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Bioterrorism continues to be a high priority in the present political climate. This is the final part of two-part series reviewing strategies for responding to, assessing, and managing possible biological threats associated with viral diseases, biotoxins, and other agents. Changes in the management of biological threats can be monitored on a number of web sites; several links are provided in this review.

— The Editor

Bioterrorism Update—Current Guidelines and Recommendations for Prevention and Treatment of Biological Threats: Part II

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Dengue, Hemorrhagic Fevers, and Biotoxins

Dengue. Dengue is the most common flavivirus infection in humans. There are an estimated 100 million cases of dengue each year. The disease is widespread and occurs in all tropical regions where *Aedes aegypti* mosquitoes are found. Dengue is present year-round, with an increasing incidence during the rainy season. Dengue has appeared infrequently in the United States since the 1940s.[1] It remains a threat because the mosquito vectors for dengue are widely dispersed in the United States, particularly in the states bordering the Gulf of Mexico.

There are four serotypes of dengue, and multiple, sequential infections can occur.[2] Symptomatic illness is quite common with the first and second episodes of dengue. Subsequent infections tend to be mild or asymptomatic.

Presentation. Dengue has an incubation period of 2-10 days. The disease starts with high fever, chills, headache, back pain, anorexia, and nausea.[3] Clinical findings include facial flushing, conjunctivitis, and a slow pulse relative to the high fever. The fever breaks on the third to fifth day and is associated with a diffuse maculopapular or morbilliform rash on the trunk. This rash spreads to the face and limbs. The soles and palms are not involved. Desquamation may occur while the rash is healing.

The patient can develop myocarditis and neurologic complications. Encephalitis, neuropathies, and Bell's palsy can occur.

Dengue hemorrhagic fever and dengue shock syndrome are more severe forms of dengue that were first described in the early 1950s. Dengue hemorrhagic fever is defined by the presence of fever thrombocytopenia, and hemoconcentration.[4] Dengue shock syndrome adds hypotension or profound shock. The disease appears to be similar to classic dengue until the second to fifth days, when the more severe symptoms start to appear. Major hemorrhagic symptoms occur in 10-15% of cases. These patients may have petechiae, ecchymoses, pleural effusions, hepatomegaly, and hypotension. Encephalopathy may occur. Plasma leakage may cause edema, hemoconcentration, and hypoalbuminemia.[5,6]

Diagnosis. Dengue virus can be cultured on mosquito cell media. Diagnosis of dengue infections can be made by serologic techniques or by IgM enzyme-linked immunosorbant assay (ELISA) after about five days of illness.

Therapy. There is no effective therapy for dengue. Treatment is entirely supportive with volume replacement and symptomatic care. Aspirin should be avoided because of the increased possibility of hemorrhagic complications.

Prophylaxis. As it naturally occurs, dengue requires a vector for transmission. There is no need for isolation procedures for patients infected with dengue. However, since diagnosis may be confused with hemorrhagic fevers, these patients should be treated with strict isolation until the diagnosis is confirmed.

Since the mosquito vectors for dengue are widely dispersed in the United States, a bioterrorism event with dengue, in the appropriate locale and during the proper season, could pose a continuing threat.

Hemorrhagic Fever Viruses. Hemorrhagic fever (HF) is a clinical syndrome with fever, myalgia, malaise, hemorrhage, and in some patients, hypotension, shock, and death. There are four families of lipid enveloped viruses with single stranded RNA that cause HF: arenavirus, bunyavirus, filovirus, and flavivirus. The arenaviruses include Argentinian, Bolivian, and Venezuelan HFs, and Lassa fever. Bunyaviruses include Hantavirus, Congo-Crimean HF virus, and Rift Valley fever virus. Ebola and Marburg are the only known members of filovirus species. The flaviviruses include dengue and yellow fever.

Transmission of the HF syndrome varies with the specific virus. All of these are potentially transmitted by aerosol.

HF viruses are transmitted by either arthropod vectors or contact with an infected animal. Humans usually are infected only as incidental hosts. Arenavirus and Hantavirus are transmitted by inhalation of rodent droppings, while Rift Valley fever and Congo-Crimean HF are transmitted from handling infected livestock. The reservoir for Lassa fever, Marburg disease, and Ebola fever is unknown. These diseases have a high lethality and are easily transmissible person-to-person. Although nosocomial transmission in Africa was interrupted with simple universal precautions, respiratory transmission has been reported by the Centers for Disease Control and Prevention (CDC). *(See Table 1.)*

Ebola and Marburg Filovirus. Ebola HF is arguably one of the most virulent viral diseases known to man. It causes death in 50-90% of all clinically ill patients. Ebola virus has been covered significantly in the popular literature and in several books and movies. There has been a recent ebola outbreak in Africa. It appears to be contact spread, and may even be a sweat risk. This accounts for close contact, family, and hospital spread.

Ebola is a member of the filoviruses that cause severe HF in humans and other primates. A closely related filovirus (Marburg) shares many characteristics. Four subtypes of Ebola have been identified: Reston, Zaire, Sudan, and Ivory Coast. Reston does not cause severe disease in humans, but it is fatal in monkeys.

Ebola virus is a a HF. It can be spread by blood and blood products, secretions, and by aerosol transmission.[7] It is highly lethal (> 50%), with a rapid course. The incubation period is 2-21 days.

This virus is well spread by body fluids, particularly blood. It is quite dangerous for the health care provider because human-to-human contact will rapidly spread the disease.

Ebola virus was first identified in 1976 in Sudan and Zaire (now called the Democratic Republic of the Congo). In Zaire, there were 318 cases with 280 deaths over two months. More than 1100 cases, with more than 800 deaths, have been documented since the virus was discovered.

Marburg was identified in 1967 in Marburg, Germany. A number of laboratory workers in Germany and Yugoslavia were handling tissues from green monkeys and developed HF and died. A total of 31 cases and seven deaths were associated with this outbreak. Marburg has caused a few sporadic cases of HF since that time.

The natural reservoir of Ebola has not been identified yet. The most recent hypothesis is an experimental observation that bats

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Table 1. The Hemorrhagic Fevers

Disease	Location	Vector	Incubation	Species
Argentine hemorrhagic fever (Junin virus)	South America	Rodent	3-12 days	Arenavirus
Bolivian hemorrhagic fever (Machupo virus)	South America	Rodent	3-16 days	Arenavirus
Brazilian hemorrhagic fever (Guanarito virus)	South America	Rodent	3-16 days	Arenavirus
Congo-Crimean HF	Africa, Asia	Tick	3-12 days	Bunyavirus
Dengue fever	Worldwide	Mosquito		Flavivirus
Ebola (Philippines = Reston)	Africa, Philippines	Unknown	2-21 days	Filovirus
Hantavirus pulmonary syndrome	Americas	Rodent	3-21	Bunyavirus
Hemorrhagic fever with renal syndrome (HFRS) (Hantaan virus)	Worldwide	Rodent	9-35 days	Bunyavirus (Most common disease of hantaviruses)
Kyanasur Forest disease	India	Tick		Flavivirus
Lassa fever	Africa	Mosquito	5-16 days	Arenavirus
Marburg fever	Africa	Unknown	2-21 days	Filovirus
Omsk hemorrhagic fever	Siberia	Tick		Flavivirus
Rift Valley fever	Africa	Mosquito	2-5 days	Bunyavirus
Venezuelan hemorrhagic fever (Sabia virus)	South America	Rodent	3-15 days	Arenavirus
Yellow fever	Worldwide	Mosquito		Flavivirus

Every VHF virus except dengue is infectious by aerosol in the laboratory and therefore requires careful barrier and aerosol quarantine.

infected with Ebola do not die from the virus. The way that the virus moves from natural reservoir to humans also remains unknown.

Presentation. All of the viral HFs present as acute febrile illnesses. Each disease has a short incubation period and presents as a similar clinical illness.

Early in the course, the signs and symptoms are non-specific and may include malaise, myalgia, and varying degrees of prostration. The initial signs include flushing, injection of the conjunctival membranes, periorbital edema, and hypotension. After 3-5 days, the patient may develop petechiae, ecchymosis, and bleeding from the gums. As the disease progresses, diffuse bleeding and generalized mucosal hemorrhage develop. The patient may have neurologic, hematologic, and pulmonary involvement. Vascular damage is widespread. Diffuse bleeding may result from both disseminated intravascular coagulopathy and hepatic dysfunction.

HF should be suspected in any patient with a severe febrile illness and evidence of vascular involvement. This may include postural hypotension, petechiae, easy bleeding, flushing, and edema.

Ebola presents with the sudden onset of fever, weakness, muscle pain, headache, and sore throat. This nondescript onset is followed by vomiting, diarrhea, kidney and liver failure, and internal and external bleeding.

An exanthem is common with the filoviruses (Marburg, Lassa, and Ebola). The only cutaneous manifestation of yellow fever is jaundice.

