

# A Primer on Biological Weapons for the Clinician, Part I

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## A BSTRACT

Although the thought of an outbreak of disease caused by the intentional release of a pathogen in a major American city was alien a decade ago, the purposeful release of anthrax via the US Postal Service and the resulting deaths from inhalation anthrax have caused a sea change in thinking about biological weapons and "bioweaponers." Most experts agree that a biological attack is imminent and the toll in suffering and death potentially great. In the event of a bioterrorist attack, the emergency physician and the hospital will most likely be the first clinical responders. However, some biologic agents produce initial symptoms that are nonspecific and thus may not have a high index of suspicion until severe morbidity or fatality results. It is imperative, then, that individual outpatient and ambulatory care providers consider biologic agents whenever a patient presents with nonspecific constitutional symptoms. This is particularly true of physicians whose practices are comprised mainly of elderly or older adult patients. Internists, family physicians, geriatricians, and others who care for elderly people will face unique clinical challenges when faced with an attack involving a biologic agent. The purpose of this article is to address the needs of internists, family physicians, geriatricians, and their counterparts with concise and current information on the Centers for Disease Control Category A pathogens, taking into account diagnostic challenges germane to elderly populations. (*Adv Stud Med.* 2003;3(2):75-86)

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**T**he use of microbes or viruses to wreak panic and death upon human populations dates back to antiquity. Probably the best-known example comes from the Book of Exodus in the Bible, which recounts 10 plagues visited upon the

Egyptians. Some medical historians and epidemiologists posit that the fifth and sixth plagues described in the Book of Exodus (the "murrain" and the "boils," respectively) were an outbreak of cutaneous anthrax, first in domesticated animals, then in their owners.<sup>1</sup> Variola, or smallpox, has been a bane to humans since prehistoric times. Centuries later, smallpox was deployed in the new world to decimate indigenous populations.<sup>2</sup> *Clostridium botulinum* toxin, long identified as a natural cause of food-borne disease, was not used as a biological weapon until the first half of the 20th century.<sup>3</sup> Today, almost 2000 years after the Biblical scourges, the world is still a place where biologic agents are used to cause death and destruction, the most recent event being the intentional release of anthrax through the US postal system in October 2001, resulting in over 20 infections and 5 deaths.<sup>4,6</sup>

Until recently, most educational programs on biologic agents have focused on "first responders" such as emergency medical technicians and public health workers, largely ignoring "front-line" caregivers, such as emergency department personnel, dermatologists, infection control personnel, pathologists, and the staff of public health organizations.<sup>7,8</sup> However, one program, developed by the University of Alabama School of Medicine's Center for Disaster Preparedness and sponsored by the Agency for Healthcare Research and Quality, uses sophisticated Internet-based technology to present case scenarios designed to teach these providers to recognize and manage a germ warfare event.<sup>9</sup> Increasingly, Internet sites such as the Centers for Disease Control (CDC) site on biological agents<sup>10</sup> and the bioterror sections of the American College of Physicians — American Society of Internal Medicine (ACP-ASIM) (<http://www.cdc.acponline.org/bioterro/>) site are aimed at primary care physicians.<sup>11</sup> Most other sites all but ignore an increasingly important segment of the physician population: internists, family physicians, and geriatricians — those who see and treat most of the elderly in this country.

There can be no ignoring the fact that the American healthcare infrastructure is woefully unprepared for the mass casualties that would result from a biological weapons deployment.<sup>12</sup> And, as would be expected, internists, family physicians, and geriatricians face particularly daunting challenges if such an event occurs. Alarming, there is a dearth of information tar-

geting these physician groups. One survey of nearly 1000 family physicians found that only one fourth felt prepared to recognize and treat the victims of a biological attack. This study concluded by recommending "more training in bioterrorism preparedness and easy access to public health and medical information in the event of a bioterrorist attack."<sup>13</sup> In addition, a review of the online offerings of professional societies for geriatricians revealed no information about the effects on senior citizens of a biological attack resulting in mass casualties.<sup>14,15</sup>

Although it cannot be disputed that emergency department physicians are at the leading edge of the "front-line" clinicians who will be the first to recognize and treat victims of a biological attack, the initial signs and symptoms of many of the most deadly agents are often so subtle and nonspecific (usually prototypical of influenza) that many victims will present to a primary care or urgent care clinic for treatment of "flu." It is also likely that early victims may present with nonspecific symptoms that mimic other common viral or bacterial maladies, such as bronchitis. If primary care clinicians and other practitioners who care for the elderly are not properly educated on the recognition and management of a biological attack, these "sentinel" victims of biological warfare may thus go unrecognized until large numbers of casualties occur.

