AMERICAN HEALTH CONSULTANTS®

Evidence-Based Medicine for the ED

Trauma Reports

Vol. 3, No. 6

Supplement to *Emergency Medicine Reports*, *Pediatric Emergency Medicine Reports*, *ED Management*, and *Emergency Medicine Alert*

Nov./Dec. 2002

One Year Later: Emergency Department Response to Biological Terrorism

Part II: Smallpox, Viral Hemorrhagic Fevers, Tularemia, and Botulinum Toxins

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The threat of bioterrorism continues to loom over the United States with emergency departments likely to be the front lines. In the second article of this two-part series, the author updates the emergency department (ED) physician on the current status of smallpox, viral hemmorhagic fevers, tularemia, and botulism as both disease entities and weapons of bioterrorism.

—The Editor

Smallpox

Clinical Features. Few diseases have rivaled smallpox as a cause of human suffering and death, with epidemics of smallpox surpassing other diseases such as plague, cholera, and yellow fever as instruments of morbidity and mortality.[1] It is ironic that the possibility of an outbreak is more feasible after this disease has not been seen in the last quarter-century and vaccination programs were halted in the wake of this accomplishment.[2-4] Known repositories of variola are limited to the two sites specified by the World Health Organization (WHO): the Centers for Disease Control and Prevention (CDC) in Atlanta and VECTOR in Novosibirsk, Russia. The former Soviet Union had created weapon forms of variola in ton quantities. While the stockpiles of smallpox reportedly were destroyed, the accounting of such is incomplete and the true disposition is uncertain.[5] In addition, other nations strongly are suspected of maintaining hidden stocks as part of clandestine biological weapons programs.[6,7]

Smallpox is extremely contagious. In one of the last outbreaks in Europe, a single index patient infected 11 others, who subsequently infected 175 others, resulting in 35 deaths. Due to the delay in clinical diagnosis, some 10,000 contacts of patients had to be quarantined and 20 million were vaccinated.[8] In conditions of low temperature and low humidity, aerosolized variola is very stable, and has resulted in widespread, hospital-based epidemics. The predominant method of transmission is by respiratory droplet requiring face-to-face (within 2 meters) contact, although patients with cough frequently generate infectious aerosols that may result in airborne spread. Infected bed linens and other fomites also have resulted in a small number of outbreaks. In previous epidemics it was common to see 10-20 secondary cases from each infected patient, eventually resulting in one-third of all contacts becoming infected.[9,10] Infectivity is maximal during the first week of rash, and is increased markedly in patients who manifest a cough.[6]

The case fatality rates are strain-dependent, with fewer than 1% in immunologically naïve patients infected with the variola minor strain, but 30% of unimmunized and 3% of vaccinated patients infected with variola major. Soviet scientists had developed strains with considerably higher virulence and transmissibility. This, coupled with the large inoculum expected from an intentional aerosol release, likely would result in much higher fatality rates.[11]

Following a 10- to 14-day incubation period, patients with smallpox present with acute onset of fever, prostration, malaise, myalgias, rigors, vomiting, backache, and cephalgia.[10] Patients appear toxic, and some fair-skinned patients will exhibit an erythematous exanthem. Acute delirium is seen in 15% of patients. After 2-3 days, the pathognomic rash begins as an enanthem on the oropharynx, and within 1-2 days develops on the face, forearms, and hands. It then spreads to the trunk and lower extremities. The lesions begin as macules and display synchronous development into deeply rooted papules. These lesions subsequently evolve into vesicles and tense, often umbilicated, pustules.[12] Approximately 8-9 days after eruption, the pustules involute and form scabs, eventually crusting on days 14-16. The crusting of the lesions is associated with resolution of fever. A week later, the crusts separate, leaving hypopigmented scars, particularly on the face.[6] Lesions may be so extensive as to appear confluent. Cough and bronchitis commonly are associated with infection, but pulmonary consolidation is unusual except in fatal cases. Secondary bacterial infections are rare. Monkeypox is identical in presentation, except that lymphadenopathy is more common and mortality is only 10-15%.[13]

Variola minor shows a similar progression of symptoms with less toxicity and often smaller lesions. Both show the typical progression starting with the face and lower arms, with fewer lesions on the abdomen, and with all lesions in adjacent anatomic areas at the same stage of development.[14] One-fifth of variola major resulted in atypical presentations. Modified smallpox often was seen in those with prior vaccination, with sparse, short-lived skin lesions and infrequent toxicity. Even those with recent immunization were susceptible to a brief upper respiratory infection after exposure. Flat-type smallpox has been reported in 2-5% of cases, with severe systemic toxicity associated with slow development of flat, soft, velvety skin lesions; it usually is fatal (95% in unvaccinated patients, 66% in vaccinated). Hemorrhagic smallpox, seen most often in pregnant women, shows a rapid progression, with development of mucosal bleeding, petechiae, and ecchymoses prior to death.[12,14] Asymptomatic infections likely are more common than previously appreciated, and virus may be recovered from the oropharynx of such individuals. The potential transmission from these asymptomatic carriers is not known, but probably is limited.[9,14]

Diagnosis. Historically, experienced clinicians in endemic areas reliably could diagnose smallpox based on clinical features. However, in nonendemic areas, variola minor frequently was confused with varicella. However, varicella lesions are more superficial, evolve in a variety of stages over a given anatomic region, spare the soles and palms, and are more prominent on the trunk.[8] Other exanthems and pustular dermatosis that were less frequently confused with smallpox lesions include erythema multiforme with bullae, contact dermatitis, and impetigo.[6,10]

Treatment. Treatment largely is supportive and symptomatic. Strict isolation to reduce secondary transmission is essential starting with onset of rash until all scabs have separated. Anyone exposed to a patient in this time period must be vaccinated and quarantined for 17 days.