HF viruses cause high morbidity and high mortality. Some may replicate well enough in cell cultures to permit their use as weapons. The filoviruses could be adapted as biowarfare agents since they are highly infectious, lethal, and can be stabilized for aerosol dissemination. Filoviruses have been considered too dangerous to use for biowarfare because there are no therapeutic measures to protect the user.

Diagnosis. Like many viral diseases, the diagnosis is best made by clinical impression. Routine labs are not helpful, although leukopenia is frequent. Clotting factors may be depressed and thrombocytopenia and may be found. Disseminated intravascular coagulation (DIC) is common. Leukopenia is not common in Lassa, Hantaan, and some severe Congo-Crimean HF. Proteinuria and/or hematuria are common. High enzyme (AST) elevation correlates with the severity of Lassa fever and jaundice is a poor prognostic sign in yellow fever.

There is no commercially available laboratory test for this disease. Diagnosis may be made with immunofluorescence, electron microscopy, or culture. Specific serodiagnostic assays have been developed for each of these viral diseases, including ELISA, immunofluorescence assays, and virus neutralization assays. Reference laboratories, such as the CDC, detect specific antigens, sequence the genes of the virus, isolate the virus in cell culture, examine it under an electron microscope, or detect IgM and IgG antibodies. Most patients are viremic at the time of presentation and culture of the virus can make a definitive diagnosis in 3-10 days.

These tests are extremely dangerous to the laboratory worker. Since these diseases are highly contagious, isolation of a viral agent with hemorrhagic symptoms should be done only in reference laboratories with P-4 containment capability. Both the CDC and U.S. Army Medical Resarch Institute of Infectious Diseases (USAMRIID) have diagnostic laboratories with P-4 containment level.

Laboratory specimens from these patients should be double-bagged and the outer bag decontaminated.

Remember that many illnesses can mimic a viral HF. These diseases include bacterial or rickettsial sepsis, malaria, Coumadin overdose, and other disease processes that can cause disseminated intravascular coagulopathy.

Therapy. Therapy is entirely supportive. Replacement of volume and blood loss is important. Because there is significant vascular permeability with these diseases, pulmonary edema due to infusion may be seen. Colloids are recommended rather than crystalloids for volume expansion. Dopamine has been used for pressure support. The use of intravascular devices and invasive hemodynamic monitoring must be balanced against the risk of hemorrhage.

The management of bleeding should be the same as for any patient with a systemic coagulopathy. Aspirin and other anticoagulant drugs should be avoided. Congo-Crimean and hemorrhagic fever with renal syndrome (HFRS) (see subsequent section on HFRS) may respond to prompt administration of ribavirin. Ribavirin has poor activity against the filoviruses (Ebola and Marburg) and the flaviviruses (dengue and yellow fever). Most patients who survive the acute illness will recover.

There are extremely limited quantities of hyperimmune serum obtained from survivors of Ebola. Experimental studies involving the use of hyperimmune sera on animals show that there is no long-term protection against the disease. Argentine HF has responded to convalescent plasma given within eight days of onset. Only limited quantities of this plasma are available.

Prophylaxis. Yellow fever is the only HF that has a vaccine. Some stocks of sera exist for Lassa, Ebola, and Marburg obtained from survivors, but these stocks are adequate only for partial protection of a few people. There are experimental vaccines for Argentine HF, Rift Valley fever, and Hantaan virus. The Hantaan virus vaccine is an experimental vaccinia-vectored vaccine available at USAMRIID. The vaccine for Argentinian HF appears to be effective for Bolivian HF as well. It is available as an investigational new drug (IND) and was developed at USAMRIID.

Ribavirin has been used for prophylaxis for Congo-Crimean HF, HFRS, and Lassa fever virus exposure. These patients should be watched for break-through disease or disease after cessation of therapy.

These patients should be placed in isolation. The CDC has developed guidelines for isolation of potential cases of viral HF. Because most physicians have very little experience with these diseases, consultation should be called as soon as possible.

Any person who has contact with contaminated fluid or secretions, or who has had close physical contact with a patient, should be kept under strict surveillance. Close contacts or medical personnel exposed to blood or secretions from HF patients should be monitored for symptoms, fever, and other signs during the established incubation period. Body temperature should be checked twice daily and isolation imposed if the patient's temperature rises above 101°F (38.3°C). Surveillance of suspected cases should be continued for at least three weeks after the date of patient's last contact.

Bodies should be cremated or buried in leak-proof material with minimal handling.

Lassa, Congo-Crimean HF, Ebola, and Marburg are particularly prone to aerosol nosocomial spread. There are well documented secondary infections in medical workers who had no parenteral exposure. Minimal protection for health care workers dealing with these patients includes: gloves, gowns, face shields, and respiratory protection with a fitted HEPA filtered respirator.

Hemorrhagic Fever with Renal Syndrome (HFRS). HFRS is caused by four strains of Hantavirus. The most severe disease is caused by the Hantaan virus distributed through the Far East, Eastern Russia, and the Balkans, and by the Dobrava virus, also found in the Balkans. A milder form of disease is associated with the Seoul virus, which has worldwide distribution. The mildest form of the disease is associated with Puumala virus, which occurs through Scandinavia, western Russia, and Europe.

HFRS is transmitted by aerosolization of infected rodent dung. The peak rates of disease occur when the rodent density and reproductively is highest, in November and December. There may be up to 100,000 naturally occurring cases of HFRS per year. The majority occur in China.

Presentation. The incubation period of HFRS is about two weeks after exposure. The severity ranges from very mild to severe disease with accompanying renal failure.

The illness begins with headache, malaise, myalgia, and fever. Symptoms progress to vomiting, abdominal pain, and lower back pain. A blanching rash occurs about the torso and the face. Petechiae may be noted within the rash and on the palate.

The febrile period lasts about 3-7 days. At the end of the febrile period, many patients develop hypotension and shock. This period of hypotension may be accompanied by DIC and bleeding diathesis. Renal failure with oliguria occurs in up to 70% of patients. Dialysis may be needed for therapy.

After the oliguric phase, the patient may begin a profound diuresis. This fluid loss may cause life-threatening hypotension and electrolyte abnormalities. Additional complications include pulmonary edema, cerebrovascular accidents, hemorrhage, and acidosis. The overall risk of death from this disease is about 5-7%.

Less severe disease is seen with the Seoul and Puumala strains of HFRS, with which the mortality is less than 1%.

Diagnosis. HFRS can be diagnosed by culture, IgM-capture ELISA, immunofluorescent antibody assays, or radioimmunoassay. HFRS is caused by a Hantavirus that is difficult to culture. It is anticipated that polymerase chain reaction techniques soon will be available for these viruses.

Laboratory findings include leukocytosis, thrombocytopenia, and proteinuria.

Therapy. Patients with HFRS should receive ribavirin. Ribavirin is a guanosine analogue that has been shown to have antiviral effect against the Hantavirus causing HFRS. The recommended loading dose is 33 mg/kg followed by 16 mg/kg every six hours for four days, then 8 mg/kg every eight hours for three days.[8,9]

Other patient care is completely supportive. It is important to avoid injudicious use of intravenous fluids to avoid edema formation. Colloids or whole blood are appropriate to treat hemorrhagic shock. Pressors are appropriate for treatment of hypotension. Dialysis can be lifesaving.

Table 2. Characteristics of Effective Biological Weapons

- Potential for massive numbers of casualties
- Ability to produce lengthy illness requiring prolonged and extensive care
- Ability of agents to spread via contagion
- Paucity of adequate detection systems
- Incubation period enables victims (and perpetrators) to widely disperse
- Nonspecific symptoms complicate early diagnosis and mimic endemic infectious diseases

Adapted from: USAMRIID's Medical Management of Biological Casualties Handbook, 4th ed. U.S. Army Medical Research Institute. February 2001.

Prophylaxis. There is no vaccine that is effective for HFRS. If spread by rodents, reduction of rodent population and avoiding contact with rodents would be appropriate. By the time patients who have been deliberately infected with this disease present to the emergency department, it is unlikely that decontamination or isolation will be useful. As always, isolation of a patient with HF is appropriate until the organism is identified.

Possible Biotoxins

Until recently, toxins were of interest only to the toxicologist, the rare patient who ingested or was exposed to these toxins, and the even rarer writer who discussed toxicological environmental emergencies. Unfortunately, several simultaneous political and scientific events have moved these toxins to a more prominent medical and social position.

Discovery that that some of these toxins have been used as agents in warfare or have been stockpiled to use in warfare have given some physicians an impetus to learn more about the effects and production of toxins for biological warfare (BW). *(See Tables 2 and 3.)* New uses for old toxins include botulinum therapy for spastic muscles and dystonia.

Botulinum Toxins. Botulinum neurotoxin is one of the most potent toxins known. The mouse lethal dose is less than 0.1 nanogram per 100 grams. It is more than 275 times more toxic than cyanide.