#### *SYNDROMIC DIAGNOSTIC APPROACH*

Primary care practitioners and geriatricians treat elderly and chronically ill adults who may present with prodromal symptoms of a viral or bacterial infection that mimics illnesses they have suffered in the past. The "had it before, got it again" method of medical decision making often employed with older, chronically ill patients would likely prove inaccurate and must be replaced by a syndromic diagnostic approach. Some now advocate this diagnostic method, which focuses on the combination of symptoms a patient reports and the signs observed by the physician, as the most accurate method of recognizing a biological attack.<sup>7</sup> Because of the unavailability of laboratory tests in low-income areas, the syndromic approach was adopted by the World Health Organization (WHO) in 1991 for diagnosing sexually transmitted infections (STIs).<sup>16,17</sup> (Syndromic diagnosis may also prove useful for diagnosing other emerging infections, such as the rapidly proliferating West Nile Virus.) Although it is not clear that a syn-

dromic approach will be effective in helping physicians and other healthcare workers recognize a biological attack, its usefulness in other areas of medicine indicates that it has significant potential to do so.<sup>18</sup>

The purpose of this 2-part article, then, is to introduce internists, family physicians, and geriatricians to the concept of syndromic diagnosis and to provide approaches for recognizing and treating suspected victims of a biological attack, while keeping in mind the challenges germane to their respective fields of practice. Currently, the CDC recognizes 3 classes of biological warfare agents (A, B, C), which are ranked alphabetically according to virulence and potential to cause public harm. This article will focus only on the Category A agents because they:

- 1) are easily weaponized,
- 2) confer high mortality when contracted, and
- 3) have the greatest potential to cause widespread public panic and social disruption (Table 1).

(Please see <http://www.bt.cdc.gov> for listings of Category B and C agents, as well as comprehensive information on bioterrorism.) Part 1 of this series will examine 3 of the Category A agents: anthrax, smallpox, and botulism.

### CLINICAL CONSIDERATIONS UNIQUE TO THE ELDERLY

The proportion of Americans over the age of 65 years continues to increase rapidly. Not surprisingly, infectious disease is primarily responsible for approximately 40% of deaths in persons over age 65 years. However, it is often a secondary cause of mortality as well. There are several elements that contribute to the susceptibility of elderly persons to infectious diseases, including biological changes, cultural factors, and sociological factors. One must further consider that America's senior citizens are not only living longer, but they are remaining active, working members of society for years, even decades after their antecedents would have entered retirement.

Even though an older person may appear vigorously healthy, the process of aging causes marked changes in the immune function of all geriatric patients. T-cell function gradually decreases, eventually causing anergy in up to 30% of the elderly. The causes of senescent immune dysfunction are not known with certainty, but recent studies point to dys- or down-

regulation of hormones, such as dehydroepiandrosterone and thyroid-stimulating hormone. Additionally, nutritional status plays an important role in maintaining healthy immune function. Up to 60% of elderly patients experience protein-energy undernutrition (PEU). Even those patients who are mildly undernourished have demonstrated deficient immunologic responses. Furthermore, concomitant deficiencies of micronutrients, particularly vitamin D, which requires regular exposure to sunlight, are also common among the elderly and infirm, and adversely affect immune function.<sup>19</sup>

While the healthy elderly person's immune function declines over time, those who have one or more comorbid illnesses suffer even greater insults to their immune systems. Diseases such as chronic lung or coronary artery disease can accelerate immune dysfunction and leave the patient with less "metabolic reserve" for combating infections. A classic example of an infectious illness that is markedly affected by coexisting chronic disease is community-acquired pneumonia. In younger patients (generally younger than 50 years old), this disease is almost always treated on an outpatient basis, yet the elderly are 3 times more likely to die of this common illness, partially as a result of the factors described above.<sup>19</sup>

Presentation of illness in the elderly population is often atypical and confounding.<sup>20</sup> Using the example of community-acquired pneumonia, altered mental status or falls may be the heraldic sign of a pulmonary infection.<sup>21</sup> Furthermore, fever, the sign that is considered the hallmark of infection in the general population, does not always occur in the older person with bacteremia

