerosol exposure.⁴ Patients develop sudden onset of influenza-like symptoms with fever, chills, and dry cough. If toxin enters the blood, mortality may be significant. The diagnosis should be suspected in the appropriate epidemiologic setting in patients with acute onset of a febrile respiratory syndrome without chest radiograph findings. Laboratory diagnosis can be at-

tempted in coordination with the public health system with antigen detection through ELISA on environmental or clinical samples. The presence of SEB in the serum is transient, but urine should be tested for SEB, and respiratory secretions or nasal swabs may detect the toxin early postexposure. Acute and convalescent sera should be drawn for antibody response. As with ricin, therapy is supportive, and no specific prophylaxis is available. An investigational toxoid vaccine is being tested but is not commercially available.

INFLUENZA-LIKE ILLNESSES

Tularemia

Francisella tularensis is a small, nonmotile, aerobic, gram-negative coccobacillus. Natural tularemia (rabbit fever or deer fly fever) usually is acquired after skin or mucous membrane contact with the carcass or body fluids of an infected animal. The clinical manifestations of tularemia depend on the route of inoculation. The different presentations include pneumonic, typhoidal, ulceroglandular, glandular, oculoglandular, oropharyngeal, and septicemic. As an aerosolized bioweapon the typhoidal form (possibly complicated by pneumonia) would likely be most common.

Onset of disease occurs an average of 3 to 5 days after inoculation (range: 1–21 days).¹¹ The typhoidal form presents with fever and an influenza-like illness, with headache, chills, rigors, myalgia, and arthralgia in the absence of skin or mouth findings and lymphadenopathy. Cases resulting from aerosol release may be complicated by pneumonia (up to 80%); in addition to the above symptoms, patients have dry cough, substernal or pleural pain, dyspnea, and/or hemoptysis.

Ulceroglandular tularemia refers to cases having the systemic symptoms of tularemia plus an ulcerated skin lesion and painful regional lymphadenopathy. Glandular tularemia presents with lymphadenopathy and fever but no ulcers. Oculoglandular tularemia occurs after inoculation of the conjunctiva and presents with purulent conjunctivitis, chemosis, periorbital edema, and conjunctival nodules or ulceration, along with preauricular or cervical lymphadenopathy. Oropharyngeal tularemia produces acute exudative or membranous tonsillitis with cervical lymphadenopathy. Any form of tularemia may be complicated by sepsis; pulse-temperature dissociation occurs in up to 42% of cases.

The diagnosis of tularemia would be suggested by a large number of patients presenting with similar influenza-like illnesses and atypical pneumonia. The differential diagnosis includes other typhoidal syndromes such as salmonella, rickettsial disease, malaria, other pneumonic processes, and other influenza-like illnesses. Laboratory diagnosis is difficult. A chest radiograph may show hilar adenopathy. A complete blood count often is normal.

An attempt should be made to culture the organism from gastric aspirates, sputum, pharyngeal exudates, or conjunctival exudates. It is isolated less commonly from blood cultures. The organism grows

in 24 to 48 hours on special media such as glucose-cysteine nutrified blood agar, cysteine-enriched broth, thioglycollate broth, buffered charcoal-yeast agar, or chocolate agar. Working with *F tularensis* is hazardous, and growing cultures should be transferred to a biosafety level 3 laboratory (ie, double-door entry into laboratory area, inward air flow, nonrecirculating air). Blood in a heparinized, citrated, or EDTA-filled tube can be sent for PCR, ELISA, and pulsed field gel electrophoresis. PCR and fluorescent antibody detection is available on other clinical specimens. Serum antibody titers do not reach diagnostic levels until approximately 2 weeks after infection, limiting the utility of serology in making an early diagnosis. In addition to the public health system of each state, information regarding testing, shipping, and handling specimens can be obtained from the CDC's Division of Vector-Borne Infectious Diseases in Fort Collins, Colorado (970-221-6400).