Antiviral therapy historically has not been useful. Both cidofovir and ribavirin inhibit variola in vitro, and both had significant but lesser activity against monkeypox and vaccinia.[15] Cidofovir, currently licensed in the United States for treatment of cytomegalovirus (CMV) retinitis at a dose of 5 mg/kg, is protective in a mouse cowpox model at a 20-fold higher dose.[16] Cidofovir only is available as an intravenous formulation, and must be administered with concomitant hydration and probenecid to reduce the risk of nephrotoxicity.[17] There are no in vivo studies of ribavirin for poxvirus infections. Other proposed antiviral therapies are undergoing study.[18,19]

Vaccination is effective in preventing infection or attenuating disease. It is possible that EDs will assist in a public health disaster by providing vaccination, and it is certain that any vaccine-related complications would require ED intervention.

Trauma Reports™ (ISSN 1531-1082) is published bimonthly by American Health Consultants, 3525 Piedmont Road, N.E., Six Piedmont Center, Suite 400, Atlanta, GA 30305. Telephone: (800) 688-2421 or (404) 262-7436.

Vice President/Group Publisher: Brenda Mooney
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Periodicals postage paid at Atlanta, GA.
(GST registration number R128870672.)

POSTMASTER: Send address changes to ***Trauma Reports***, P.O. Box 740059, Atlanta, GA 30374.

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Subscription Prices

FREE to subscribers of *Emergency Medicine Reports, Pediatric Emergency Medicine Reports, Emergency Medicine Alert*, and *ED Management.*

For nonsubscribers, the price is $199.

U.S. possessions and Canada, add $30 plus applicable GST. Other international orders, add $30.

Back issues: $66. One to nine additional copies, $159 each; 10-20 additional copies, $119 each.

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Financial Disclosure

In order to reveal any potential bias in this publication, and in accordance with Accreditation Council for Continuing Medical Education guidelines, Drs. Dietrich (editor in chief), Bowman, Diebel, Falcone, Hanlon, Jones, Mahadevan, Perkin, Santanello, Savitsky, and Stafford (editorial board members), and Winograd (peer reviewer) report no relationships with companies related to the field of study covered by this CME program. Dr. Coonan (author) is a former infectious disease officer at USAMRIID and does ongoing consulting work.

Vaccination within five years prior to or within 2-3 days after natural exposure provides almost complete protection.[12] Revaccination is associated with prolonged immunity. To add a margin of safety, the WHO recommends revaccination if exposure occurs more than three years after vaccination. Vaccination 4-5 days after exposure attenuated natural disease and reduced death rates.[8]

Vaccinia immune globulin (VIG) has limited potential as a post-exposure prophylactic agent if given within a week of exposure in conjunction with vaccination.[10] It is given at a dose of 0.6 cc/kg, often requiring multiple intramuscular injections (as the volume for a typical adult is 42 cc), and can be repeated in 2-3 days if symptoms progress. Supplies are available through the CDC. It was derived for treatment of complications of vaccination, including eczema vaccinatum and some cases of progressive vaccinia. It also can be used in cases of severe generalized vaccinia. It is not effective in post-vaccination encephalitis, and is of no benefit in treatment of smallpox.[20]

Following successful dermal inoculation with the vaccine (referred to as a "take"), a papule forms after 4-5 days. This often intensely pruritic papule evolves over 2-3 days to an umbilicated vesicle or pustule, with surrounding erythema and induration peaking a week after initial appearance. Regional lymphadenopathy and mild systemic symptoms with fever are common. The pustule frequently ruptures prior to forming a scab, which separates with scarring two weeks later. The vaccination site must be covered with a non-occlusive dressing (e.g., a gauze pad) until the scab separates, and strict hand washing after contact with any drainage is essential to limit the inadvertent inoculation of additional sites or persons.[10,12,20] Occlusive dressings result in maceration and extensive local infection and should be avoided. Systemic antihistamines and non-narcotic analgesics often are useful for patient comfort. Common adverse effects which require only symptomatic treatment include nonspecific erythematous or urticarial eruptions, which may be confused with generalized vaccinia, as well as erythema multiforme.[20] Generalized vaccinia results in a vesicular eruption 7-9 days after vaccination, often accompanied by fever. The eruption usually is self-limited, requiring therapy only in immunocompromised patients.[10]

While most vaccinees experience mild morbidity that rarely interferes with activity, serious complications occur in 0.13% of primary vaccinations and an order of magnitude less often in revaccination.[21] The most common complication, accounting for over half of the serious adverse effects, is accidental inoculation of a site distant to the inoculation. Infection of the face, genitals, and rectum are common, but usually self-limited. More concerning are ocular infections, which account for one-fifth of accidental infections, which can result in corneal injury with permanent defects. One-fifth of accidental ocular infections occurred due to contact with a vaccinated person.[22] Ocular infection responds reasonably well to VIG and topical idoxuridine (one drop in affected eye q1h while awake, q2h while asleep).[10] However, if keratitis is established, there is an increased risk of corneal scarring with use of VIG, and its use is contraindicated.[20]

Eczema vaccinatum results in extensive or even generalized vaccinia infection in patients with eczema or other exfoliative skin disorders and, perhaps, burn victims. The disease usually is self-limited, but as many as one in 10 cases can be fatal.[10] It occurs independent of the current degree of eczema. Treatment with VIG is indicated and usually effective. If vaccination is essential, it can be done with concomitant administration of VIG.[20] VIG also is indicated in cases of vaccinia necrosum, a progressive vaccinia infection with extensive local destruction and metastatic lesions. Progressive vaccinia occurs only in patients with deficiencies in cell-mediated immunity and is fatal in three-quarters of cases.[10] Post-vaccination encephalitis complicates 12 per 1 million primary vaccinations, and two per 1 million revaccinations. VIG is ineffective and is not indicated.[20]

Routine contraindications to vaccination include immunosuppression, eczema, pregnancy, household contact with individuals with contraindications, or in children. Prior experience with vaccination showed very rare congenital infections, usually fatal, after primary vaccination of pregnant mothers. Prior to smallpox eradication, vaccination routinely was done in children, and in the face of exposure, this should not deter vaccination. In the face of a documented exposure to smallpox, it may be necessary to vaccinate even those with contraindications with concomitant VIG administration.[11,20]