Table 1. CDC Category A Biological Warfare Agents

|   |
|---|
| <i>Bacillus anthracis</i> - Anthrax           |
| Variola - Smallpox                            |
| <i>Clostridium botulinum</i> toxin - Botulism |
| <i>Francisella tularensis</i> - Tularemia     |
| <i>Yersinia pestis</i> - Plague               |
| Viral hemorrhagic fevers (VHF)                |

or viremia. Baseline dementia or other cognitive impairment often further confounds the diagnosis of an infection.<sup>22</sup>

Thus, it is clear from the small body of knowledge we have about the immunophysiology of the elderly that they will present the internist, family physician, or geriatrician with a plethora of diagnostic challenges in the event of an attack with a biological agent.

## BACILLUS ANTHRACIS

### BACKGROUND

A zoonotic disease of herbivores, anthrax is a ubiquitous, soil-dwelling, gram-positive rod capable of forming spores. Although no transmission of anthrax from person to person has been documented, the disease can be contracted during exposure to infected animals, animal products, or industrial sources. Its pseudonym, "woolsorters disease," refers to the cutaneous and inhalational forms of infection that plagued workers in the garment industry during Britain's 19th-century industrial apogee. Primary meningitis and gastroenteritis associated with anthrax have been reported, but they are extremely rare and much less likely to be the presenting forms in the wake of a biological attack than inhalational anthrax; however, all forms of the disease will be reviewed here.

### CUTANEOUS ANTHRAX

Although some authors estimate that over 90% of natural anthrax cases occur in the cutaneous form, and clinical reports from patients who survived the postal service attack indicate that they initially contracted the inhalational variant,<sup>23,24</sup> some postal workers were infected via the skin. Patients who contract cutaneous anthrax usually have a history of occupational exposure, and the organisms are introduced at the site of a pre-existing break in the skin, such as a cut or scratch. Within 2 to 3 days of infection, a small papule may erupt with or without a vesicle. The lesion progresses to an ulcer surrounded by edema, then to the familiar black eschar. Bacterial (usually staphylococcal) superinfection can occur. The mortality rate for untreated victims is higher than 20%.<sup>25,26</sup>

### GASTROINTESTINAL ANTHRAX

Due to more fastidious food handling practices, the gastrointestinal (GI) version of *B anthracis* is rarer in developed nations than poorer ones. However, the first bioterrorist attack in the United States was attempted in

1984 by a religious cult in Oregon, who tainted salad bars with salmonella.<sup>27</sup> Therefore, intentional GI anthrax infection is plausible and warrants mention. Upper GI tract involvement is characterized by ulcerations of the mouth or esophagus. Nausea and vomiting often denote lower tract disease. Sepsis can occur if treatment is delayed.<sup>28</sup>

### INHALATIONAL ANTHRAX

The inhalational form of anthrax was once an infectious disease relic, worthy of mention only as a phenomenon of historical interest. Indeed, from 1979 to 1999, an average of only 1 case per year was reported to the CDC.<sup>29</sup> However, its deliberate and lethal deployment in October 2001 caused a surge of intense interest in the epidemiology and treatment of anthrax.<sup>6</sup>

When anthrax spores are aerosolized near human populations, those from 2 to 5 microns in size are capable of reaching the distant airways and aveoli, while larger spores are cleared by the mucociliary transport mechanisms of the upper airways.<sup>30</sup> If distal pulmonic infection occurs, the spores eventually germinate and release large amounts of anthrax toxin, as well as capsular antigens, which are the main elements of its virulence.<sup>29</sup> Anthrax toxin is composed of 3 proteins: edema factor, protective antigen, and lethal factor. When released in sufficient quantity, these compounds quickly overwhelm local immunologic defense mechanisms. Mediastinal lymph nodes are the usual primary target, but the infection then quickly spreads to the systemic circulation, causing fulminant sepsis and death if left untreated or if treatment is delayed.<sup>26</sup>

### CLINICAL PRESENTATION

The clinical presentation of inhalational anthrax consists of 2 phases<sup>31</sup>:

*Phase 1:* Approximately 4 days after initial infection, patients will present with myalgias, malaise, fatigue, fever, GI symptoms, and perhaps a nonproductive cough. Hemorrhagic meningitis may occur in up to 50% of victims. The insidious nature of the early phase of the disease is marked by the fact that these symptoms may improve before they lead to the second, often fatal, stage of the infection.