Untreated typhoidal tularemia has a case fatality rate of about 35%, but the disease responds well to antimicrobial therapy. In children, the treatment of choice is gentamicin 2.5 mg/kg every 8 hours for 14 days. For postexposure prophylaxis, doxycycline can be given at 2.2 mg/kg twice daily for 14 days (up to 100 mg twice daily). A live attenuated vaccine is available to protect laboratory workers.

Brucellosis and Q Fever

Brucellosis is considered a class B disease by the CDC. Patients with brucellosis infection will present with symptoms similar to influenza: irregular fever, chills, malaise, headache, cough, fatigue, weight loss, nausea, and vomiting. Mortality is <2%, but an untreated infection may persist for months.¹² Brucellosis occasionally is complicated by bone or joint involvement. Endocarditis is a rare complication. Hepatosplenomegaly sometimes is seen on physical examination.

Abnormal laboratory studies often include anemia and thrombocytopenia. Chest radiograph findings are variable. An attempt should be made to culture the organism from blood, bone marrow, or other tissues. Because the organism grows slowly, cultures should be incubated for at least 21 days. The organism is a small gram-negative coccobacillus that is oxidase-positive; it vigorously hydrolyzes urea. Serum may be sent for ELISA or agglutination testing. Antibody titers usually are positive after 1 week.

Therapy should be continued for 6 weeks (or more with central nervous system disease or endocarditis), and relapses may occur (usually because of premature discontinuation of treatment). Treatment of serious infections consists of streptomycin 15 mg/kg intramuscularly twice daily (up to 2 g/d) or gentamicin 2.5 mg/kg every 8 hours plus ciprofloxacin 15 mg/kg/d or rifampin 20 mg/kg/d in 2 divided doses. Oral trimethoprim/sulfamethoxazole 10 mg/kg/d (of trimethoprim), doxycycline, or tetracycline can be used as well for less serious infections. For central nervous system disease, a third-generation cephalosporin with rifampin is appropriate. Postexposure prophylaxis may be provided using doxycy-

cline 2.2 mg/kg twice daily (up to 100 mg twice daily) or ciprofloxacin 15 to 20 mg/kg twice daily (up to 500 mg twice daily) for 3 weeks. No vaccine is available.

Q fever is also a Class B agent. It generally is self-limited even without therapy and has low mortality, but significant morbidity. It is caused by the rickettsial organism *Coxiella burnetii* and presents as a febrile illness with influenza-like systemic symptoms lasting 2 days to 2 weeks. In addition to headache, fatigue, and myalgia, about one third of patients will develop hepatitis, and half of the patients with Q fever will have abnormal chest radiograph findings.⁴ Cough will be noted in only 50% of those with chest radiograph findings. Some patients may develop endocarditis. As a potential bioterrorist agent, Q fever would be difficult to differentiate clinically from viral illnesses or other causes of atypical pneumonia. Serologic tests for Q fever include indirect fluorescent antibody and complement fixation tests. ELISA testing is also available at research labs such as the United States Army Medical Research Institute of Infectious Diseases (USAMRIID).

Standard treatment is with tetracycline or doxycycline. It is unclear whether the risk of dental staining associated with use of tetracyclines is outweighed by benefit of treatment in children <8 years old. Treatment generally shortens the course of the disease and should be continued until the patient is afebrile for 2 to 3 days.

ACUTE RASH WITH FEVER

Smallpox

The history of smallpox (*variola major*) as a bio-weapon can be traced back to the distribution of contaminated blankets by British forces to Native Americans during the French and Indian Wars.¹³ It is not necessary to restate here the potential of smallpox as a modern bioweapon or the possible grave consequences of its deliberate reintroduction. Suffice it to say that the report of a single case of smallpox would be an international public health emergency.