Viral Hemorrhagic Fevers

Clinical Features. The viral hemorrhagic fevers (VHF) are prominent emerging infectious diseases. A variety of enveloped RNA-containing viruses are capable of causing severe illness marked by fever, shock, multi-organ failure, and hemorrhagic diathesis of varying severity. Recent outbreaks of Ebola hemorrhagic fever (EHF) in West Africa and Crimean-Congo hemorrhagic fever (CCHF) in Pakistan have highlighted the high mortality and potential for person-to-person transmission.[23] Increasing concern about the public health impact of VHF and potential to extend beyond traditional geographic boundaries is heightened by the potential for these highly infectious viruses to be used as terrorist weapons.[24,25] While technically difficult to produce in quantities similar to the former Soviet Union, small-scale production suitable for terrorist use can be accomplished in a typical two-car garage with minimal modifications.[26]

The filoviruses, Ebola and Marburg, have been responsible for severe explosive outbreaks and sporadic nosocomial cases. A well-documented, large outbreak occurred in Zaire in 1995, with 316 cases and an 80% fatality rate.[27-30] One-quarter of those infected in the Kikwit, Zaire, outbreak were health care workers.

The arenaviral hemorrhagic fevers are caused by Lassa fever virus, from Africa, and the Tacaribe complex of South American viruses: Machupo (Bolivian), Junin (Argentinean), Sabia (Brazilian), Guanarito (Venezuelan), and the recently described North American Whitewater Arroyo virus.[31-33] Human infection results from inhalation of infected rodent waste products, and may be transmitted person-to-person. Lassa fever is a substantial public health problem in West Africa, and accounts for one-quarter of febrile hospital admissions and deaths.[34]

CCHF has a wide endemic area, with sporadic tick-borne outbreaks and frequent hospital-centered outbreaks, marked by a

high incidence of fatal infections in health care providers.[33,35]

The filoviruses are associated with high-level viremia and widespread cytopathic effects without evidence of concomitant immunologic effect. Thrombocytopenia and lymphopenia with marked lymphoid depletion of bone marrow, spleen, liver, and peripheral lymph nodes only partially account for the immunosuppression.[36,37] While evidence of a consumptive coagulopathy occurs in the majority of patients, it is likely that direct viral destruction of endothelium and direct viral toxic effects are substantial contributors.[38,39] Hepatopathy without icterus usually is evident with elevations of aspartate aminotransferase (AST) greater than alanine aminotransferase (ALT).[40,41] Myocarditis and encephalitis appear common, but frequency depends on strain-specific features.[42] The virus survives in immunological privileged sites, such as the anterior chamber of the eye or the testes, which likely accounts for the delayed clinical features and protracted excretion of infectious virus in semen in survivors.[43-45] Similarly, the arenaviruses result in substantial thrombocytopenia, lymphopenia, and necrosis of liver, spleen, and adrenals without associated inflammatory response.[46]

All are highly infectious by aerosol in very low titers; perhaps as little as a single virion is infectious. All but yellow fever have been associated with person-to-person transmission and nosocomial epidemics. In the Kikwit Ebola outbreak, one-third of the physicians and one-tenth of the nurses contracted Ebola. The filoviruses are found in large amounts in and on skin. Physical contact with intact skin appears to be sufficient for transmission.[47] It appears, based on a small number of animal and epidemiological observations, that a minority of patients can generate infectious aerosols.[43,48-50] Argentine hemorrhagic fever (AHF) and Bolivian hemorrhagic fever (BHF) appear less transmissible, with occasional person-to-person spread, but may be secreted in semen after recovery, resulting in infection in intimate partners.[51] Guidelines for management of these patients are based on the infrequent generation of highly infectious aerosols, and call for strict respiratory and mucosal protection, negative airflow precautions, and isolation and decontamination of all bodily fluids.[24,35,52,53]

All agents of VHF present as a similar, non-specific febrile illness. Myalgias, malaise, prostration, and headache are nearly universal. Orthostatic symptoms and relative bradycardia appear common. The arenaviruses typically present with insidious onset. Common physical findings include evidence of diffuse capillary leak with hypovolemia, conjunctival injection, flushing, and petechia.[42,54-57]

Significant hemorrhage is present inconsistently and the absence of a bleeding diathesis should not dissuade the clinician from considering the possibility.[41] Minor bleeding—typically gingival, gastrointestinal, or oozing from vascular puncture sites—is seen in approximately 13% of AHF infections (Junin virus); 50% of VHF cases (Guanarito virus) and 40% of Ebola (Zaire strain) infections.[54,55]

Ebola typically presents with significant gastrointestinal (GI) symptoms, with non-bloody diarrhea present in more than 80% of patients and vomiting in 60%. Sore throat is a symptom in two-thirds of patients. Chest pain was a prominent feature in the Ebola-Sudan (EBO-S) outbreaks, but was not prominent in patients afflicted with Ebola-Zaire (EBO-Z) or Marburg disease.[58] A non-pruritic morbilliform or macular rash frequently is seen in fair-skinned individuals. The disease progresses in a biphasic manner with apparent recovery after the first week. A minority will have mild disease and continue to convalesce gradually over the next six weeks with frequent sequelae, while the majority will develop the hemorrhagic signs, tachypnea, hiccoughs, encephalopathy, normothermia, and oliguria that precede death.[59]

AHF, the most common and best characterized of the South American arenaviruses, typically presents 6-14 days after exposure, but the incubation period may range from four to 21 days. Onset is insidious, with fevers, chills, anorexia, myalgias, and malaise progressing over several days to prostration, tremor, cephalgia, abdominal pain, photophobia, and GI motility disturbance. Sore throat, nasal congestion, and cough are distinctly absent, and are helpful in limiting the differential diagnosis. Examination may reveal flushing of the face and upper torso with edema and hyperemia of the conjunctiva, gingiva, and oropharynx. Petechiae of the soft palate and axilla are common, along with small palatal vesicles and cervical lymphadenopathy. Patients often develop neurologic disease within a week of presentation, with a wide range of central nervous system (CNS) dysfunction, including ataxia, decreased deep tendon reflexes, and hyperesthesia. Three-quarters of patients will improve over the second week of illness, with the others manifesting bleeding, progression of CNS disease, shock, and secondary bacterial infections, particularly pneumonias. Convalescence is protracted, and up to 10% of antihemophilic factor A (AHF) patients treated with immune plasma developed a late onset self-limiting neurologic syndrome. Mortality ranges from 15-30%, with coma, severe bleeding, seizures, and oliguria portending poorer outcome. Treatment with immune plasma or ribavirin has reduced this to approximately 1%.[51,60]

