Bioterrorism on the Home Front
A New Challenge for American Medicine

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ON OCTOBER 4, 2001, IT WAS ANNOUNCED THAT a 63-year-old man had been hospitalized in Palm Beach County, Florida, with inhalational anthrax.[1] This was the first recognized case of inhalational anthrax in the United States since 1976, and the first in US history to result from an intentional human act. As such, it ushered in a new era for the United States, one in which the hypothetical threat of lethal bioterrorism has become a stark reality. Importantly, the juxtaposition of this event with the vicious terrorist attacks on the World Trade Center and the Pentagon, despite no proven connection at this time, has resulted in a heightened state of concern in the United States and in other countries.

Since October 4 and as of November 7, the Centers for Disease Control and Prevention (CDC) has confirmed a total of 10 cases of inhalational anthrax and 7 cases of cutaneous anthrax.[2] Five additional cases have been identified as being suspicious for cutaneous anthrax. All but 1 of these cases appear to have been directly linked to the US postal system. The epidemiologic link of the apparently isolated case of the 61-year-old Bronx resident and employee of a Manhattan hospital who died of inhalational anthrax remains a mystery. Clinical cases of cutaneous or inhalational anthrax have clustered in the Boca Raton, Fla, New York City/New Jersey, and Washington, DC, areas. However, traces of anthrax spores, which likely are secondary contamination from identified primary sources of anthrax spores, have been found in distant locations such as Indianapolis, Ind, and Kansas City, Mo. More than 30 000 people are estimated to have received antibiotics as a consequence of possible exposure to anthrax spores.[2] The need for continual reevaluation of conventional wisdom regarding this disease as well as other potential bioterrorist threats has been made clear from these recent experiences. In this regard, the cross-contamination of mail and the special vulnerability of postal workers are 2 of the most unexpected epidemiologic findings thus far.

The 4 patients described in this issue of THE JOURNAL by Mayer and colleagues[3] and Borio and colleagues[4] provide a graphic account of the serious clinical consequences of inhalational anthrax. While one needs to be cautious in drawing generalizations from a handful of cases, several points can be made at this time from the available information. First, it is quite clear that with early recognition and rapid, aggressive initiation of appropriate antibiotic treatment, inhalational anthrax is a serious but nonetheless treatable disease. Of the 10 cases of inhalational anthrax reported at this point in the current outbreak, 4 have died, 3 have been released from the hospital continuing successful treatment, and 3 (including the 2 patients in the report by Mayer et al) are recovering while continuing to receive therapy. The fact that 6 of these patients have survived provides hope that the published mortality rates of 86% to 97% for inhalational anthrax[5] may not be accurate in the year 2001. Second, although there did not appear to be any clear-cut signs of early anthrax infection, certain characteristics were common among all 4 cases reported by Mayer et al and Borio et al. These included tachycardia disproportionate to the degree of fever, normal or elevated white blood cell counts, and abnormalities on chest radiographs or chest computed tomographic (CT) images. Among the radiographic changes were evidence of a widened mediastinum, pulmonary infiltrates, and pleural effusions. Abdominal pain or chest discomfort was noted in 3 of the 4 cases.

Based on these observations, primary care clinicians should be encouraged to obtain chest radiographs and consider chest CT scanning to aid in the diagnostic workup of patients in whom inhalational anthrax is a diagnostic consideration.[6] As influenza season approaches, it is likely that front-line physicians will be faced with the dilemma of attempting to rule out a diagnosis of early anthrax in patients with influenza or other viral illnesses. The combination of a careful history ascertainment with attention to potential environmental exposure and the use of appropriate radiologic studies should be able to reduce the inevitable widespread use of antibiotics during the upcoming influenza season. Moreover, although chest radiography and rapid diagnostic kits for influenza might prove helpful as adjuncts to other diagnostic tools, these should not be used as definitive diag-

See also pp 2549, 2554, and Patient Page.

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nostic tests, particularly if they yield negative results. Viral diseases other than influenza A or B can present with "flu-like" symptoms, and the chest radiograph may be read as normal early in the course of inhalational anthrax.

Importantly, strong weight should be placed on the epidemiologic setting within which the patient presents. Of note, all 4 patients described in this issue of *JAMA* worked at the Brentwood postal distribution center just outside of Washington, DC, and, thus, were possibly exposed to the same source of anthrax. The 2 patients who survived were admitted on October 19 and 20, while the 2 patients who died were admitted on October 21 and 22.[7] Thus, the index of suspicion of the clinicians within the context of the epidemiologic setting should play an important role in guiding decisions regarding further diagnostic testing and therapeutic interventions.

Bacillus anthracis is a spore-forming, nonhemolytic, nonmotile gram-positive rod. The organisms that have been identified thus far during the current outbreak appear indistinguishable and have uniformly been susceptible to ciprofloxacin, doxycycline, chloramphenicol, clindamycin, rifampin, vancomycin, clarithromycin, penicillin, and amoxicillin.[7] The *B anthracis* genome includes both a cephalosporinase and an inducible penicillinase. For this reason, it is not advisable to rely on either cephalosporins or penicillins alone for treatment. Current CDC recommendations for initial treatment of inhalational anthrax[7] include intravenous ciprofloxacin or doxycycline along with 1 or 2 additional agents. The successful regimen of ciprofloxacin, rifampin, and clindamycin used by Mayer and colleagues[3] was in keeping with these recommendations. While there are no prior published data regarding the use of clindamycin to treat inhalational anthrax in humans, it has been suggested that clindamycin may provide both an antimicrobial as well as an antitoxin activity.[3] The recommended duration of therapy for inhalational or cutaneous anthrax is 60 days.[7,8]