Smallpox is a DNA virus of the genus *Orthopoxvirus*. Vaccinia virus, the source of the modern live-virus vaccine, also is a member of this genus but is much less contagious. Smallpox infection occurs through respiratory droplets. The incubation period lasts approximately 2 weeks (range: 7–17 days), and patients commonly present with high fever, malaise, prostration, headache, and backache. A maculopapular rash appears on the oral and pharyngeal mucosa, face, and forearms and spreads to the trunk and legs. The rash becomes vesicular within 1 to 2 days and then becomes pustular. The pustules are round, tense, and deep. After approximately 8 to 9 days after onset of the rash, crusts form which eventually scab. Occasionally encephalitis will occur. Death ensues during the second week of illness and may be secondary to toxemia from circulating immune complexes and soluble variola antigens.

Approximately 10% of cases of smallpox occur in a hemorrhagic or malignant form. In the uniformly fatal hemorrhagic form, the incubation period is

shorter. The patient presents with high fever, abdominal pain, and headache and then develops petechiae and hemorrhage into the skin and mucous membranes. Death occurs about the fifth or sixth day after the rash appears.

The malignant form also is frequently fatal. The prodrome period is similar to the hemorrhagic form. The patient develops confluent soft, flat, velvety vesicular lesions that do not progress to pustules, and, if the patient survives, eventually peel away or disappear without forming scabs.

Variola minor is a less severe variant of the disease with a smaller number of skin lesions that often is seen in people with partial immunity from earlier vaccination.

The early diagnosis of a sentinel case of smallpox is vital. An important clinical diagnostic tool is the fact that all lesions will progress at the same rate. This contrasts with varicella (chickenpox), in which lesions progress in clusters and all 4 stages of lesions may be present at the same time. In addition, varicella lesions usually are concentrated on the trunk rather than the face or extremities and spare palms and soles whereas smallpox generally is distributed centrifugally.

The initial laboratory specimens should be collected by someone who has been vaccinated recently (within 10 years) and wears gloves and a mask. Orthopoxviruses can be seen easily on electron microscopic examination (clinical picture readily differentiates smallpox from vaccinia). Vesicular or pustular fluid can be placed on a cotton swab or in a hematorvir tube and placed in a vacutainer tube. Scabs may be picked off with forceps and also placed in a vacutainer tube. The vacutainer tubes then should be sealed with tape at the juncture of stopper and tube. This tube should be enclosed in a second, watertight container. The CDC and USAMRIID currently are the only high-containment facilities to which specimens should be sent for diagnosis. Those institutions and the state and/or local health department should be contacted immediately for shipping and diagnostic information. Definitive identification of the virus involves growing it in cell culture or on chorioallantoic egg membrane. In addition, various biological assays such as PCR and restriction fragment-length polymorphisms can be done quickly in specialized laboratories.

Pre- and postexposure prevention strategies are evolving. Routine smallpox vaccination ceased in 1972. Currently, approximately 15 million doses of the vaccinia vaccine exist in the United States, and a new tissue cell culture vaccine is being developed. Recent studies have demonstrated that the vaccine can be diluted 5 to 1 and still retain its efficacy (R. B. Couch, personal communication, December 3, 2001). The prevailing wisdom regarding adults has been that immunity wanes after 10 years, but there is strong evidence that at least partial immunity remains for 50 years or more. A brief recent review of that evidence can be found in *Science*.¹⁴

Current postexposure therapy is supportive. Cidofovir, an investigational nucleoside analog DNA polymerase inhibitor, may be useful if given early

postexposure, but must be given intravenously and has been associated with significant renal toxicity. Patients admitted with smallpox must be isolated in a negative pressure room with high-efficiency particulate air filtration. Contact and airborne isolation precautions are required. A mask should be worn by all individuals entering the room. All waste and linen should be autoclaved before being incinerated or laundered.

All contacts should be interviewed, vaccinated, and placed under surveillance. The administration of vaccine within 4 days of exposure may prevent or ameliorate illness. Vaccinia immune globulin is available for those having reactions to vaccinia administration or for immunocompromised patients. Contacts should have daily temperature recordings for 17 days postexposure, and if fever $>101^{\circ}\text{F}$ is noted during that period, the contact should be isolated at home until it is determined whether the disease has developed. If disease occurs, all contacts of the patient should be vaccinated.