Lassa fever differs only slightly in presentation from the South American arenaviruses, with less neurologic involvement, less prominent bleeding diathesis, and inconsistent thrombocytopenia or leukopenia.[61-63] Recovery typically takes 10 days. A minority develop edema, encephalopathy, tachypnea, hypotension, and bleeding manifestations portending a poor outcome.[64] Higher case fatality rates occur in pregnant women and fetal loss is universal.[65] Lymphopenia may be seen, but white blood cells may be unaffected or may reflect a neutrophilia, particularly in severe cases.[61,66] Disseminated intravascular coagulation (DIC) is not associated with Lassa fever. An elevated AST (> 150 U/L) is associated with worse prognosis and is an indication for initiation of ribavirin therapy.[34,67,68]

Most VHFs present with nondiagnostic features in a seriously ill-appearing patient with multiple organ involvement similar to other biowarfare (BW) agents and endemic diseases of the tropics. Misdiagnoses have been common. Similar presentations are shared by a variety of tropical viral agents, such as yellow fever, dengue, and the Hantaviruses responsible for hemorrhagic fever with renal syndrome, and Rift Valley fever, all of which have limited BW potential and can present with hemorrhagic manifesta-

tions. Other tropical diseases include malaria and leptospirosis, which have been seen in conjunction with Ebola outbreaks in the past, and may confound the diagnosis and treatment of both. Other diseases considered in the differential diagnosis include typhoid fever, borreliosis, septicemic plague, typhus, dysentery, acute African trypanosomiasis, fulminant meningococcemia, or other causes of sepsis with DIC.[33,69]

Diagnosis. Any evidence of a bleeding diathesis should result in isolation and aggressive diagnostic testing, to include attempts at viral isolation at one of the reference laboratories with biocontainment capabilities.[33,52,70] Lymphopenia and thrombocytopenia commonly are seen in all VHF syndromes and are ubiquitous in arenaviral disease, and a platelet count of fewer than 100,000 or WBC fewer than 4500 is 100% sensitive.[54] Almost all patients will have laboratory evidence of a consumptive coagulopathy, but rarely full-blown DIC may be present. Similarly, all patients with arenaviral disease display proteinuria, which also is common in the other VHFs.[71-73]

Laboratory diagnosis of VHF is difficult, and even routine blood tests (e.g., CBC and chemistries) pose severe hazards to laboratory workers. If VHF is in the differential, the laboratory must be warned, and physiochemical viral inactivation must be employed.[52,74,75]

Viral culture often is essential to establish the diagnosis. Most patients have intense viremia at presentation and viral cultures can yield a specific diagnosis in 3-10 days. This must only be attempted under BSL-4 conditions by experienced technicians. Samples should be sent to a reference laboratory *(See Insert)*, after contacting the laboratory to arrange shipping and packaging details.

Rapid diagnostic testing is available for all the VHF agents, and antigen detection tests show remarkable sensitivity in acute disease. These tests are available through the reference laboratory system, and some may be available at local level B or C laboratories, as they do not require biocontainment after specimen inactivation.

Treatment. All VHF syndromes require barrier nursing and intensive supportive care, which has been shown to improve outcomes. Invasive procedures and IM injections should be avoided. No therapy available, including interferon, antibody preparations, or currently marketed antiviral drugs, is effective against the filoviruses.[76-79] Intensive efforts at developing new drugs have been promising.[80,81] Antibody preparations, chiefly in the form of serum or plasma from convalescent patients, reduces mortality of the South American arenaviruses, but is no longer available in the United States, and may be associated with late-onset neurological disease.[82-84] Uterine evacuation, in pregnant patients, improves survival in Lassa Fever and is indicated as fetal loss is ubiquitous.[65]

Ribavirin inhibits the arenaviruses, RVF, and CCHF.[79,85] Ribavirin is well tolerated with mild reversible hemolytic anemia as the only consistent adverse effect.[17,52,85] The initial dose is 30 mg/kg IV given over one-half hour in saline or 2 g orally. Intravenous ribavirin is available through the reference centers listed in the Insert. Survival benefit has been shown in large studies with the arenaviruses. Although experience with ribavirin in RVF and CCHF is limited, it is recommended.[68,79,83,86-90]

Tularemia

Clinical Features. Tularemia is a zoonotic infection that in many ways resembles brucellosis and plague. Sporadic outbreaks in the United States continue to occur, with frequent misdiagnosis.[91] While hospital microbiology laboratory acquired infections are common, person-to-person transmission has not been described.[92,93] Aerosolized *F. tularensis* is highly infectious, with 10-50 organisms required to establish infection in healthy adult humans.[94]

Tularemia's incubation period typically is 3-6 days, dependent on route and dose of inoculation, but may range from 1 to 21 days.[95,96] As many as six different clinical forms of tularemia have been described, depending on the site of local infection and degree of dissemination. Common presentations include local ulceration and lymphadenopathy (ulceroglandular), lymphadenitis (glandular), conjunctivitis with lymphadenopathy (oculoglandular), ulcerative or exudative pharyngitis, and pneumonia.[93,97] Ingestion of contaminated water commonly results in pharyngitis, abdominal pain, and fever. Regardless of the presenting form, systemic symptoms of asthenia, malaise, fatigue, myalgias, low back pain, headache, chills, and fever usually are seen.[92]

In approximately one-quarter of all cases, systemic dissemination may occur following one of the localized forms or in the absence of other signs, resulting in the typhoidal presentation.[94] Diagnostic considerations include typhoid fever, typhus, brucellosis, Legionella infection, Q fever, malaria, disseminated mycobacterial or fungal infections, rickettsiosis, endocarditis, primary HIV infection, toxic-shock syndrome, and other causes of sepsis. Mortality approaches 33% in typhoidal cases, in contrast to only 4% in ulceroglandular disease.[94,95]