*Phase 2:* This phase, which can last 24 hours, is marked by the sudden onset of respiratory distress, hypoxemia, and cyanosis. Stridor may occur due to tracheal compression of grossly enlarged mediastinal lymph

nodes. Chest radiography classically shows a widened mediastinum and pleural effusions. Unfortunately, the radiographic presentation of anthrax is not unique; other agents such as histoplasmosis or tuberculosis must be included in the differential diagnosis.

#### CLUES TO DIAGNOSIS IN THE ELDERLY

The deliberate infection of approximately 20 persons via the US postal system in October 2001 provided much information from which experts derived syndromic clues to the diagnosis of inhalational anthrax<sup>32</sup>:

- Relationship to a possible source (eg, postal workers exposed to tainted mail)
- Clinical features such as drenching sweats and GI symptoms not usually seen with influenza or other infections
- Radiographic findings (eg, widened mediastinum, pleural effusions)
- Rapid progression to sepsis
- Isolation of *B anthracis* in patients with similar clinical presentation.

The clinician must consider that the early symptoms of inhalational anthrax are very non-specific. For example, elderly patients with chronic obstructive pulmonary disease (COPD) may present with malaise and cough, which the clinician may attribute to chronic bronchitis or a viral upper respiratory illness. Even relatively healthy older persons are more susceptible to community-acquired, self-limited viral illnesses that mimic influenza (eg, respiratory syncytial virus, rhinoviruses, adenoviruses, parainfluenza virus, etc)<sup>33</sup> than the general population. Therefore, soon after an attack, the clinician may not suspect an agent of biological warfare is the source of infection. The key is to recognize the constellation of symptoms in their appropriate context. Has one patient presented with a flu-like illness or have several experienced such symptoms in a relatively short period of time? Are any of the presenting symptoms unusual or concomitant with anthrax exposure as delineated above? Table 2 compares symptoms of anthrax with those of influenza and nonspecific viral syndromes (NSVS).

#### LABORATORY DIAGNOSIS

Gram stain of blood culture or lesion specimen are the recommended tests for confirming a diagnosis of anthrax.<sup>27</sup> Gram stain of blood from individuals with more advanced disease usually reveals large Gram-positive rods. Sputum studies

are rarely revealing; cerebro-spinal fluid (CSF) microscopic inspection may show bacilli if meningitis accompanies the primary illness.<sup>28</sup> According to CDC guidelines, nasal swabbing should not be used as a diagnostic test to rule out infection.<sup>35</sup> The test may be of epidemiological utility but has no clinical role at present. Any patient suspected of having anthrax should have blood and other fluid samples sent to a confirmatory laboratory that is part of the Lab Response Network for Bioterrorism (LRN).<sup>25</sup> A state or local health department or the CDC will be able to direct the clinician to a laboratory that is part of the network within his or her region. (For state and territorial public health laboratory-contact information, see [http://www.aphl.org/docs/clinical\\_lab\\_alerts/statelabcontacts.pdf](http://www.aphl.org/docs/clinical_lab_alerts/statelabcontacts.pdf).)

#### TREATMENT

Some controversy surrounds the antibiotic choice and duration of treatment for anthrax. There are no published data to support different treatment strategies for the elderly or infirm. Thus, from a generic point of view, all recommendations indicate that early administration of antibiotics and aggressive supportive care are cornerstones of therapy; general treatment guidelines are outlined below.

Table 2. Symptoms/Signs of Anthrax vs Flu vs Nonspecific Viral Syndrome<sup>33,34</sup>

| Symptom, Sign   | Inhalational Anthrax | Influenza | Nonspecific Viral Syndrome |
|-----------------|----------------------|-----------|----------------------------|
| Fever           | +++++                | +++++     | +++                        |
| Myalgias        | +++                  | ++++      | ++++                       |
| Rhinorrhea      | +/-                  | ++++      | +++                        |
| Headache        | ++                   | +++       | ++++                       |
| Chest pain      | +++                  | +         | +                          |
| Nausea/vomiting | ++++                 | +/-       | +/-                        |
| Odynophagia     | +                    | +++       | +++                        |
| Malaise         | +++++                | ++++      | ++++                       |
| Dyspnea         | ++++                 | +/-       | +/-                        |

+/- = <= 10%; + = 10-20%; ++ = 20-40%; +++ = 40-60%; ++++ = 60-80%; +++++ = 80-100%

Official antimicrobial therapy in adults:<sup>36</sup>

- 1) Contained casualty setting
  - a. Ciprofloxacin 400 mg IV\* q 12 h or
  - b. Doxycycline 100 mg IV\* q 12 h

PLUS

- 1-2 additional antibiotics to which *B anthracis* is sensitive
- 2) Mass casualty setting/post exposure prophylaxis
  - a. Ciprofloxacin 500 mg po q 12 h or
  - b. Doxycycline 100 mg po q 12 h

PLUS

Amoxicillin, 500 mg po q 8 h†

\*May switch to po when clinically indicated.