Viral Hemorrhagic Fevers

Viral hemorrhagic fever agents are RNA viruses that normally are transmitted to humans from animal reservoirs or arthropod vectors. They come from the families Filoviridae (eg, Ebola and Marburg), Arenaviridae (Lassa fever, Argentine, Bolivian, Venezuelan, and Brazilian hemorrhagic fevers), Bunyaviridae (Rift Valley fever, Congo-Crimean hemorrhagic fever, and hantavirus), and flaviviruses (yellow fever and dengue). Most are considered serious potential biowarfare threats because of the current or future potential to be aerosolized and their very high morbidity and/or mortality.

The mechanism of hemorrhage and coagulopathy differs between members of the group.⁴ Disseminated intravascular coagulation has been implicated in some of these viruses (Rift Valley fever, Ebola, and Marburg). In others, the cause is multifactorial and may include liver disease and marrow injury in addition to direct vascular damage and increased capillary permeability. Early findings include fever, myalgia, prostration, conjunctival injection, flushing, mild hypotension, and petechiae. Shock and mucous membrane hemorrhage then develop. Renal involvement is proportional to cardiovascular compromise except in hemorrhagic fever and renal syndrome (caused by bunyaviruses).

Some clinical clues may suggest a specific etiologic agent. Prominent jaundice and hepatitis are seen more often in Rift Valley fever, Congo-Crimean hemorrhagic fever, Ebola, Marburg, and yellow fever. Lassa fever causes severe peripheral edema secondary to capillary leak, but little hemorrhage. Rift Valley fever virus infection is associated often with retinitis. Central nervous system and hemorrhagic manifestations are common after infection with arenaviruses indigenous to South America.

The clinical picture is most important in arriving at an etiologic diagnosis, but nonspecific laboratory tests may be helpful. Thrombocytopenia (except in Lassa) and leukopenia (except in Lassa, hanta, and Congo-Crimean hemorrhagic fever) are seen com-

monly. Multiple specimens can be sent for definitive diagnosis, including heparinized blood for culture and red top tube for serum, as well as stool and nasal swabs, which should be placed in viral transport medium. Viremia usually is detectable at presentation, and antigen ELISA and antibody studies can be performed at the CDC or USAMRIID.

Treatment generally is supportive, although ribavirin may help lower the morbidity and mortality in some viral hemorrhagic fevers (it has no activity against the filoviruses and flaviviruses). Clinicians should be aware of the possibility of pulmonary capillary leak in patients receiving aggressive fluid resuscitation. The benefits of invasive monitoring for critically ill patients should be weighed against the risk of hemorrhage. Coagulopathy and clinical bleeding should be managed in the standard fashion. Intramuscular injections should be avoided. Investigational vaccines are available for some of the hemorrhagic fever viruses, such as Rift Valley fever and Argentine hemorrhagic fever, and are being studied in others.

NEUROLOGIC SYNDROMES

Botulism

There are 4 types of naturally occurring human botulism: infant, foodborne, wound, and intestinal. Inhalation of aerosolized botulinum toxin results in similar toxin-mediated clinical symptoms. There are 7 antigen types, A through G. Disease is produced as a result of irreversible toxin binding to peripheral cholinergic synapses and blockade of acetylcholine release, resulting in paralysis.

Symptoms usually occur 12 to 24 hours after exposure (range: 6 hours to 8 days).⁴ Clinical illness is characterized by a descending flaccid paralysis, and early symptoms include dysphagia, dysarthria, diplopia, dysphonia, and ptosis. The descending paralysis may result in respiratory muscle impairment and subsequent death. Patients are alert without fever. The differential diagnosis of acute paralytic illness includes Guillain-Barré syndrome, Eaton-Lambert syndrome, tick paralysis, myasthenia gravis, and nerve gas attack. Epidemiologically, the diagnosis would be suggested by the appearance of a large number of patients with similar syndromes. Nerve gas release results in immediate symptoms.