Primary pulmonary tularemia, the chief form expected following aerosolization, presents with abrupt onset of high fevers, rigors, dyspnea, nonproductive cough, pleuritic chest pain, and diaphoresis. It may result in systemic disease without localizing pulmonary disease or progress to a fulminant, fatal pneumonia.[92] The pulmonary form is indistinguishable from other common causes of community-acquired, zoonotic, fungal, and tubercular pneumonia. A pulse-temperature discrepancy occurs in up to 42%.[95] Production of purulent sputum or hemoptysis are seen in a minority.[98,99] Pneumonia also may complicate dissemination from localized infection and present with a more indolent course, chronic fevers, cachexia, fatigue, and lymphatic suppuration. It is seen in 83% of typhoidal cases.[95]

Pulmonary findings are nonspecific, with rales and friction rubs most often described. Radiographic findings may mimic tuberculosis, with multiple granulomatous lesions, hilar adenopathy and effusions, or may present with typical pneumonic findings such as subsegmental or lobar consolidation.[100] The triad of oval opacities, hilar adenopathy, and pleural effusions are strongly suggestive of tularemia, but are seen only in a minority of cases.[99]

Exam may show evidence of simultaneous extrapulmonary inoculation, most typically pharyngitis. The ulcerative and exudative pharyngitis commonly is confused with infectious mononucleosis, adenoviral tonsillopharyngitis, or streptococcal pharyngitis. It may become membranous, similar in appearance to diphtheria.[101,102]

Localized infection resulting in ulceroglandular or oculoglandular tularemia remains the most common natural presentation. Localized disease may occur even with aerosol exposure.[92] The majority develop an abrupt fever, with variable complaints of chills, malaise, fatigue, cough, and headache. Fever, as well as the other systemic symptoms, may remit and recur for weeks to months.[93] Following cutaneous inoculation, patients develop a small, painful, papule which rapidly necroses and ulcerates. Lymphadenopathy may occur as an isolated finding, or may persist well beyond the acute febrile illness.[95] Ocular manifestations are analogous, with corneal or conjunctival ulcerations, conjunctivitis and anterior chamber inflammation, or even frank hypopyon.[103] Meningitis is an exceedingly rare manifestation.

The ulceroglandular form of tularemia may be mistaken for the cutaneous form of anthrax, sporotrichosis, and *Mycobacterium marinum*. However, the papule and ulcer of tularemia are painful with local adenitis, in sharp distinction to that of the more edematous anthrax, which has minimal discomfort.[99] Other considerations include pyogenic infections, cat-scratch disease, syphilis, chancroid, and herpetic whitlow.

In addition to the pathognomonic skin lesions, a wide range of disseminated dermatological manifestations has been described, and may occur in up to one-third of patients within the first two weeks of illness, including diffuse maculopapular and vesiculopapular eruptions, erythema multiforme, acneiform lesions, urticaria, and, most commonly, erythema nodosum.[14,104]

Diagnosis. Routine laboratory studies are nonspecific. Lymphocytosis occasionally is seen, but the lymphocyte count is most often within normal limits. Up to one in four may show microscopic pyuria, which may lead to misdiagnosis of pyelonephritis. Minimal transaminase and lactate dehydrogenase elevations reflect hepatic infection and infrequently patients may develop rhabdomyolysis with the associated elevation of creatine phosphokinase (CPK).[95]

Francisella tularensis is difficult and dangerous to cultivate in hospital microbiology laboratories.[105] The organism is not typically seen on Gram stain of clinical specimens, but may be cultured from blood, lymph node aspirate, pharyngeal swabs, sputum, and cutaneous or corneal ulcers. Modern automated blood culture systems detect *F. tularensis* in at least 60% of bacteremic cases, but misidentification is common.[106,107]

Due to the difficulties with culture, diagnosis typically is accomplished via serology.[108] Cross-reactivity to Brucella and Legionella is seen. Polymerase chain reaction (PCR) is emerging as a valuable tool, with rapid return of accurate results without the risk of laboratory acquired infection.[109-111] Additional diagnostic assistance can be obtained through the Division of Vector-Borne Infectious Disease, CDC, Ft. Collins, CO (dvbid@cdc.gov). *(See Insert.)*

Treatment. Untreated, most patients have a prolonged debilitating febrile illness lasting months. Antibiotic treatment may result in a rapid improvement, but a substantial number of patients have a suboptimal response, particularly if ineffective antibiotic therapy is used, therapy is abbreviated, or if there is a delay in initiation of treatment.[92,112] A Jarisch-Herxheimer-like reaction may be seen with initiation of antibiotic therapy. Streptomycin or gentamycin for 10-14 days is the standard treatment regimen, although longer or repeated courses may be required.[9,92,113,114] Streptomycin-resistant organisms were engineered and investigated by both the United States and Soviet programs.[92] Ceftriaxone has an unacceptably high treatment failure rate and should not be used.[115] Doxycycline and chloramphenicol have been used extensively, but have higher treatment failure and relapse rates than the aminoglycosides, particularly in those with immunocompromise or chronic systemic disease.[116,117] A minimum of 14 days of treatment is recommended.[92] The addition of chloramphenicol to an aminoglycoside is recommended in the rare cases of meningitis.[118] Fluoroquinolones, principally ciprofloxacin, have been used in a limited number of cases, appear to be very effective, and are a reasonable first-line alternative to the aminoglycosides.[49,116] A 10-day course is recommended.[92]

Limited studies in humans demonstrate that a two-week course of a tetracycline, but not a shorter course, is effective for post-exposure prophylaxis.[120] Ciprofloxacin (or other fluoroquinolone) also is recommended.[92]

Botulinum Toxins

Clinical Features. Botulinum toxins are the most toxic substance known, with an inhalational LD50 of 3 ng/kg, approximately 100,000 times as toxic as sarin.[121] In addition, it is easy to manufacture and is well absorbed via aerosol.[122] A gram of botulinum toxin potentially could kill 1 million people. The quantity of botulinum produced by Iraq would have been sufficient to kill three times the total living human population.[123]