†May be started only after 14 days of fluoroquinolone or doxycycline.

Ciprofloxacin has been the first choice among antimicrobials to treat anthrax and is certainly the most well known. However, doxycycline also is effective, especially for patients with central nervous system (CNS) involvement because it penetrates the blood-brain barrier better than ciprofloxacin. Other fluoroquinolones have not been widely studied but are thought to be effective. For example, levofloxacin is thought to be as efficacious as ciprofloxacin. First-line agents should be combined with other antimicrobials to which anthrax is known to be sensitive (eg, rifampin, vancomycin, clarithromycin).<sup>36</sup> Amoxicillin can be used for postexposure prophylaxis (PEP).<sup>36</sup>

Published guidelines recommend the duration of therapy should be 60 days, although some researchers recently advocated either:

- 1) Antimicrobial therapy for 100 days or
- 2) 40 or more days of antimicrobials, combined with 3 doses of anthrax vaccine for 4 weeks. There are no known cases of inhalational anthrax resulting from postexposure treatment.<sup>34</sup>

#### ANTHRAX VACCINE

The anthrax vaccine is not available to the general population and is not recommended for use unless a person has a high likelihood of anthrax exposure. However, per CDC guidelines, vaccination is recommended as postexposure prophylaxis for persons with known exposure to inhalational anthrax, but only under investigational new drug protocols. It is thought that PEP vaccination may reduce the length of antimicrobial therapy in some patients. The

CDC provides no data on treatment for geriatric patients or those with chronic illnesses.<sup>37,38</sup>

#### SMALLPOX (VARIOLA MAJOR AND MINOR)

##### BACKGROUND

Another malady familiar to the ancient world, smallpox has caused human death for eons and has been reported on every continent except Antarctica.<sup>39</sup> Its use as a bioweapon may first have occurred more than 600 years ago when the Spanish explorer Francisco Pizarro exposed the Incans of South America by presenting them with a "gift" of contaminated clothing.<sup>2</sup> Paradoxically, this disease, one of the most deadly human scourges, was declared "eradicated" by the World Health Organization in May of 1980; routine vaccinations ceased in the early 1970s. However, both the United States and the former Soviet Union maintained small quantities for research purposes.<sup>40-43</sup>

Despite the 1972 Biological Weapons Convention banning the development or procurement of biological weapons, US intelligence sources have documented that in the former Soviet Union, research on smallpox as a biological weapon was, ironically, undertaken in the year of its "eradication."<sup>41</sup> More alarming, after the disintegration of the USSR in 1992, many Soviet bioweapons experts, then jobless, were thought to have sold their services to potentially hostile nations or states, now presumed to harbor terrorist groups.<sup>28</sup>

Smallpox could be (and has been) a very effective biological weapon, primarily because<sup>2,44</sup>:

- 1) Smallpox is easily aerosolized.
- 2) The infective dose of the virus is very small.
- 3) Detailed, updated clinical data on the virus are scarce.
- 4) There is no pharmacotherapy proven effective for smallpox infection.
- 5) The mortality of variola major is extremely high.

Furthermore, although most US citizens over 30 years of age were vaccinated against smallpox during the WHO eradication effort, some experts contend there is likely little residual immunity in the elderly population to protect victims from an intentional release of the virus.<sup>2</sup> The subject of lingering immune protection by vaccinia, however, is controversial. Other experts have demonstrated immune longevity of 50 years.<sup>45</sup> It is thought that in previously endemic areas, repeated exposure may have augmented postvaccination immunity.<sup>46</sup> Thus, since there is

no consensus (or prospective data) on the immune status of previously vaccinated adults, it would be prudent to assume that a previously vaccinated individual exposed to smallpox has minimal immunity.