Electromyography may be helpful in diagnosis, but generally diagnosis should be made on a clinical and epidemiologic basis. Serum, feces, and gastric aspirates should be obtained for toxin assays. The state public health laboratories should be contacted and may work in conjunction with the National Botulism Surveillance and Reference Laboratory (404-639-3867).¹⁵

Treatment consists of supportive care, management of secondary infections, and passive immunization with equine antitoxin. Botulinum equine antitoxin is available for types A, B, and E from the CDC through state and local health departments. Use of the antitoxin requires skin testing. Patients are injected intradermally with 0.1 mL of a 1:10 dilution of antitoxin. If no reaction occurs, a slow infusion of

antitoxin (10 mL diluted 1:10 normal saline) can be given intravenously. If a wheal and flare appears, patients should be desensitized over at least 3 to 4 hours. Diphenhydramine and epinephrine should be available during administration. An investigational toxoid vaccine is available for high-risk laboratory workers and the military but takes several months to confer immunity; therefore, it is not recommended for postexposure prophylaxis.

Venezuelan Equine Encephalitis and Related Viruses

Venezuelan equine encephalitis, Eastern equine encephalitis, and Western equine encephalitis viruses are members of the *alphavirus* genus of togaviridae. They are considered category B agents and are candidates for use as biowarfare agents because they are highly infectious as aerosols and are stable during storage.⁴ Initial symptoms of infection include fever, headache, and myalgias. Fewer than 5% of patients develop neurologic involvement. Most of the survivors recover fully with no residual symptoms.

Initial leukopenia followed by leukocytosis is common, as is cerebrospinal fluid lymphocytosis. Of the 3 viruses Eastern equine encephalitis has the highest mortality rate. Nevertheless, the mortality rate in infants following Western equine encephalitis infection may reach 10%.

These viruses can be recovered from serum early in the illness and often can be recovered from cerebrospinal fluid. PCR is available at reference laboratories which can be identified by calling the state health department. Antibodies are detectable by the second week of illness. Treatment is symptomatic. A live, attenuated vaccine for Venezuelan Equine encephalitis is available for at-risk laboratory personnel. No person-to-person transmission has been reported, and therefore standard precautions are all that is necessary for isolation.

BLISTERING SYNDROME

T2 Mycotoxin

Trichothecene mycotoxin can be recovered from filamentous fungi such as *Fusarium*, *Trichoderma*, *Stachybotrys*, and others. The toxin is heat stable. It can be aerosolized in a form known as "yellow rain" and works by inhibiting protein synthesis in rapidly dividing cells such as those of bone marrow, skin, and mucosa.

Diagnosis usually is made on the basis of clinical and epidemiologic findings after a large-scale release. Symptoms begin minutes to hours after exposure with burning of skin, which progresses to blistering and necrosis.⁴ Patients also may cough or experience sore throat and hemoptysis. The differential diagnosis includes chemical blistering agents, such as mustard gas, which have an odor and can be detected rapidly by field chemical tests. In a mycotoxin attack, a pigmented oily residue may be seen on patients and in the immediate environment. No rapid test is available, but blood, tissue, and environmental samples can be tested with gas liquid chromatography to confirm mycotoxin exposure.

Treatment includes removal of clothing and decontamination of skin. Activated charcoal can be given if the toxin has been swallowed. Eye exposure should be treated with saline irrigation.