Naturally occurring food-borne outbreaks of botulism remain public health emergencies. While each outbreak averages 2.5 patients, approximately half have only a single victim.[123] The three largest outbreaks involved a total of 121 patients, illustrating the potential for even accidental poisonings to generate mass casualties, with half presenting with clinical symptoms to an ED.[124] Due to the implications of on-going exposure, the delayed and often insidious onset, and possible geographic dissemination, a nation-wide surveillance system is in place through the CDC.[125]

Most cases present within 36-72 hours (range 6 hours to 8 days) with an afebrile symmetric descending flaccid paralysis with a clear sensorium.[126,127] Depending on dose and route, the presentation can range from a subtle motor weakness to acute profound flaccid paralysis with respiratory arrest. The initial GI symptoms associated with food-borne outbreaks are thought to be due to other microbial by-products and would not be seen if purified toxin was released.[123,125]

Presenting complaints include weakness, blurred vision, diplopia, dry mouth, and dysarthria.[124] Facial muscle weakness and diminished ocular motility mimicking cranial neuropathies may result in a diagnostic delay. Typically, the initial sign of progression is a loss of head control. While the sensorium remains clear, and sensory features are uncommon, acral paresthesias due to hyperventilation are well described. Patients may appear obtunded due to the hypotonia.[123] Deep tendon reflexes may be

preserved initially, but diminish with progression, in sharp contrast to Guillain-Barré syndrome and the descending Miller-Fisher variant.[129] Constipation and urinary retention are common.[130] Ptosis and upper extremity weakness may indicate progression to the point that respiratory compromise may require mechanical ventilation.[131] Respiratory failure may be prolonged, typically requiring 2-8 weeks of ventilatory support.[128] Without mechanical ventilation, fatality rates are approximately 60%; with contemporary ICU care, the rate is now 5-10%.[126]

Prompt clinical diagnosis is critical. Delays and misdiagnosis are common and are associated with worse outcomes.[132,133] Other clinical entities with similar presentations that would suggest the need to consider botulism include myasthenic crisis, cholinergic crisis, Guillain-Barré syndrome, basilar artery insufficiency, tick paralysis, Eaton-Lambert syndrome, and various drug and toxin intoxications.[124,134,135] Prominent symmetric bulbar motor and anti-muscarinic features strongly support botulism.

Routine laboratory and radiographic studies are usually normal or non-diagnostic. However, serum chemistries may reveal other diagnoses, such as abnormalities of calcium or potassium, an elevated CPK suggesting a myopathic process, an elevated CSF protein suggesting Guillain-Barré syndrome, evidence of stroke or mass on computed tomography of the brain or CSF evidence of CNS infection, especially tuberculous or fungal meningitis.[128,136]

Urgent consultation with a neurologist in equivocal cases may facilitate diagnosis, as electomyogram (EMG) findings are highly suggestive.[137] Early clinical botulism may respond to anticholinesterase therapy similar to myasthenia gravis.[128,136] Serum samples should be collected (4-6 vacutainer tubes; red or tiger top) prior to administration of antitoxin or cholinesterase inhibitors, as it interferes with the gold-standard mouse bioassay.[123] The mouse bioassay is very sensitive and specific, but is time consuming and is not widely available. New diagnostic modalities remain limited.[138,139] The more sensitive stool cultures and PCR, while helpful in food-borne outbreaks, would not be helpful if preformed toxin was released intentionally.[140]

Treatment. If significant oral exposure is suspected, activated charcoal may be effective at reducing absorption.[141] Any exposed or symptomatic patients should be treated with antitoxin, admitted and followed closely for respiratory failure.[9,142,143] In cases of mass casualty exposure, the decision to withhold administration of antitoxin until development of symptoms may be necessary. Patients who present late in the course with stable or improving symptoms do not require antitoxin.[123]

Patients who are not mechanically ventilated should be cared for in a reverse Trendelenburg position with sufficient head and neck support to prevent airway occlusion. Patients admitted will require frequent neurologic assessments with careful attention to ability to handle secretions and otherwise protect their airway. Pulmonary function testing may show a decrease in vital capacity and inspiratory force prior to onset of hypercarbia.[144] Clindamycin and aminoglycoside antibiotics should not be administered because they may precipitously worsen neuromuscular function.[145-149] Succinylcholine should be used with caution.[150] Aspiration or loss of a patent airway usually precedes hypoventilation. The need for mechanical ventilation ranges from 20% to 60% of cases.[123] Once respiratory compromise occurs, treatment is mechanical ventilation, which usually is sufficiently prolonged to mandate tracheostomy.[131] Efforts to stockpile ventilators for emergency use are ongoing.[151] Recovery is prolonged with frequent complications associated with protracted immobilization and tracheal intubation.

There is a single commercially available antitoxin, a trivalent (containing anti-A, anti-B, and anti-E activity) equine preparation made only by Connaught Laboratories. Small-scale production of other products is limited to Japan and two European suppliers.[125] Given early in the course, it arrests progression of neurologic disease, shortens duration of mechanical ventilation and reduces mortality.[142] In one series, administration within 12 hours of presentation reduced intubation rates from 85% to 57% and duration of mechanical ventilation from a median of 54 days to 11 days.[131] Patients with significant wheal and flare will require intensive desensitization over several hours. While it is usually well tolerated, up to 9% of recipients will manifest typical serum sickness or urticaria and 2% will have life-threatening reactions.[152] A single vial will neutralize several lethal doses and is sufficient for naturally occurring botulism.[153] Additional doses theoretically may be needed following exposure to large amounts of purified toxin.

An investigational equine F(ab′)2 product with activity against toxin types A, B, C, D, E, and F has been developed and tested by the U.S. Army. It is available for clinical use under a compassionate use protocol.[154] Adjunctive therapy with guanidine or amino-pyridines is not effective.[155]

The trivalent equine antitoxin is stockpiled by the CDC in airports in New York, Chicago, Atlanta, Miami, Los Angeles, San Francisco, Seattle, and Honolulu. In addition, the state health departments of California and Alaska maintain their own stores. Additional stocks are held by the U.S. Army, and can be accessed by CDC officials. Canada maintains its own supply, but other members of the Pan American Health Organization are served by the CDC. This system allows most patients to be treated with antitoxin within 12 hours of contact with public health authorities.[125]

Any suspected case of botulism is a public health emergency. Local health departments work closely with the CDC's Food-borne and Diarrheal Disease Branch on a 24-hour-a-day basis. Emergency consultation, including diagnostic and treatment recommendations and provisions for antitoxin is available by calling (404) 639-2888.[125]

A formalin inactivated toxoid containing toxin types A, B, C, D, and E has been in use since the 1950s under an Investigational New Drug protocol to protect at-risk laboratory workers. It is safe and well tolerated, although the current product is rather painful on injection.