Botulism was first described by Mueller (1735-1793) and Kerner (1786-1862) in Germany. They associated the disease with ingestion of insufficiently cooked "blood sausages" and described death by muscle paralysis and suffocation. In the early 1900s, botulism commonly occurred in the United States and nearly destroyed the canned food industry.[10]

The major source of botulinum toxin is the organism *Clostridium botulinum.* There are seven serotypes produced by clostridia species. These serotypes are similar, but do not cross-react to immune reactions. They are released as a single polypeptide chain of about 150,000 daltons, which is cleaved to generate two disulfide linked fragments. The heavy fragment (H1 100,000 daltons) is involved in cell binding and penetration, while the light chain is responsible for the toxic intracellular effects.

The toxins are easily denatured and survive fewer than 12 hours in air. Sunlight deactivates the toxins within 1-3 hours, and standard water treatment chemicals inactivate the toxin within 20 minutes. The toxin does not absorb through intact skin. There is no secondary aerosol from exposed patients. Decontamination is not expected to be a significant problem for the medical worker.

Clinical Effects. Two natural types of poisoning occur. In the first type, food tainted with clostridia species is stored or processed in a way that allows the anaerobic organisms to grow and multiply. As they grow, they produce and release toxin. If the food is not subsequently heated to destroy the toxin, clinically significant amounts can be consumed. The toxin passes through the gut into the general circulation and is distributed throughout the body. In the second type, usually found in infants, the organisms colonize and produce their toxin in the gut. The clinical effects of the two types of botulism are the same.

The onset of symptoms in inhalation botulism usually occurs 12-36 hours after exposure. It varies according to the amount of toxin absorbed and easily could be shorter after a biowarfare attack. When a low dose of toxin is inhaled, the symptoms may take a longer time to develop.

After intoxication with botulinum toxin, cranial nerve palsies with eye symptoms such as blurred vision, diplopia, ptosis, and photophobia become prominent early. Dysphonia and dysphagia follow. The victims then develop decreased bowel function and muscle weakness that can progress to a flaccid paralysis. The patient generally will be awake, oriented, and afebrile. Development of respiratory failure may be quite rapid after initial symptoms develop. Progression from the onset of symptoms to respiratory failure may take as few as 24 hours in cases of food-borne botulism. When severe respiratory muscle paralysis is present, the patient may be cyanotic or have carbon dioxide retention.

The tremendous potency of botulinum toxin is due to an absolute neurospecificity. Botulinum toxin penetrates into the cell and blocks release of acetylcholine, preventing neuromuscular transmission and leading to muscle weakness.[11] Botulinum toxin is thought to preferentially affect active neuromuscular fibers and has been shown in rats to have a greater affect when nerve activity is greater.[12] It also may affect the central nervous system.[13] The local injection of botulinum toxin has been used clinically to treat involuntary focal muscle spasms and dystonic movements.

It is difficult to distinguish organophosphate nerve agent poisoning from botulism. Isolated cases have a wider differential diagnosis, including Guillain-Barrè syndrome, myasthenia gravis, and tick paralysis.

In intoxication with a nerve agent, inhibition of acetylcholinesterase causes an accumulation of acetylcholine. In botulism, the problem is lack of a neurotransmitter in the synapse. Use of anticholinergic agents such as atropine would cause worsening of symptoms. Nerve agents cause copious respiratory secretions, whereas a decrease in secretions would be likely with botulism.

Detection. The occurrence of an epidemic of afebrile patients with a symmetric, progressive neurologic disorder that ends in flaccid paralysis strongly suggests botulinum intoxication. Individual cases maybe confused with neuromuscular disorders such as Guillain-Barrè syndrome or tick paralysis. Myasthenia gravis may be easily confused with botulinum intoxication, since the edrophonium or Tensilon test may be transiently positive in botu-

Table 3. Potential Biologic Agents Used for Terrorism

CATEGORY A — HIGH-PRIORITY AGENTS INCLUDE ORGANISMS THAT:

- Can be easily disseminated or transmitted from person to person
- Cause high mortality, with a potential for major public health impact
- Might cause public panic and social disruption
- Require special action for public health preparedness

CATEGORY B — SECOND-PRIORITY AGENTS INCLUDE AGENTS THAT:

- Are moderately easy to disseminate
- Cause moderate morbidity and low mortality
- Require specific enhancements of the CDC's diagnostic capacity and disease surveillance

These agents have been used or considered as biological weapons.

CATEGORY C — THIRD-PRIORITY AGENTS INCLUDE ORGANISMS THAT ARE EMERGING PATHOGENS THAT COULD BE GENETICALLY ENGINEERED FOR MASS DISSEMINATION.

- These agents may be easily available.
- These agents may be easily produced or disseminated
- These agents have the potential for high morbidity and mortality and, therefore, may have a major public health impact.

Preparedness for Category-C agents requires ongoing research into disease detection, diagnosis, treatment, and prevention.

Adapted from: Khan AS, Morse S, Lillibridge S. Public health preparedness for biological terrorism in the USA. *Lancet* 2000;356:1179-1182; CDC. Biologic threats http://www.bt.cdc.gov/agent/agentlist.asp accessed on 10/10/2001.

Diseases Proposed for Biowarfare (Category Designation [i.e., A, B, C] Noted Where Applicable)

Note: These tables are not inclusive. Many other diseases could be adapted to biowarfare.

TOXINS PROPOSED FOR BIOWARFARE

Botulinum toxins[A]
Clostridium perfringens toxins[B]
Mycotoxins (trichothecenes group)
Palytoxin
Ricin[B]
Saxitoxin
Staphylococcal enterotoxin B[B]
Tetrodotoxin

BACTERIA PROPOSED FOR BIOWARFARE

Anthrax[A]
Brucellosis[B]
Cholera[B]
Melioidosis
Plague[A]
Shigella[B]
Tularemia[A]
E. coli O157:H7[B]
Salmonella species[B]
Multidrug-resistant tuberculosis[C]
Burkolderia mallei (glanders)[B]

CHLAMYDIA PROPOSED FOR BIOWARFARE

Psittacosis

RICKETTSIA PROPOSED FOR BIOWARFARE

Q fever[B]
Rocky Mountain spotted fever

VIRUSES PROPOSED FOR BIOWARFARE

Chikun-Gunya fever
Junin Argentine hemorrhagic fever[A]
Bolivian hemorrhagic fever[C]
Crimean-Congo hemorrhagic fever[C]
Dengue fever[C]
Eastern equine encephalitis[B]
Ebola fever[A]
Hantavirus[C]
Korean hemorrhagic fever (Hantaan)[C]
Lassa fever[A]
Marburg virus[A]
Omsk hemorrhagic fever[C]
Rift Valley fever
Russian Spring-Summer encephalitis[C]
Smallpox (variola major)[A]
Venezuelan hemorrhagic fever
Western equine encephalitis[B]
Yellow fever[C]
Influenza
Nipah virus[C]
Venezuelan encephalomyelitis[B]
West Nile fever

MISCELLANEOUS PROPOSED FOR BIOWARFARE

Histoplasmosis
Coccidiomycosis
Cryptosporidium parvum[B]

lism. If a lumbar puncture (LP) is done, the spinal fluid will be normal in patients with botulism, which distinguishes it from all of the viral and bacterial meningitis and encephalitis infections.

Current laboratory tests are not helpful in the clinical course. Detection of botulinum may be done by mouse bioassay or by liquid chromatography. Use of radioimmunoassay and radioreceptor assays also have been reported. A DNA probe has been designed for detection of botulinum toxin, which would expedite diagnosis markedly.[14] Detection of toxin in clinical or environmental samples sometimes is possible with ELISA or similar testing.

Prophylaxis and Treatment. Treatment is supportive. Respiratory failure may require prolonged (weeks to months) ventilatory support. If ventilatory support is available, then fatalities likely are to occur in fewer than 5% of the exposed population. Full recovery may take up to a year.

An equine antitoxin is available and may be of some help in

both food-borne and aerosol botulism. This is available from the CDC and protects against A, B, and E toxins. It has been used for treating ingestion botulism and should be given as soon as the diagnosis is made. It does not reverse paralysis, but does prevent progression of the disease. There is no human-based antitoxin currently available, but human-based antitoxin testing is now in progress. It will not help in types C and D intoxication.

Penicillin has been recommended, but its use is controversial because release of toxin in the gut may worsen neurologic symptoms through lysis of bacterial cells in the gut or wound.[15] It would be ineffective if the problem is a direct toxin release.

Botulinum toxoid vaccine is available.[16,17] The CDC provides a pentavalent antitoxin that gives protection from toxin types A, B, C, D, and E but provides no protection against the F and G toxins. The military believes that F and G type toxins are unlikely to be used in warfare because the strains of *C. botulinum* that produce toxins F and G are difficult to grow in large quantities. If new techniques allow production of toxins F and G in large quantities, the pentavalent antitoxin will be useless. A heptavalent antitoxin against types A-G is available in limited supply at USAMRIID in Fort Detrick.