### CLINICAL PRESENTATION

The clinical hallmarks of smallpox infection are no longer presented in standard infectious disease texts, so only historical information is available to the clinician.<sup>39</sup> Additionally, some bioweapons authorities believe that more virulent and vaccine-resistant strains have been developed, possibly making it difficult to predict the clinical course of those infected with aerosolized smallpox during an attack.<sup>2</sup> Nonetheless, the historical characteristics of the disease are described here.

Smallpox infection occurs from the direct inhalation of aerosols from infected patients. Indirect infection from heavily contaminated fomites also is possible. The incubation period has been reported to average 10 to 14 days, but periods as short as 7 days and as long as 19 days have been described.<sup>39</sup> The postincubation viral prodrome has been reported to be the acute onset of high fever (up to 104°F), malaise, headache, and back pain. Some reports have noted associated delirium. The well-described centrifugal (peripheral→central) rash of smallpox begins in the oral mucosa (buccal, palatal, or pharyngeal). The rash then spreads to the face and forearms and progresses centrally, in what is termed a “synchronous” fashion. That is, all the lesions change morphology at approximately the same time. The rash morphology progresses from papules, to vesicles, then to pustules, and finally to crusted lesions. When oral lesions appear, the risk of person-to-person contact is greatest.<sup>44</sup> The onset and progression of the rash is relatively slow, occurring over a 9- to 10-day period. A milder, much less common variant (variola minor) occurs in those who have previously been inoculated but now have declining immunity.

After an individual is exposed to aerosolized smallpox, virions immediately seed the respiratory tract and then the regional lymph nodes. Following this primary viremia is a latent phase lasting up to 2 weeks, during which time the virus replicates in the major organs of the body. The majority of viral replication (and thus, toxicity) occurs in the liver and spleen.<sup>9</sup> Morbidity and mortality are the result of overwhelming viremia, leading to disseminated intravascular

coagulation, septic shock, cardiovascular collapse, respiratory failure, or multiorgan system failure.<sup>28</sup> Secondary bacterial infection also is likely to be contributory in the majority of cases. The mortality of fulminant (variola major) smallpox infection is as high as 60%, while that of the minor variant has been reported to be as low as 1%.<sup>44</sup>

### CLUES TO DIAGNOSIS IN THE ELDERLY

Smallpox has the potential to be the deadliest of the pathogens that can be readily weaponized, and the elderly or immunocompromised are especially at risk. Some authors posit that the clinical presentation of smallpox is so unique that it would be difficult for the clinician to mistake it for other entities that cause a disseminated rash.<sup>2</sup> However, others have argued that dozens of conditions have symptoms that could confound the diagnostician. One author lists the following entities as having been most frequently mistaken for smallpox<sup>44</sup> (Table 3):

- Chickenpox (varicella)
- Herpes zoster
- Vaccinia (cowpox)
- Insect bites
- Drug eruptions (eg, Stevens-Johnson syndrome)
- Disseminated herpes simplex

Of these, severe chickenpox is most often the causative and confounding agent in younger individuals. One must remember, however, that older

Table 3. Smallpox vs Chickenpox vs Herpes Zoster: Distinguishing Clinical Features

| Feature           | Smallpox     | Chickenpox    | Herpes zoster       |
|-------------------|--------------|---------------|---------------------|
| Incubation period | 7 to 17 days | 10 to 21 days | Latent re-infection |
| Prodrome          | Yes          | Yes           | Yes                 |
| Prodrome duration | 2 to 3 days  | 1 to 2 days   | 2 to 3 days         |
| Prodrome symptoms | HA/BA/F/M    | F/M           | Dermatomal pain     |
| Rash              | Macules      | Maculopapules | Vesicular lesions   |
| Rash distribution | Centrifugal  | Truncal       | Dermatomal          |
| Rash progression  | Synchronous  | Asynchronous  | Dermatomal          |

HA = headache; BA = backache; F = fever; M = malaise.

individuals with an isolated vesicular or papular rash would more be more apt to have contracted herpes zoster in which the rash erupts in a dermatomal distribution. By contrast, the rash of variola erupts in a centrifugal pattern, beginning in the mouth and spreading to the upper extremities, whereas the chickenpox rash is usually seen first as patches of vesicles on the trunk. Furthermore, the smallpox rash is characteristically synchronous, meaning that all of the lesions progress from macules to scabs at the same time. In addition, the rash seen with chicken pox, in contrast to smallpox, progresses in an asynchronous fashion.<sup>28,44</sup>

Also, elderly patients presenting with delirium, fever, and headache might be diagnosed as having acute bacterial meningitis. The elderly often present with delirium due to other underlying medical conditions, pre-existing dementia, or adverse drug reactions.<sup>19</sup> Many elderly or immunocompromised individuals may not develop very high fever but present with delirium only. Therefore, careful history taking and syndromic awareness are keys to recognizing the symptoms of exposure to smallpox during a biological attack.