Although botulinum toxin has little potential for secondary aerosolization, aerosol release may require surface decontamination to avoid ingestion of persistent toxin.[121]

Use of Tetracyclines and Fluoroquinolones in Pregnant, Nursing, or Pediatric Patients

Although tetracyclines and fluoroquinolones usually are not used in children, nursing mothers, or pregnant women, their use for life-threatening infections is justified and recommended by the CDC, the Food and Drug Administration, the American Academy of Pediatrics, and the American College of Obstetricians and Gynecologists.[156-160] A growing body of literature on the safety of fluoroquinolones, particularly ciprofloxacin, suggests that risks are minimal and that clinicians should not hesitate to use them for serious infections.[161-169] Adverse effects of tetracyclines in pregnant women and in children are well described, but are acceptable in the face of life-threatening disease. In addition, doxycycline appears to be much safer than tetracycline, with no reports of untoward effects in children or in pregnancy.[170-173] Initiate therapy in children with ciprofloxacin (10-15 mg/kg/dose po q 12 hours not to exceed 1 g per day) or doxycycline (2.2 mg/kg/dose po BID not to exceed 100 mg po BID). If penicillin susceptibility is confirmed in a patient with anthrax, initiate or change to oral amoxicillin 80 mg/kg/day TID (maximum 500 mg/dose), or to trimethoprim sulfate if susceptible plague is isolated.[174]

Summary

Detection of a biological weapons attack hinges on a clinical suspicion, followed by laboratory investigations. Circumstances that should prompt immediate contact with surrounding EDs and urgent consultation with public health and law enforcement authorities include:

1) Any unusual temporal or spatial clustering of infectious diseases, especially if serious pulmonary symptoms or hemorrhagic diathesis are prominent or if stereotypical features are present;

2) Multiple, previously healthy patients with presentations of sepsis or fulminant pneumonia in otherwise healthy patients;

3) Clinical diagnosis or suspicion of smallpox;

4) Acute flaccid paralysis with prominent bulbar symptoms, suggesting botulism; and

5) Isolation of pathognomonic organisms; especially variola virus, agents of viral hemorrhagic fever, engineered or highly drug resistant *Bacillus anthracis, Yersinia pestis,* or isolation of genetically identical organisms from multiple regions.

There is little, if any, risk of contamination to health care workers following simple decontamination (removal of contaminated clothing and a soap and water shower). However, pneumonic plague, smallpox, and the viral hemorrhagic fevers present a substantial risk for secondary spread and explosive epidemics. Respiratory protection is required to care for these patients. Isolation or quarantine of cases and contacts is essential.

Viral cultures should be sent *only* to USAMRIID, CDC, or comparable facilities in other countries, via the local public health system.

Additional rapid and confirmatory diagnostic tests are available through the public health laboratory response network (NLRN).

Hospitals and EMS agencies should not participate in testing of environmental samples or materials suspected of harboring infectious agents. Any such concerns should be directed immediately to law enforcement agencies, which have the responsibility and expertise to address these issues.

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Physician CME Questions

To earn CME credit for this issue of Trauma Reports*, please refer to the enclosed Scantron form for directions on taking the test and submitting your answers.*

1. Which of the following is true regarding smallpox?
   A. The predominant method of transmission is by respiratory droplets.
   B. Smallpox is minimally contagious.
   C. Infectivity is not increased in patients with smallpox and a cough.
   D. Variola minor strains have the highest mortality rates.
   E. Variola minor lesions usually are larger than variola major.

2. Which of the following is/are true regarding the management of smallpox?
   A. Strict isolation is essential.
   B. Treatment largely is supportive.
   C. Anyone exposed to a patient with contagious smallpox should be vaccinated and quarantined for 17 days.
   D. Antiviral therapy historically has not been useful.
   E. All of the above

3. Which of the following is true regarding vaccination following exposure to a patient with contagious smallpox?
   A. An individual vaccinated 1 year ago requires a repeat dose of the vaccine.
   B. An exposed individual optimally should be vaccinated within 2-3 days of exposure.
   C. An individual vaccinated six years ago does not require a second dose of the vaccine.
   D. VIG is a highly effective post-exposure prophylactic agent.
   E. VIG is very effective against post-vaccination encephalitis.

4. Which of the following is a potentially serious complication associated with the smallpox vaccine?
   A. Urticarial eruptions
   B. Erythema multiforme
   C. Accidental inoculation of the eye
   D. Generalized vaccina in a non-immunocompromised host
   E. Mild systemic symptoms and regional lymphadenopathy

5. Which of the following is/are true regarding filoviruses?
   A. The filoviruses are associated with a high level of viremia.
   B. Thrombocytopenia and lymphopenia may occur.
   C. Hepatopathy without icterus may be present.
   D. Myocarditis is common.
   E. All of the above.

6. Which of the following is *not* typical for the presentation of a patient with a VHF infection?
   A. Severe tachycardia
   B. Myalgias
   C. Headache
   D. Orthostatic symptoms
   E. Hypovolemia

CME Objectives

Upon completing this program, the participants will be able to:

a.) Recognize or increase index of suspicion for diseases that may result from biological terrorism;

b.) Be educated about rapid stabilization, and the isolation of patients with exposure to or evidence of smallpox, viral hemorrhagic fevers, tularemia, and botulinum toxins;

c.) Understand various diagnostic and treatment modalities for diseases associated with biowarfare; and

d.) Understand both likely and rare complications that may occur.

7. Which of the following is true regarding AHF?
   A. It is an uncommon South American filovirus.
   B. Its onset typically is acute.
   C. Sore throat, nasal congestion, and cough typically are present.
   D. Patients often develop neurologic disease within a week of presentation.
   E. Treatment with immune plasma or ribavirin is ineffective.