A pentavalent toxoid of type A, B, C, D, and E is available for pre-exposure prophylaxis. It is available as an IND only. This product has been given to several thousand volunteers and workers at risk because of their occupations. It induces sufficient serum antitoxin levels. It requires three injections with a yearly booster for complete protection. There are very limited quantities, and it is expected that this toxoid would be reserved for groups judged to be at very high risk for exposure.

All available antitoxins are derived from horse serum. Patients should be tested for possible allergic reaction to horse serum before receiving the antitoxin.

Clostridium Toxins. Tetanus neurotoxin is secreted by *Clostridium* species in similar fashion to botulinum. The toxin is a single, 150,000 dalton polypeptide that is cleaved into two peptides held together by disulfide and non-covalent bonds. The intoxication occurs at extremely low concentrations of toxin, is irreversible, and like botulism, requires activity of the nerve to cause toxicity to that nerve.

Clostridium perfringens also secretes at least 12 toxins and can produce gas gangrene (clostridial myonecrosis), enteritis necroticans, and clostridium food poisoning. One or more of these toxins could be produced as a weapon. The alpha toxin is a highly toxic phospholipase that could be lethal when delivered as an aerosol.

Clinical Effects. Where botulinum toxin causes a flaccid paralysis, tetanus causes spastic paralysis. The tetanus neurotoxin migrates retroaxonally (up the nerve fiber), and by transcytosis reaches the spinal inhibitory neurons, where it blocks neurotransmitter release and thus causes a spastic paralysis. Despite the seemingly different actions of tetanus and botulism, the toxins act in a similar way at the appropriate cellular level. The clinical effect in humans is well documented and includes twitches, spasms, rictus sardonicus, and convulsions.

Clostridium perfringens alpha toxin would cause vascular leaks, pulmonary damage, thrombocytopenia, and hepatic damage. Inhaled *Clostridium perfringens* would cause serious respiratory distress.

Detection. Acute serum and tissue samples should be collected for further testing. Specific immunoassays are available for both perfringens and tetani species. Bacteria may be cultured readily.

As with most of these toxins and diseases, specific laboratory findings may be too late to be of clinical use.

Prophylaxis and Treatment. Clostridium perfringens and tetanus generally are sensitive to penicillin, the current drug of choice. There are some data that treatment with either clindamycin or rifampin may decrease *Clostridium perfringens* toxin production and give better results.

Most medical providers are aware of the schedule for tetanus immunizations. It is unlikely that there will be any use of this toxin in the United States due to widespread tetanus immunization.[18]

There is no specific prophylaxis against most of the *Clostridium perfringens* toxins. Some toxoids for enteritis necroticans are available for humans. Veterinary toxoids are in wide use.

Ricin. Ricin is a type II ribosome inactivating protein produced by the castor bean plant and secreted in the castor seeds. Ricin is toxic, but can be made and used in large quantities. Ricin has a high terrorist potential due to ready availability, easy processing, and widespread reporting.

Ricin is available worldwide by simple chemical processing of the castor bean. Ricin can be extracted cheaply in large quantities, using low technology. The toxin is quite easy to extract from the mash left by pressing castor oil from the castor beans (about 5%). It can be prepared as a liquid, crystals, or dry powder. It can be disseminated as an aerosol, injected into a victim, or used to contaminate food or water on a small scale.

Although ricin is a natural product of the castor bean plant, ricin has been produced from transgenic tobacco using gene transfer principles. Large amounts of toxin would be able to be produced easily by this transgenic method.[19]

Ricin is composed of two hemagglutinins and two toxins: RCL III and RCL IV. The toxins are dimers with a molecular weight of about 66,000 daltons. Each dimer is made up of two polypeptide chains joined by a disulfide bond. Once inside the cell, ricin depurinates an adenine from rRNA and thereby inactivates the ribosome, killing the cell.

Clinical Effects. The clinical picture depends on the route of exposure. The toxin is quite stable and extremely toxic by many routes of exposure, including inhalation.

Castor bean ingestion causes rapid onset of nausea, vomiting, abdominal cramps, and severe diarrhea followed by vascular collapse. Death occurs on the third day.

Inhalation of ricin will cause nonspecific weakness, cough, fever, hypothermia, and hypotension. Symptoms occur about 4-8 hours after inhalation. The onset of profuse sweating some hours later would signify termination of the symptoms. Lethal human exposures have not been described. In the animal, respiratory symptoms, including necrosis and alveolar infiltrates, are followed by cardiovascular collapse about 24-36 hours after inhalation. Death will occur about 36-48 hours after inhalation. High doses by inhalation appear to produce severe enough pulmonary damage to cause death.

Ingestion causes necrosis within the gastrointestinal tract, local hemorrhage and intrahepatic, splenic, and renal necrosis. It

does not cause lung irritation when administered by other routes.

At least one fatality has been documented as a direct result of ricin employed in biowarfare. In 1978, two men were shot by ricin-impregnated pellets. The pellets were coated with wax that was designed to melt at body temperature and release the ricin.

When injected, ricin can cause disseminated intravascular coagulopathy due to the hemagglutinin components. Microcirculatory failure and multiple organ failure follow.

Detection. ELISA for blood or histochemical analysis may be useful in confirming ricin intoxication. Ricin causes marked immune response, and sera should be obtained from survivors for measurement of antibody response. Polymerase chain reaction (PCR) can detect castor bean DNA in most ricin preparations.

Standard laboratory tests are of little help for the diagnosis of ricin intoxication. The patient may have some leukocytosis, with neutrophil predominance.

The pleomorphic picture of ricin intoxication would suggest many respiratory pathogens and may be of little help in diagnosis. The chest x-ray may have bilateral infiltrates. Arterial blood gas tests (ABGs) may show hypoxemia, and a leucocytosis rich in neutrophils may be noted.

Prophylaxis and Treatment. There is no approved immunologic or chemoprophylaxis at this time. Respiratory protection will prevent inhalation exposure and is the best prophylaxis currently available. Ricin has no dermal activity and is not transported through the skin.

There is ongoing effort to produce both active immunization and passive antibody prophylaxis suitable for humans. These techniques have been used in animals, but currently are not available for humans.

Treatment is supportive and includes both respiratory support and cardiovascular support as needed. Early intubation, ventilation, and positive end expiratory pressure combined with treatment of pulmonary edema is appropriate. If oral ingestion is suspected, then lavage followed by cathartics is appropriate. Since ricin is a large molecule, charcoal is of little use in ingestions.

Saxitoxin. Saxitoxin is a dinoflagellate toxin responsible for paralytic shellfish poisoning. It also is found in several species of puffers and other marine animals and was discovered in 1927.[20] The toxin is very soluble in water, is heat stable, and is not destroyed by cooking. The lethal dose is 1-2 mg. There are multiple, related toxins with substitutions at key positions.

Clinical Effects. It is similar in effects and treatment to tetrodotoxin, which is discussed in a later section. Onset of symptoms occurs within minutes of exposure. Death may occur within 2-24 hours. If the patient survives, normal functions are regained within a few days.

Detection. A mouse unit is the minimum amount of toxin that will kill a 20-gram mouse within 15 minutes. There is a standardized mouse assay for routine surveillance, and immunoassays are available.

Prophylaxis and Treatment. There is no antidote, so symptomatic treatment is appropriate. Antibodies for tetrodotoxin frequently will protect against saxitoxin.[21]

Staphylococcal Enterotoxin. Staphylococcal enterotoxins are proteins of 23,000-29,000 daltons. They are the extracellular products of coagulase-positive staphylococci. Since they normally exert their effect on the gut, they are called enterotoxins. Staphylococcal enterotoxin B (SEB), molecular weight 28,494 daltons, is one of the toxins that commonly causes food poisoning in improperly handled or refrigerated foodstuffs. Staphylococcal food poisoning is familiar to emergency physicians.

The toxin is markedly different in action when it is inhaled. SEB causes symptoms when inhaled at very low doses in humans (< 1/100th of the dose needed to cause gastrointestinal symptoms).

The organism that produces this agent is readily available and could be tailored to produce large quantities of the toxin. Related toxins include the toxic shock syndrome (TSST-1) and exfoliative toxins (staphylococcal-mediated exfoliative dermatitis).

Clinical Effects. The disease begins 1-12 hours after exposure with the sudden onset of fever, chills, headache, myalgia, and a nonproductive cough. The cough may progress to dyspnea and substernal chest pain. In severe cases, pulmonary edema may be found. Nausea, vomiting, and diarrhea are common. GI symptoms may accompany respiratory exposure due to inadvertent swallowing of the toxin after inhalation.

With the exception of dehydration and postural hypotension, the physical examination often is normal. The only physical finding of note is conjunctival injection. In very severe cases, the chest x-ray may show infiltrates.