Nonhuman primate data[9,10] and data from the Sverdlovsk outbreak[11] have indicated that *B anthracis* spores can retain their ability to germinate for an extended period following inhalation. Based on these data, the current CDC recommendation is that all individuals exposed to anthrax spores receive a 60-day course of antibiotics as postexposure prophylaxis.[12] The lack of anthrax cases thus far among the individuals exposed to the contaminated letter in the Hart Senate office building suggests that this approach is effective. Current recommendations by the CDC[7] for postexposure prophylaxis regimens in adults include either ciprofloxacin, 500 mg orally every 12 hours, or doxycycline, 100 mg orally twice per day, with dose adjustments in children (ciprofloxacin, 10-15 mg/kg orally every 12 hours, or doxycycline, 2.2 mg/kg orally twice daily for children ≤45 kg or ≤8 years). The US Food and Drug Administration (FDA) has approved these 2 drugs as well as procaine penicillin for this indication. Given the adverse effects of ciprofloxacin and doxycycline in children, the CDC also recommends that if the isolate is determined to be sensitive to penicillin, children should be switched to amoxicillin, 80 mg/kg (not to exceed 500 mg per dose) orally every 8 hours. Additional work is needed to expand the range of antibiotics approved by the FDA for this indication.

Bacillus anthracis has several characteristics that makes it a particularly virulent organism.[13,14] These include an antiphagocytic poly-D-glutamic acid capsule and 2 toxins, lethal toxin and edema toxin. These 2 toxins are formed when the respective toxin factors, lethal factor or edema factor, bind to the protective antigen protein. Immunity to anthrax appears to be antibody mediated and has been conferred in animal studies by immunization with either a cell-free culture supernatant of *B anthracis* absorbed to aluminum hydroxide (anthrax vaccine adsorbed [AVA]) or recombinant protective antigen. The AVA vaccine is currently in use by the US military. The efficacy of this vaccine in humans was established in the mid-1950s in a cohort of 1249 mill workers in New Hampshire and Pennsylvania who processed raw imported goat hair.[15] The recombinant protective antigen vaccines are currently under development.

The recent outbreaks of inhalational and cutaneous anthrax have brought an ancient disease into the arena of high-tech medicine. This juxtaposition is an important reminder on the one hand of the levels of sophistication of the currently available armamentarium of diagnostics and therapeutics, and on the other hand of the importance of the fundamentals of sound clinical medicine. Because of the advances in imaging, microbiology, antibiotics, and critical care, certain patients have survived who, in a different era, almost certainly would have succumbed to this disease. However, this might not have been possible without the insight gained from taking a careful history, including an occupational and environmental history, and having a high index of suspicion for a rare disease. Rapid dissemination of information via the Internet also has been invaluable in keeping the public informed and physicians aware of the latest developments and recommendations in a rapidly evolving story. The CDC's bioterrorism Web site (http://www.bt.cdc.gov) has been a consistent source of the latest information and recommendations.

There is no reason to believe this will be an isolated act of bioterrorism. In fact, it is likely that additional attacks involving *B anthracis* and perhaps other pathogens will occur. Each will present the health care community with a new set of challenges and a need for rapid dissemination of reliable, up-to-date information. To successfully deal with these challenges, prompt sharing of information among law enforcement authorities, public health officials, and front-line health care providers will continue to be essential. The alertness, open-mindedness, and sound clinical judgment of physicians and other health care professionals will be critical to the successful public health response to current and future threats.

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Initiating Antiretroviral Therapy During HIV Infection

Confusion and Clarity

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HIGHLY ACTIVE ANTIRETROVIRAL THERAPY (HAART) has changed the landscape of human immunodeficiency virus (HIV) care in the developed world. Many patients with access to antiretroviral therapy (ART) have benefited from the dramatic reductions in mortality and morbidity, and HIV disease has become one of relative chronicity for most but not all infected patients.[1-3]

The success of HAART has now led to research into approaches to rid virally suppressed patients of residual HIV reservoirs.[4] Nonetheless, as with several chronic diseases, the treatment often has significant adverse effects.[5] This is the case with virtually all drugs in the various classes of antiretroviral compounds approved by the Food and Drug Administration.[5] As such, physicians have dealt with a pendulum effect in decisions regarding when to initiate therapy during HIV infection.[5-7]

Following the development of HAART, many physicians were quite aggressive in treating patients at virtually any stage of this human retroviral disease, almost regardless of the CD4 T-lymphocyte count and plasma HIV RNA level. Because of the increasingly reported serious adverse effects of the diverse drug constituents of HAART, studies were conducted to attempt to determine the time at which initiation of ART was most efficacious, based on clinical end points and surrogate markers. Clinical guidelines[5-7] are now suggesting potential benefit in initially withholding ART for certain therapy-naive patients based on baseline CD4 T-lymphocyte counts and plasma viral RNA levels. Nonetheless, this approach has remained extremely controversial in clinical retrovirology. In this issue of THE JOURNAL, Phillips et al[8] and Hogg et al[9] report 2 large studies that add some clarity to this contentious issue.

The article by Phillips et al[8] examines the correlation between the plasma HIV RNA response to ART and baseline CD4 T-lymphocyte counts and plasma HIV RNA levels. This analysis of 3 large cohort studies in Europe evaluated 3430 therapy-naive patients. The authors found no difference in achieving undetectable plasma viral RNA levels, defined as less than 500 copies/mL at 32 weeks, regardless of baseline CD4 T-lymphocyte count or plasma HIV RNA level. Of note, a relatively large percentage (85%) of the total patients in this study achieved this level of viral suppression at 32 weeks. There was also no difference in viral rebound, regardless of baseline CD4 T-lymphocyte count or plasma viral load. However, a baseline plasma viral RNA level greater than 100 000 copies/mL did yield a slower rate of viral suppression after treatment.

See also pp 2560 and 2568.

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