8. Which of the following is true of management of a patient with VHF infection?
   A. Interferon decreases the duration of the illness.
   B. Antibody preparations reduce the infectivity of the patient.
   C. Ribavirin inhibits arenaviruses, RVF, and CCHF.
   D. Barrier nursing is not necessary.
   E. Invasive procedures and IM injections may be performed without caution.

9. Which of the following is/are associated with botulism?
   A. Weakness
   B. Blurred vision
   C. Dysarthria
   D. Facial muscle weakness
   E. All of the above

10. Which of the following is true regarding the diagnostic work-up of a patient with potential botulism?
   A. Routine laboratory studies are typically normal or non-diagnostic.
   B. CPK usually is elevated.
   C. CSF protein usually is high.
   D. CT scan of the brain may show diffuse edema.
   E. EMG findings typically are not helpful.

In Future Issues: **Rapid Sequence Intubation**

Summary of Major Agents

DISEASE	CLINICAL PRESENTATION	DIAGNOSTIC STUDIES	TREATMENT
Anthrax			
Inhalational	Nonspecific prodrome of fever, dyspnea, cough, retrosternal chest discomfort followed by respiratory failure and hemodynamic collapse. Mediastinal widening universal in late stage, pulmonary infiltrate seen in up to 25% and meningitis in 50%.	Blood culture and Gram stain, CSF Gram stain and culture, chest x-ray or CT, antigenemia by ELISA/PCR/CL	Ciprofloxacin (other fluoroquinolones likely effective, but largely untested; penicillin (amoxicillin acceptable); gentamycin or streptomycin. Add chloramphenicol if evidence of meningitis. Bodily fluids and secretions may generate spores if left in contact with air, and must be disinfected (e.g., soaked in bleach, incinerated, autoclaved). Aspiration of pustule may increase risk of bacteremia. Steroids effective for controlling edema, if required for airway impingement.
Cutaneous	Pruritic papule that progresses to pustule. Local edema and adenopathy common.	Gram stain and culture from under eschar	
Pneumonic plague	Fulminant pneumonia with hemoptysis, sepsis, and disseminated intravascular coagulation (DIC)	Sputum for Gram stain, culture, IFA	*Respiratory protection and droplet precautions (isolation room or cohort).* Avoid lactam antibiotics, if possible. Streptomycin or gentamycin with chloramphenicol for meningitis. Tetracyclines effective. Quinolones likely effective, but unproven. TMP/SMZ less effective.
Botulism	Bulbar neuropathy (diplopia, ptosis, dysarthria), mydriasis, xerostomia followed by descending paralysis with preserved cognition with respiratory failure in 12-72 hrs. Afebrile.	EMG helpful but not diagnostic; may see response to edrophonium, difficult to detect in serum.	Intubation for respiratory failure. If antitoxin is given, it will arrest progression, shorten requirement for mechanical ventilation, and reduce mortality.
Smallpox	Severe prostrating febrile illness with synchronous evolution of pustules, particularly on face and arms.	Pharyngeal swabs or scabs (BSL-4)	Cidofovir effective in mice. Vaccinia immune globulin 0.6 mL/kg IM within 72 hours of exposure in conjunction with Vaccinia vaccine. *Isolation essential to prevent dissemination.*
Pneumonic tularemia	Acute, nonspecific febrile illness with ulcerations, pharyngitis, and pneumonia	Blood, pharyngeal, or ulcer swabs for culture or PCR; serology	Gentamycin or streptomycin. Ciprofloxacin (other fluoroquinolones likely effective, but largely untested); doxycycline (or other tetracycline) less effective. Add chloramphenicol if evidence of meningitis.
Filovirus hemorrhagic fever	Severe disease, marked weight loss, prostration, late encephalopathy, and bleeding. Often see maculopapular rash. 25-90% case fatality.	Viral antigen in blood. Viral isolation	Supportive. *Isolation essential to prevent dissemination.*
Arenavirus hemorrhagic fever	Prostration, shock, bleeding, CNS disease (less common in Lassa fever). Thrombocytopenia, leukopenia, and proteinuria.	Viral antigen or IgM detection; viral isolation	Ribavirin. High titer plasma for AHF no longer readily available. Isolation advisable, at least droplet precautions.
Brucellosis	Protracted recurrent fever, depression, fatigue, myalgias, arthritis, endocarditis, meningitis, sacroiliitis, orchitis, and septic abortion. Cytopenias common.	Blood or bone marrow culture. PCR. Serology by ELISA, agglutination, or dipstick assay.	Prolonged treatment with doxycycline plus rifampin, streptomycin, or gentamycin. Fluoroquinolones plus rifampin, streptomycin, or gentamycin. TMP/SMZ less effective.
Q fever	Acute influenza-like illness, rare fulminant disease. High mortality due to endocarditis in predisposed patients. Liver function test (LFT) levations common.	Culture or animal inoculation (BSL-3) impractical. Serology widely available.	Macrolide, tetracycline, or fluoroquinolone for acute disease. Macrolide should be combined with rifampin if used for pneumonia. Doxycycline plus rifampin, chloroquine, or hydroxychloroquine if underlying valvular pathology.

Research and Reference Laboratories*

* **Initial contact and consultation, as well as specimen submission, is through state and local health departments. Phone numbers are available in the blue pages of the phone book or online listings at www.statepublichealth.org/directory.php or www.cdc.gov/other.htm or www.cdc.gov/ncidod/diseases/hanta/hps/noframes/statecon.htm.**

NAME	PHONE NUMBER	INTERNET
Centers for Disease Control and Prevention (CDC), Atlanta, GA	Tel: (770) 488-7100, (emergency response) (404) 639-1115 (special pathogens) or (404) 639-2888 (24 h)	www.bt.cdc.gov/ and www.cdc.gov/ncidod/dvbid/
Vector Borne Disease Laboratory, Fort Collins, CO	(970) 221-6400	
U.S. Army Medical Research Institute of Infectious Disease (USAMRIID), Fort Detrick, MD	(888)-872-7443	www.usamriid.army.mil