In food-borne SEB, fever and respiratory involvement are not found and the gastrointestinal symptoms predominate. Patients would be expected to have nausea, vomiting, and diarrhea if they swallow the toxin.

The fever may last up to five days and rise to 106°F. The patient may have chills, rigors, and prostration. Sickness may last as long as two weeks, and severe exposures may cause fatalities.

Detection. Lab tests are not helpful. Sedimentation rate (ESR) may be elevated, but this is a nonspecific finding. A chest x-ray usually is normal, but may have increased intrastitial markings and possible pulmonary edema.

Prophylaxis and Treatment. There is no significant treatment regimen available. Therapy is entirely supportive. There is no current prophylaxis available, although experimental immunization has been reported. The value of steroids is unknown.

There is no human vaccine available for immunization against SEB. A vaccine candidate is in advanced development for testing.[22] Naturally acquired immunity has been noted, but does not confer complete protection, even for natural gastrointestinal disease.

SEB does not pass through intact skin. Secondary aerosols are not a hazard. Decontamination is with soap and water. All potentially exposed foods should be promptly destroyed.

Tetrodotoxin. Tetrodotoxin is a potent neurotoxin produced by fish, salamanders, frogs, octopus, starfish, and mollusks, most notably the puffer (also called the globefish or blowfish).[23] The dangers of tetrodotoxin poisoning were known by the ancient Egyptians (2400-2700 BC). All organs of the freshwater puffer are toxic, with the skin having the highest toxicity, followed by gonad, muscle, liver, and intestine. In salt water puffers, the liver

is the most toxic organ. The lethal dose of tetrodotoxin is only 5 mcg/kg in the guinea pig.

Puffer intoxication is a serious public health problem in Japan and more than 50 people each year are intoxicated. Raw puffer fish, commonly called fugu, is a delicacy in several Southeast Asian countries, including Japan. Consumption of fugu causes mild tetrodotoxin intoxication with a pleasant peripheral and perioral "tingling" sensation. Improperly prepared fugu may contain a lethal quantity of tetrodotoxin. Fatalities have gradually decreased because of the increased understanding of the toxin and careful preparation of the puffer for food.[24] Cooking the food will not dissipate the toxin. Tetrodotoxin is heat stable.

There are several microbial sources of tetrodotoxin, including *Pseudomonas, Vibrio, Listonella,* and *Alteromonas* species. Although there is only one known bacteria that has produced tetrodotoxin toxicity in humans, there is a significant potential for genetic alteration of common species of bacteria to produce tetrodotoxin.[25]

Tetrodotoxin is well known for its ability to inhibit neuromuscular function by blocking the axonal sodium channels.[26] Cranial diabetes insipidus has been reported in critically ill patients. Mortality from tetrodotoxin is thought to be due to hypoxic brain damage from prolonged respiratory paralysis.

Clinical Effects. The clinical symptoms and signs of tetrodotoxin poisoning are similar to those of the acetylcholinesterase poisons.[27] Clinical symptoms include nausea, vomiting, vertigo, perioral numbness, unsteady gait, and extremity numbness. Clinical symptoms begin within 30 minutes of ingestion. The speed of onset depends on the quantity of the toxin ingested. The symptoms progress to muscle weakness, chest tightness, diaphoresis, dyspnea, chest pain, and finally paralysis. Hypotension and respiratory failure are seen in severe poisonings. Patients frequently will complain of being cold or chilly. Paresthesias spread to the extremities, with symptoms often more pronounced distally. Death can occur within 17 minutes after ingestion of tetrodotoxin.

Detection. Detection of tetrodotoxin is by mouse bioassay[28] or by liquid chromatography. Use of radioimmunoassay and radioreceptor assays also has been reported. An in vitro colorimetric cell assay against a rabbit antiserum has been developed and may be more rapid than older methods, but as yet is not available publicly.[29]

Prophylaxis and Treatment. At present, there is no known antidote for tetrodotoxin intoxication. There are numerous anecdotal treatments of survivors with supportive therapy alone. Certainly, respiratory support and airway management will be lifesaving for a majority of these patients. Gastric lavage will remove unabsorbed toxin from the gut and is used in puffer fish intoxication. Activated charcoal has been reported to effectively bind the toxin and may be employed in ingestions.

4-Aminopyridine has been used to treat tetrodotoxin intoxication in laboratory animals.[30] 4-Aminopyridine is a potent potassium channel blocker and enhances impulse-evoked acetylcholine release from presynaptic motor terminals. There have been no human studies of its use as an antidote. 4-aminopyridine can cause muscle fasciculation and seizures in a dose-dependent phenomenon.

Naloxone has been proposed as a possible antidote, since the opiates and tetrodotoxin have similar molecular configurations.[31] There are no reports of this in either laboratory or clinical use.

Active and passive immunization is possible for tetrodotoxin. Although this has been demonstrated in laboratory animals, there is no known available immunization for tetrodotoxin.[32] Tolerance does not develop on repeated puffer fish exposure. Monoclonal antibodies have been produced and have protected laboratory animals against lethal doses of tetrodotoxin.[33,34]

Trichothecene Mycotoxins. The trichothecene mycotoxins are a group of more than 40 compounds produced by fungi (Fusarium, a common grain mold). They achieved fame in the 1970s as the best candidates for the infamous "yellow rain" found in Laos, Cambodia, and Afghanistan. Naturally occurring trichothecenes have caused moldy corn toxicosis in animals.

They are potent inhibitors of protein synthesis, inhibit mitochondrial respiration, impair DNA synthesis, and destroy cell membranes. They cause bone marrow suppression and suppress mucosal protein synthesis. They are the only class of toxin that causes skin damage. They cause blisters within minutes to hours after skin exposure.

The toxins are small molecular weight nonvolatile compounds that are extremely stable in the environment. Hypochlorite solution does not inactivate these toxins. They retain their bioactivity even when autoclaved.

Clinical Effects. Consumption of trichothecenes causes weight loss, vomiting, bloody diarrhea, and diffuse hemorrhage. This was found by the Russians when contaminated bread was ingested and caused alimentary toxic aleukia (AKA). Within days, the gastrointestinal symptoms progressed to bone marrow depression with neutropenia and secondary sepsis. Survivors developed bleeding from all body orifices and diffuse bleeding into the skin.

The onset of the illness occurs within hours and death may occur within 12 hours with significant inhalation exposure. Early symptoms are eye pain, tearing, redness, and a foreign body sensation in the eye. The patient may have nasal itching, burning, blistering, epistaxis, and bloody rhinorrhea. Mouth and throat exposure causes pain and blood-tinged saliva and sputum. Skin exposure may result in burning skin pain, erythema, blistering, tenderness, and progression to skin necrosis with blackening and sloughing of skin surfaces.

Inhalation exposure adds respiratory distress and failure to the picture. The patient may start with dyspnea, wheezing, and cough before progressing to respiratory distress.

Systemic toxicity occurs with any route of exposure. The patient develops weakness, prostration, dizziness, ataxia, and loss of coordination. The symptoms progress to tachycardia, hypotension, and shock. A late effect is bone marrow depression with pancytopenia and secondary sepsis and bleeding.

Detection. There is no readily available diagnostic test, although reference laboratories may be able to help with gas-liquid chromatography. There are some polyclonal and monoclonal antibodies for detection in liquid or solid samples.

Pathologic specimens should include blood, urine, lung washings, stool samples, and stomach contents. Urine samples are most useful for this purpose because the metabolites can be detected as long as 28 days after exposure to the agent.

Table 4. Online Resources

- CDC Pandemic Plan: Describes a pandemic plan for influenza. Includes a one-to-one comparison with bioweapons release and a flu pandemic: http://www.cdc.gov/od/nvpo/pandemicflu.htm#PANPLAN
- CDC's bioterrorism preparedness and response web site: http://www.bt.cdc.gov
- USAMRIID's Medical Management of Biologic Casualties Handbook: http://www.nbc-med.org
- Anthrax information: http://www.nbc-med.org/SiteContent/MedRef/OnlineRef/GovDocs/Anthrax/index.htm
- Biological Agent Information Papers, U.S. Army Institute of Infectious Diseases: http://www.nbc-med.org/SiteContent/MedRef/OnlineRef/GovDocs/BioAgents.html
- Smallpox information: http://www.nbc-med.org/SiteContent/MedRef/OnlineRef/FieldManuals/medman/SmallPox.htm
- Medical aspects of chemical and biological warfare: http://www.nbc-med.org/SiteContent/HomePage/WhatsNew/MedAspects/contents.html
- USAMRIID web site: www.usamriid.army.mil
- Association of Professionals in Infection Control and Epidemiology (APIC). Site contains bioterrorism response plan: www.apic.org.
- Johns Hopkins University Center for Civilian Biodefense: www.hopkins-biodefense.org.
- Anthrax Vaccine Implementation Program: www.anthrax.osd.mil

Web sites accessed on Nov. 12, 2001.