Thus, the astute clinician must be aware of:

- 1) the likelihood of a smallpox attack,
- 2) other similar cases reported in a hospital or community,
- 3) the key clinical features of the disease,
- 4) common agents that can be confused with smallpox, and
- 5) possible clinical presentations unique to older patients or those with immune dysfunction.

#### TREATMENT

An index case of smallpox constitutes a global public health emergency. Should a patient be suspected of having smallpox, she or he must be admitted to an intensive care unit room that has a negative pressure generator and high efficiency particulate air filtration system. All hospital workers must exercise airborne and contact precautions and all those at risk for exposure should be vaccinated. Individuals who cannot be vaccinated because of contraindications should not care for infected patients.<sup>44</sup> All healthy contacts should be vaccinated immediately.

The treatment for smallpox is supportive, although the antiviral medication cidofovir, used for the treatment of cytomegalovirus (CMV) retinitis, has been shown to be effective against other pox and DNA viruses in laboratory animal tests; in vitro activity against variola has been

observed as well.<sup>47,48</sup> Rifampin may also have some efficacy.<sup>9</sup>

Because of the risk to hospital workers and the lack of human trials demonstrating an effective treatment, home care has been proposed as a viable alternative to hospitalization in the wake of a smallpox attack.<sup>28</sup> However, this option is not currently recommended by public health officials.

#### VACCINATION

Current CDC guidelines state that the general population will not be vaccinated against smallpox. However, a large-scale public vaccination program would be initiated at the first sign of an outbreak of the disease, beginning with any immediate contacts who can be identified. Currently, only health care workers and other "first responders" and military personnel will receive the vaccine under the auspices of the US government.<sup>49</sup> Current thinking holds that individuals who contract smallpox may have their disease course ameliorated if they are vaccinated within 4 days of exposure.<sup>28</sup>

#### BOTULISM

##### BACKGROUND

Ironically, the toxin produced by *Clostridium botulinum* is both a Category A pathogen and a Food and Drug Administration-approved medical treatment. The most lethal toxin known to humans (theoretically requiring only 1 gram to kill 1 million individuals),<sup>28</sup> its use is approved to treat strabismus and cervical torticollis.<sup>3</sup> It has also gained popularity as an "off-label" drug for a variety of other medical conditions and cosmetic applications.

The use of botulinum toxin as an agent of bioterror is a modern phenomenon. Japan's infamous Unit 731 poisoned Manchurian prisoners with it in the 1930s. This is the first reported use of botulinum toxin to intentionally inflict harm.<sup>3</sup> The United States first developed botulinum toxin during World War II, in response to allegations that Nazi Germany had produced biological weapons containing the poison. In the early 1990s, Iraq is purported to have produced up to 20 000 liters of botulinum toxin for weaponization,<sup>28</sup> a sufficient quantity to thrice eradicate the human race.<sup>51</sup>

An obligate, spore-forming anaerobe, the gram-positive bacillus *Clostridium botulinum* is ubiquitous in soil. The toxin it produces is a 2-chained polypeptide of which 7 distinct types exist, conventionally named A through G. Types A, B, and E are usually responsible for

human cases and C and D affect only nonhuman animals.<sup>52</sup> Botulinum toxin exerts its effects by blocking acetylcholine release from the terminal membrane of presynaptic motor neurons, resulting in a descending flaccid paralysis. The 3 naturally occurring forms of botulism (food-borne, wound, and intestinal) cause fewer than 200 casualties each year in the United States (There were 138 instances reported in 2000, the last year for which complete data are available.<sup>52</sup>)

Despite the potency of botulinum toxin and efforts to weaponize it, this toxin is not an ideal biological weapon. Most experts posit that it would be deployed in aerosol form, which would be problematic because the toxin would likely degrade minutes after release. However, some scientists argue that the release of concentrated toxin over a point source (eg, a large outdoor public event such as a football game) could harm or kill 10% of those targeted. Furthermore, other forms of deployment, such as the intentional contamination of food supplies, might cause significant public panic and social disruption.<sup>3</sup> The fear that municipal water supplies would make an easy target is largely unfounded: tons of toxin would be required because the effects of dilution and chlorination processes used by many municipalities for water treatment would render the toxin ineffective.<sup>28</sup>