LABORATORY RESPONSE NETWORK

The Laboratory Response Network was created to link the public health laboratory system and to detect potential cases of bioterrorism efficiently.^{2,16} The Laboratory Response Network consists of 4 levels of laboratories (A through D), each with specific tasks. Level A laboratories generally are nonpublic health clinical laboratories. They should be used to quickly rule out the presence of bacterial biological threats in clinical specimens only, using standard microbiologic procedures: Gram stain, oxidase, catalase, hemolysis, motility, satelliting, B-lactamase production, and urease production. Those clinical specimens and isolates in which a potential bioterrorist agent cannot be excluded should be forwarded to Level B and C laboratories. In addition, in cases where bioterrorism is suspected strongly, clinical specimens may be forwarded to Level B and C laboratories directly. Rapid diagnostic tests are done in Level B, C, or D laboratories exclusively.

Level B laboratories are local and state public health agencies that have the capability to test for specific agents from clinical and environmental specimens. Level C laboratories are located at various state health agencies, academic research centers, and federal facilities and should have advanced capacity for rapid identification of biological agents. Level D laboratories are specialized federal facilities (CDC and USAMRIID) with a number of functions and specifications. They have biosafety level 4 (highest level) containment capability. They have experience in the diagnosis of rare diseases such as smallpox and Ebola. They develop and evaluate new tests for implementation in Level B and C laboratories, archive organisms used in a biological attack, have the capacity to detect genetically modified agents, and type the organism implicated in an outbreak.

CONCLUSION

Pediatricians will have multiple roles in dealing the threat of bioterrorism. When possible, the pediatrician must be able to allay parental fears. For example, rapid tests for influenza A and B and for RSV are widely available and, when appropriately obtained, may be useful in obtaining alternative diagnoses and thus calming nervous parents. In addition, the pediatrician must be able to recognize, diagnose, and treat diseases related to potential bioterrorist agents. He or she will have to identify the appropriate laboratory for testing of suspicious clinical specimens rapidly and interact with that laboratory expeditiously and efficiently. The laboratory will be aided considerably if it is notified of the suspected disease before receiving the specimen.

When bioterrorism is strongly suspected, or testing in a Level A lab is unable to rule out a potential bioterrorist agent, the public health authorities and, when deemed appropriate, the Federal Bureau of Investigation must be notified. In general, questions

TABLE 1. Emergency Contacts and Educational Resources

Health Department information	
State Health Department Web sites	www.cdc.gov/other.htm#states
Phone numbers for State Health Departments	www.asmtusa.org/pasrc/StateLabContacts.pdf
Phone numbers for Local Health Departments	depts.washington.edu/~hsic/phealth/lhd/index.html
Emergency contacts	
CDC Bioterrorism Preparedness and Response Center	1-770-488-7100
National Pharmaceutical Stockpile Hotline	1-770-488-7516
USAMRIID Emergency Response Line	1-888-872-7443
National Response Center	1-800-424-8802 or 1-202-267-2675
Domestic Preparedness Help Line	1-800-368-6498
US Public Health Service Emergency Preparedness Office	1-800-USA-NDMS or www.ndms.dhhs.gov
Selected Web information resources	
American Academy of Pediatrics bioterrorism information Web site	www.aap.org/advocacy/releases/cad.htm
CDC bioterrorism information Web site	www.bt.cdc.gov
Johns Hopkins Center for Civilian Biodefense Studies	www.hopkins-biodefense.org
USAMRIID Web site	www.usamriid.army.mil
American Society for Microbiology Web site	www.asmtusa.org/pcsrc/bioprep.htm

regarding the appropriate laboratory for specific tests should be directed to individual local or state health departments. Web links and information regarding health department phone numbers, other emergency contacts, and educational resources can be found in Table 1.

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ASYMMETRIC FRAMING

“You could tell a woman her breast cancer risk is ‘high’—2% in 5 years—or you could take the opposite tack and tell her that there’s a 98% chance that she will not develop breast cancer within 5 years. If you want to sell her tamoxifen, you’ll focus on the first aspect; if you want to calm her anxiety, you’ll focus on the second.”

Reynold T. Disease prediction models aim to guide medical decision making. *Ann Intern Med*. 2001; 135:637–640

Submitted by Student

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