The symptoms will be similar to a chemical agent attack. The clinician must ensure that mustard or other vesicant agents are not present.

Prophylaxis and Treatment. Ascorbic acid has been proposed to decrease the lethality. This has been studied in animals only, but because ascorbic acid has few side effects and is cheap, it should be used in all suspected cases.

Dexamethasone (1-10 mg IV) also has been shown to decrease lethality as late as three hours after exposure to these toxins.

In ingestions, charcoal or superactivated charcoal will absorb any remaining toxin and decrease lethality. The eyes should be irrigated with normal saline or water to remove toxin. The skin should be thoroughly washed with soap and water. The only protection is appropriate mask and protective clothing.

Summary

The threat of bioterrorism and biological weapons being used against the United States is high. Awareness of this threat and education of our medical care providers, public health officials, law enforcement personnel, and leaders is crucial.

Compared to conventional, chemical, and nuclear weapon threats, biological weapons are unique in their ability to cause disruption and panic.

In many parts of the country, emergency departments routinely have 4-8 hour waits for current patient loads. Most physicians won't think about bioterrorism until they have several cases of a suspicious disease in their emergency department on their shift. *(See Table 4.)* If the disease has common initial symptoms such as fever, sniffles, and a sore throat, and occurs in the winter, they wouldn't think about it until many patients start to arrive in their ED, urgent care center, or medical office. This may be 5-10 days after the initial exposure, and these now-exposed medical providers will be part of the second wave. Some of the new casualties will be lethally sick and some simply will be very scared. The patients with the usual illnesses will continue to need emergency care, but may be far sicker due to a mild infection on top of their already fragile health.

Moreover, unlike natural disasters, demands on medical care in each community from a massive biological weapon release may last 6-8 weeks until the "first wave" of infection is complete. Like the typical disaster, essential community servants themselves (e.g., medical care personnel, police, firefighters, ambulance drivers, and other first responders) will be just as likely —or even more likely (because of increased exposure)— to be affected by influenza or other pandemic than the general public.

Responsible biowarfare planning should make a hospital administrator consider staffing for 10 times (or more) his/her rated bed capacity and thinking about where the extra cots, blankets, gloves, and gowns are going to come from; how he/she is going to get them to the hospital; and how he/she is going to staff when 25% of the staff are casualties and 50% of the staff is so panicked that they want to stay home. This includes not just physicians and nurses; the efforts of registration clerks, cooks, lab technicians, security personnel, and even janitorial services are critical.

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Physician CME Questions

81. Clinical findings with dengue include which of the following?
    A. Facial flushing
    B. Conjunctivitis
    C. Quick pulse
    D. Both A and B are correct

82. Hemorrhagic fever is a clinical syndrome that may present with which of the following?
    A. Myalgia
    B. Malaise
    C. Fever
    D. Hypotension
    E. All of the above

83. Ebola is a member of which of the following families?
    A. Arenavirus
    B. Filovirus
    C. Bunyavirus
    D. Flavivirus

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5. If the publication had Periodicals authorization as a general or requester publication, this Statement of Ownership, Management, and Circulation must be published; it must be printed in any issue in October or if the publication is not published during October, the first issue printed after October.
5. In item 16, indicate date of the issue in which this Statement of Ownership will be published.
6. Item 17 must be signed.

Failure to file or publish a statement of ownership may lead to suspension of second-class authorization.

PS Form **3526**, September 1999 *(Reverse)*

84. Diagnosis of a hemorrhagic fever is *best* made by which of the following?
    A. Bone marrow culture
    B. Serology
    C. Clinical impression
    D. Pleural fluid

85. Which of the following hemorrhagic fevers has a viable vaccine?
    A. Yellow fever
    B. Ebola
    C. Marburg
    D. Lassa

86. Symptoms of inhalation botulism usually occur in patients how long after exposure?
    A. One hour
    B. 3-5 hours
    C. 12-36 hours
    D. One week

87. Tetanus causes which of the following effects in humans?
    A. Spastic paralysis
    B. Rictus sardonicus
    C. Convulsions
    D All of the above

88. Symptoms of ricin inhalation will manifest in:
    A. about 4-8 hours.
    B. 24 hours.
    C. 36 hours.
    D. about three hours.

Emergency Medicine Reports CME Objectives

To help physicians:

- quickly recognize or increase index of suspicion for specific conditions;
- understand the epidemiology, etiology, pathophysiology, and clinical features of the entity discussed;
- be educated about how to correctly perform necessary diagnostic tests;
- take a meaningful patient history that will reveal the most important details about the particular medical problem discussed;
- apply state-of-the-art therapeutic techniques (including the implications of pharmaceutical therapy discussed) to patients with the particular medical problems discussed;
- understand the differential diagnosis of the entity discussed; understand both likely and rare complications that may occur;
- and provide patients with any necessary discharge instructions.

In Future Issues:

Head Trauma/
Subdural Hematoma

BIOTERRORISM WATCH

Preparing for and responding to biological, chemical and nuclear disasters

Flu or anthrax? First inhalational cases yield clues for clinicians to make the critical call

Use case history, blood work, X-rays, rapid tests

There is a postal worker in your emergency department (ED) with flulike symptoms.

That once insignificant observation about occupation and illness now triggers a detailed algorithm created by the Centers for Disease Control and Prevention (CDC) in Atlanta. **(See algorithm, p. 2.)** Is it flu or inhalational anthrax? Whether a realistic question or not, it is what many of your incoming patients may be asking — particularly if another wave of anthrax scares coincides with a nasty influenza season. Many of the initial symptoms are similar, but investigators dealing with the first inhalational anthrax cases have gleaned out key indicators that will help clinicians make the call.

"It is important to take a careful history from the [patients] when they present," says **Julie Gerberding**, MD, acting deputy director of CDC's National Center for Infectious Diseases. "If the [patients are] mail handlers in a professional environment — where they're dealing with large amounts of mail that is not their own — then the index of suspicion should be raised and more testing should be done to be sure there aren't additional clues to suggest that it is not a common viral infection."

Using the first 10 cases of inhalational anthrax as a baseline patient profile, the CDC reports that the median age of the patients was 56 years (range: 43-73 years), and seven were men.[1]

The incubation period from the time of exposure to onset of symptoms when known (seven cases) was seven days (range: five to 11 days).

The initial illness in the patients included fever (nine) and / or sweats / chills (six). Severe fatigue or malaise was present in eight, and minimal or nonproductive cough in nine. One had blood-tinged sputum. Eight patients reported chest discomfort or pleuritic pain. Abdominal pain or nausea or vomiting occurred in five, and five reported chest heaviness. Other symptoms included shortness of breath (seven), headache (five), myalgias (four), and sore throat (two). The mortality rate was 40% for the 10 patients, much lower than historical data indicated. Indeed, one of the critical reasons to recognize inhalational anthrax early is that it is far more treatable than originally thought.

The CDC gathered comparative data on the symptoms and signs of anthrax and influenza, finding, for example, that only 20% of the anthrax patients reported sore throat.[2] Flu sufferers report a sore throat in 64% to 84% of cases. Likewise, 80% of the anthrax cases reported symptoms of nausea and vomiting. That symptom is reported in only 12% of flu cases. Shortness of breath appears to be another key distinguishing symptom, affecting 80% of the anthrax patients but seen in only 6% of flu patients.

"One of the other clues that we are noticing is that the patients with inhalation anthrax actually do not have nasal congestion or a runny nose,"

(Continued on page 3)