#### CLINICAL PRESENTATION

The effects of an intentional botulinum toxin release are distinct from those of other Category A agents: the toxin does not cause flu-like symptoms of fever, malaise, and myalgias. The natural forms can cause GI symptoms; however, experts assert the weaponized form would not.<sup>3</sup> The descending paralysis universally affects the bulbar musculature. In fact, the absence of a bulbar palsy rules out botulinum toxin as the offending agent. This distinct clinical triad distinguishes the symptoms of botulism from those of other diseases:

- Descending flaccid paralysis involving the bulbar musculature
- Absence of fever
- Clear sensorium

Patients with botulism may present with a syndrome that is classically termed the “4 Ds”:

- Dysphonia
- Dysarthria
- Diplopia
- Dysphagia

While each of the 3 toxins that affect humans causes very similar disease manifestations, the presentation will vary from patient to patient. Certain features of the bulbar palsies may mimic confusion or obtundation due to facial muscle paralysis. Older patients often present with altered mental status as the sentinel sign of other acute illnesses (dehydration, pneumonia, CNS infection, urosepsis, etc). Therefore, botulism intoxication, particularly in the elderly, may be misdiagnosed at early stages of the disease, unless there is a high suspicion of an intentional attack (or naturally-occurring outbreak). Botulism is often confused with other neurological conditions, such as Guillain-Barre syndrome or myasthenia gravis. It is worth noting that during a natural outbreak in Canada, 28 persons became ill and all of them were misdiagnosed, some as having factitious illness.<sup>3</sup>

#### CLUES TO DIAGNOSIS IN THE ELDERLY

Because these signs are usually manifest in other CNS diseases, elderly victims would perhaps be triaged as victims of stroke (dysarthria, dysphonia) or malignancy (dysphonia, dysphagia). Therefore, the astute clinician needs to know the cardinal clinical features of botulism poisoning (Table 4). In theory, an attack with botulinum toxin would result in a mass casualty event, and the staff of a medical facility would expect to see several cases within a small time frame.

Table 4. Botulism vs Stroke vs Delirium: Distinguishing Clinical Features

| Feature     | Botulism | Stroke   | Delirium |
|-------------|----------|----------|----------|
| Dysarthria  | Yes      | Yes      | No       |
| Confusion   | No       | Possible | Yes      |
| Diplopia    | Yes      | Possible | No       |
| Dysphonia   | Yes      | Possible | No       |
| Hemiparesis | No       | Yes      | No       |
| Dysphagia   | Yes      | Possible | No       |

### TREATMENT

There is no definitive treatment for botulism; however, supportive care is mandatory, particularly mechanical ventilation to counter respiratory muscle paralysis. Also, equine antitoxin should be given as soon as possible after botulism is suspected; it can be obtained from the CDC via local or state health departments.<sup>51</sup>

Vaccination is also an option, especially if botulism is highly suspected or diagnosed early, since administration of antitoxin may not only shorten the course or lessen the severity of the illness, but also may prevent neurological sequelae. Although anaphylaxis has been reported in vaccinated patients, the current recommended dose is lower than in the past. Regardless, any patient with known or suspected hypersensitivity should undergo a toxin challenge. A trivalent vaccine is available from state and local health departments or from the CDC.<sup>3,28</sup>

The symptoms of botulism poisoning can last for weeks, which places elderly patients at risk for nosocomial infections and long-term debilitation, especially since many patients will require enteral or parenteral nutrition. There are no published studies to date that recommend the elderly or immunocompromised patient should receive different therapeutic regimens for botulism poisoning.

### CONCLUSION

Biological weapons are no longer confined to a government laboratory or a writer's imagination. The use of biological weapons has increased in recent years, and the threat of more widespread use appears credible. In the event of an attack, primary care physicians will be challenged to diagnose and treat the victims. This may be particularly difficult in the elderly, in whom the symptoms and signs of infection caused by a biological agent may mimic those of more common illnesses. Therefore, internists, family physicians and geriatricians will need to be vigilant and to be well informed about the fundamental aspects of diagnosing and treating the victims of a bioweapons attack.<sup>3</sup>

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