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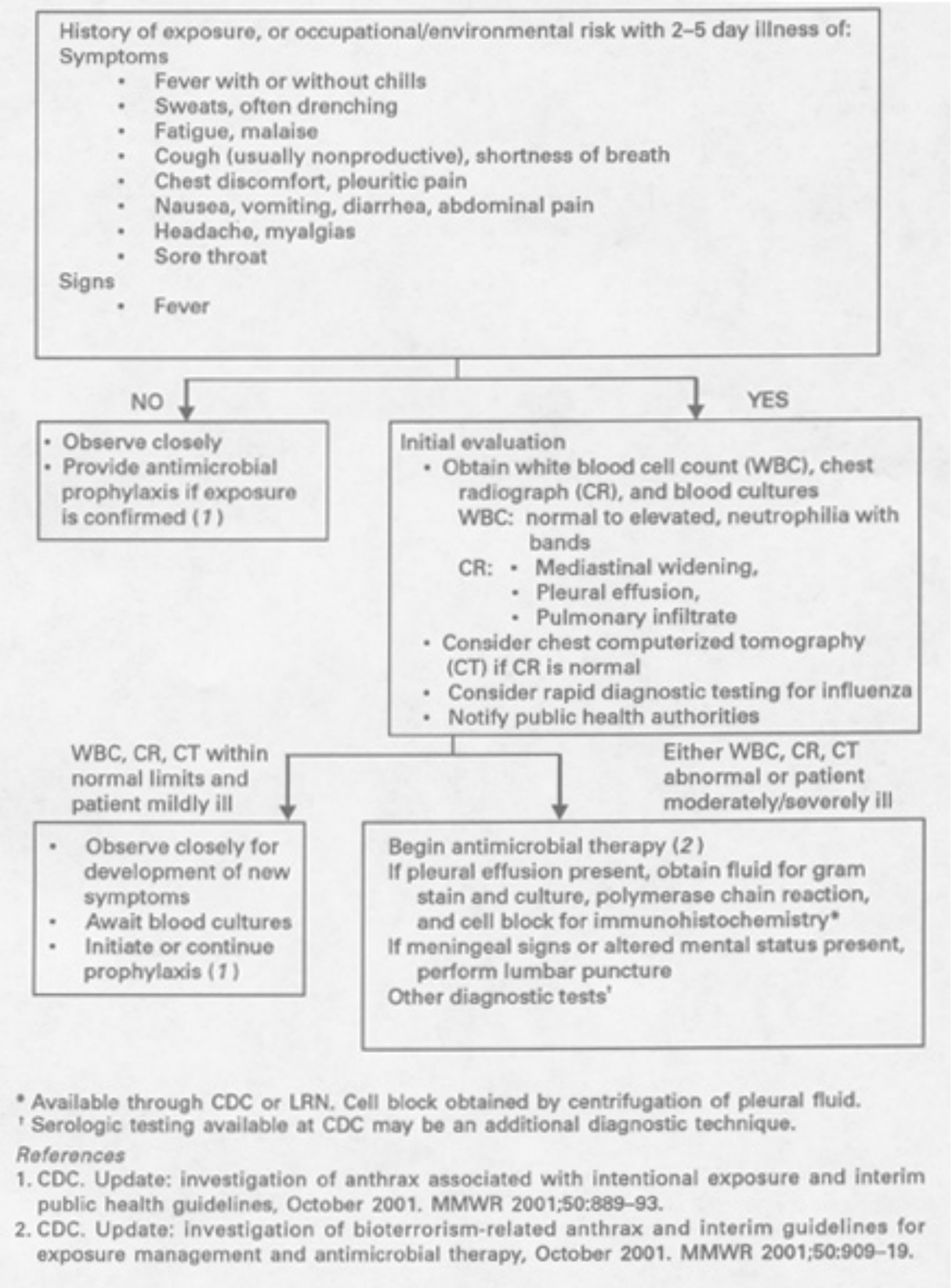
Clinical Evaluation of People with Possible Inhalational Anthrax



Source: Centers for Disease Control and Prevention. Update: Investigation of bioterrorism-related anthrax and interim guidelines for clinical evaluation of persons with possible anthrax. *MMWR* 2001; 50:945.

Gerberding says. "They don't have the symptoms of an upper-respiratory tract infection. They have a more systemic chest presentation, and that may be another distinguishing characteristic."

Another finding on initial blood work is that none of the inhalational anthrax patients had a low white blood cell count (WBC) or lymphocytosis when initially evaluated. Given that, CDC officials note that future suspect cases with low WBC counts may have viral infections such as influenza. Chest X-rays were abnormal in all patients, but in two an initial reading was interpreted as within normal limits. Mediastinal changes including mediastinal widening were noted in all eight patients who had CT scans. Mediastinal widening may be subtle, and careful review of the chest radiograph by a radiologist may be necessary, the CDC advises.

Complementing the CDC's effort, are the observations of the few clinicians who have actually seen inhalational anthrax cases come into their hospital systems. Two inhalational anthrax cases, both of which survived, were admitted to the Inova Healthcare System in Fairfax, VA (near Washington, DC).

"Clinically, I think the history of the people who presented here is useful," says **Allan J. Morrison Jr.**, MD, MSc, FACP, health care epidemiologist for the Inova system. "They stutter-stepped toward their pulmonary symptoms. That had some mild symptoms and then they were sort of 'meta-stable.' They were not relentlessly progressing. Then they progressed with symptoms more aggressively. Whereas with influenza — in our experience — once you start to get sick, it just keeps on progressing with very high fevers, chills, muscle aches, and pains. As a consequence, we feel there should be a good way to differentiate the two."

Since anthrax is a realistic concern in the Washington, DC, area, what about the aforementioned scenario of symptomatic postal workers in the ED?

"We would take a very aggressive history, not only of occupation but physically where they have been," Morrison says. "If they are symptomatic and have been in or work around a 'hot zone' — a location from which anthrax has either been cultured environmentally or patients have come from there — we will err on the side of being very aggressive about working up anthrax. By that I mean chest X-rays, chemistry profile, [etc.]"

In addition, the hospital system pushed early flu vaccination programs for staff and the surrounding community. "We want to move toward herd immunity," he says. "We are also working with our local hospitals to make sure that they have access to the rapid influenza tests. So for diagnosis — for obvious reasons — it is very helpful to make that distinction early."

One such rapid test is ZstatFlu (ZymeTX Inc., Oklahoma City), which the company claims can yield a diagnosis of influenza A or B some 20 minutes after a throat swab. The test detects neuraminidase, an influenza viral enzyme. However, Gerberding cautions clinicians not to rely solely on such tests. Rather, they should use the results of tests in combination with the patient history and clinical presentation, she says.

"So it is a constellation of history, clinical findings, and laboratory tests," she says. "Hopefully, when we get these all together, we'll be able to at least reduce the anxiety among some people and help clinicians diagnose those patients who really do require the antibiotic treatment. What we don't want to have happen is for everybody coming in with the flu to get an antibiotic because that undermines a whole other set of public health issues relating to antimicrobial resistance and proper management of influenza."

Even the vaccinated can still have flu

Complicating the issue is the fact that the flu vaccine efficacy can vary annually, but is usually 70% to 90% protective, says **Keiji Fukuda**, MD, a medical epidemiologist in the CDC influenza branch. Thus, depending on how well the vaccine matches the circulating strain, a certain portion of flu patients will tell clinicians they have been immunized. But in addition to vaccine breakthrough infections, there is a plethora of other viral and respiratory pathogens that will be creating similar symptoms, he says. In a somewhat sobering reminder — given that at this writing, the total anthrax cases remained in the double digits — Fukuda notes that a typical flu season will send 114,000 people to the hospital and 20,000 to their graves.

"There has been an awful lot of attention on the [anthrax] cases, but the bottom line is that there have been few cases, and these cases generally have occurred in a limited number of communities within a limited number of groups," he says. "And so the epidemiologic message is that anthrax really has not been diagnosed in most parts of the country, whereas we expect to see millions and millions of flu cases all over the place."

If facilities are faced with an onslaught of patients with respiratory illness there are several measures they can take, he notes. Those include:

- Reduce or eliminate elective surgery.
- Relax staff-to-patient ratios within the limits of your licensing agency.
- Emphasize immunizing staff so more staff are available.
- Identify ways to bring in extra staff to help out with the patients.
- Set up walk-in flu clinics to triage the patients.

Reference

1. Centers for Disease Control and Prevention. Update: Investigation of bioterrorism-related anthrax and interim guidelines for clinical evaluation of persons with possible anthrax. *MMWR* 2001; 50:941-948.

2. Centers for Disease Control and Prevention. Consideration for distinguishing influenza-like illness from inhalational anthrax. *MMWR* 2001; 50:984-986. ■

CDC moving quickly on smallpox front

Immunizations, training, vaccine dilution studied

Though officially stating it has no knowledge of any impending use of smallpox as a bioweapon, the Centers for Disease Control and Prevention (CDC) is scrambling with conspicuous speed to be ready for just such an event.

CDC workers from a variety of specialties are not only receiving smallpox vaccinations, they are being trained to give them to others using the old bifurcated needle scarification technique. And, even as creation of a new vaccine is fast-tracked, researchers are trying to determine if the current stockpile of 15.4 million doses can be expanded fivefold by simply diluting the vaccine.

Based on such actions, it is fair to say the agency is at least highly suspicious that the known stocks of smallpox virus are not safely ensconced in their official repositories in Russia and the United States.

"CDC is putting together a number of teams, which will probably total [more than] 100 employees, that could be quickly dispatched in a moment's notice to assist state and local health departments and frontline clinicians investigate suspect cases of smallpox," **Tom Skinner**, a spokesman for the CDC, tells *Bioterrorism Watch.*

"They are Epidemic Intelligence Service (EIS) officers, laboratorians, and others. Part of this includes vaccinating them against smallpox," he explains.

But while confirming that the CDC teams are being trained to administer the vaccine, Skinner would not specify who would be vaccinated following a smallpox bioterror event. "We have a smallpox readiness plan," he says. "Issues around vaccination are covered in that plan. That plan is being finalized. It is considered an operational plan. If we have a case tomorrow, it could be implemented. It covers who should be vaccinated and when."

The general consensus among bioterrorism experts is that those exposed would be vaccinated because the vaccine can prevent infection and possibly death even if given several days out. Likewise, health care workers and their family members would want vaccine if they were expected to care for the infected. Some aspect of quarantine would no doubt come into play because, unlike anthrax, it will be critical to separate the first smallpox cases and their contacts from the susceptible population.

Another aspect of CDC preparations includes the smallpox vaccine dilution study, which is being headed up by **Sharon E. Frey**, MD, associate professor of infectious diseases and immunology at Saint Louis University School of Medicine.

The vaccine, known as Dryvax, is no longer produced, but there are 15.4 million doses left. Frey and colleagues are looking at dilution studies that could maintain vaccine efficacy while increasing the available stock by millions of doses. In a study last year, Frey tried a one to 10 vaccine dilution, which would create a stockpile of more than 150 million doses. However, the resulting vaccine had only a 70% effective rate.

"The undiluted vaccine has about a 95% take rate," she tells *BW*. "It is not perfect, but we would like to be as close to that as we could be."

The new study will include a one to five dilution, which should show greater efficacy while increasing the stockpile to more than 75 million doses.

"We are looking at a 'take' rate for the vaccine, in other words how many people actually develop a typical lesion and whether they have a strong neutralizing antibody response to the vaccine," Frey says. "We know that the vaccine is still good. We actually titered the vaccine and it is very similar to its original titer," she adds. ■

Emergency Medicine Reports
The Practical Journal for Emergency Physicians

Bioterrorism: Part II

The Hemorrhagic Fevers

Disease	Location	Vector	Incubation	Species
Argentine hemorrhagic fever (Junin virus)	South America	Rodent	3-12 days	Arenavirus
Bolivian hemorrhagic fever (Machupo virus)	South America	Rodent	3-16 days	Arenavirus
Brazilian hemorrhagic fever (Guanarito virus)	South America	Rodent	3-16 days	Arenavirus
Congo-Crimean HF	Africa, Asia	Tick	3-12 days	Bunyavirus
Dengue fever	Worldwide	Mosquito		Flavivirus
Ebola (Philippines = Reston)	Africa, Philippines	Unknown	2-21 days	Filovirus
Hantavirus pulmonary syndrome	Americas	Rodent	3-21	Bunyavirus
Hemorrhagic fever with renal syndrome (HFRS) (Hantaan virus)	Worldwide	Rodent	9-35 days	Bunyavirus (Most common disease of hantaviruses)
Kyanasur Forest disease	India	Tick		Flavivirus
Lassa fever	Africa	Mosquito	5-16 days	Arenavirus
Marburg fever	Africa	Unknown	2-21 days	Filovirus
Omsk hemorrhagic fever	Siberia	Tick		Flavivirus
Rift Valley fever	Africa	Mosquito	2-5 days	Bunyavirus
Venezuelan hemorrhagic fever (Sabia virus)	South America	Rodent	3-15 days	Arenavirus
Yellow fever	Worldwide	Mosquito		Flavivirus

Characteristics of Effective Biological Weapons

- Potential for massive numbers of casualties
- Ability to produce lengthy illness requiring prolonged and extensive care
- Ability of agents to spread via contagion
- Paucity of adequate detection systems
- Incubation period enables victims (and perpetrators) to widely disperse
- Nonspecific symptoms complicate early diagnosis and mimic endemic infectious diseases

Adapted from: USAMRIID's Medical Management of Biological Casualties Handbook, 4th ed. U.S. Army Medical Research Institute. February 2001.

Online Resources

- CDC Pandemic Plan: Describes a pandemic plan for influenza. Includes a one-to-one comparison with bioweapons release and a flu pandemic: http://www.cdc.gov/od/nvpo/pandemicflu.htm#PANPLAN
- CDC's bioterrorism preparedness and response web site: http://www.bt.cdc.gov
- USAMRIID's Medical Management of Biologic Casualties Handbook: http://www.nbc-med.org
- Anthrax information: http://www.nbc-med.org/SiteContent/MedRef/OnlineRef/GovDocs/Anthrax/index.htm
- Biological Agent Information Papers, U.S. Army Institute of Infectious Diseases: http://www.nbc-med.org/SiteContent/MedRef/OnlineRef/GovDocs/BioAgents.html
- Smallpox information: http://www.nbc-med.org/SiteContent/MedRef/OnlineRef/FieldManuals/medman/SmallPox.htm
- Medical aspects of chemical and biological warfare: http://www.nbc-med.org/SiteContent/HomePage/WhatsNew/MedAspects/contents.html
- USAMRIID web site: www.usamriid.army.mil
- Association of Professionals in Infection Control and Epidemiology (APIC). Site contains bioterrorism response plan: www.apic.org.
- Johns Hopkins University Center for Civilian Biodefense: www.hopkins-biodefense.org.
- Anthrax Vaccine Implementation Program: www.anthrax.osd.mil

Web sites accessed on Nov. 12, 2001.

Potential Biologic Agents Used for Terrorism

CATEGORY A — HIGH-PRIORITY AGENTS INCLUDE ORGANISMS THAT:

- Can be easily disseminated or transmitted from person to person
- Cause high mortality, with a potential for major public health impact
- Might cause public panic and social disruption
- Require special action for public health preparedness

CATEGORY B — SECOND-PRIORITY AGENTS INCLUDE AGENTS THAT:

- Are moderately easy to disseminate
- Cause moderate morbidity and low mortality
- Require specific enhancements of the CDC's diagnostic capacity and disease surveillance

These agents have been used or considered as biological weapons.

CATEGORY C — THIRD-PRIORITY AGENTS INCLUDE ORGANISMS THAT ARE EMERGING PATHOGENS THAT COULD BE GENETICALLY ENGINEERED FOR MASS DISSEMINATION.

- These agents may be easily available.
- These agents may be easily produced or disseminated
- These agents have the potential for high morbidity and mortality and, therefore, may have a major public health impact.

Preparedness for Category-C agents requires ongoing research into disease detection, diagnosis, treatment, and prevention.

Adapted from: Khan AS, Morse S, Lillibridge S. Public health preparedness for biological terrorism in the USA. *Lancet* 2000;356:1179-1182; CDC. Biologic threats http://www.bt.cdc.gov/agent/agentlist.asp accessed on 10/10/2001.

Diseases Proposed for Biowarfare (Category Designation [i.e., A, B, C] Noted Where Applicable)

Note: These tables are not inclusive. Many other diseases could be adapted to biowarfare.

TOXINS PROPOSED FOR BIOWARFARE

Botulinum toxins[A]
Clostridium perfringens toxins[B]
Mycotoxins (trichothecenes group)
Palytoxin
Ricin[B]
Saxitoxin
Staphylococcal enterotoxin B[B]
Tetrodotoxin

BACTERIA PROPOSED FOR BIOWARFARE

Anthrax[A]
Brucellosis[B]
Cholera[B]
Melioidosis
Plague[A]
Shigella[B]
Tularemia[A]
E. coli O157:H7[B]
Salmonella species[B]
Multidrug-resistant tuberculosis[C]
Burkolderia mallei (glanders)[B]

CHLAMYDIA PROPOSED FOR BIOWARFARE

Psittacosis

RICKETTSIA PROPOSED FOR BIOWARFARE

Q fever[B]
Rocky Mountain spotted fever

VIRUSES PROPOSED FOR BIOWARFARE

Chikun-Gunya fever
Junin Argentine hemorrhagic fever[A]
Bolivian hemorrhagic fever[C]
Crimean-Congo hemorrhagic fever[C]
Dengue fever[C]
Eastern equine encephalitis[B]
Ebola fever[A]
Hantavirus[C]
Korean hemorrhagic fever (Hantaan)[C]
Lassa fever[A]
Marburg virus[A]
Omsk hemorrhagic fever[C]
Rift Valley fever
Russian Spring-Summer encephalitis[C]
Smallpox (variola major)[A]
Venezuelan hemorrhagic fever
Western equine encephalitis[B]
Yellow fever[C]
Influenza
Nipah virus[C]
Venezuelan encephalomyelitis[B]
West Nile fever

MISCELLANEOUS PROPOSED FOR BIOWARFARE

Histoplasmosis
Coccidiomycosis
Cryptosporidium parvum[B]

Supplement to *Emergency Medicine Reports*, November 19, 2001: "Bioterrorism Update—Current Guidelines and Recommendations for Prevention and Treatment of Biological Threats: Part II." *Author:* **Charles Stewart, MD, FACEP,** Emergency Physician, Colorado Springs, CO. *Emergency Medicine Reports' "Rapid Access Guidelines."* **Editor-in-Chief:** Gideon Bosker, MD, FACEP. **Vice President and Group Publisher:** Brenda Mooney. **Editorial Group Head:** Valerie Loner. **Managing Editor:** Suzanne Zunic. For customer service, call: **1-800-688-2421.**