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Recommended Citation

Howell JM, Mayer TA, Hanfling D et.al. Screening for inhalational anthrax due to bioterrorism: evaluating proposed screening protocols. Clinical Infectious Disease, 2004 Dec 15;39(12):1842-7.

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Screening for Inhalational Anthrax Due to Bioterrorism: Evaluating Proposed Screening Protocols

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Eleven known cases of bioterrorism-related inhalational anthrax (IA) were treated in the United States during 2001. We retrospectively compared 2 methods that have been proposed to screen for IA [1, 2]. The 2 screening protocols for IA were applied to the emergency department charts of patients who presented with possible signs or symptoms of IA at Inova Fairfax Hospital (Falls Church, Virginia) from 20 October 2001 through 3 November 2001. The Mayer criteria [1] would have screened 4 patients (0.4%; 95% CI, 0.1%–0.9%) and generated charges of $1900. If 29 patients (2.6%; 95% CI, 1.7%–3.7%) with ⩾5 symptoms (but without fever and tachycardia) were screened, charges were $13,325. The Hupert criteria [2] would have screened 273 patients (24%; 95% CI, 22%–27%) and generated charges of $126,025. In this outbreak of bioterrorism-related IA, applying the Mayer criteria would have identified both patients with IA and would have generated fewer charges than applying the Hupert criteria.

Eleven known cases of bioterrorism-related inhalational anthrax (IA) were treated in the United States during October and November 2001. After its analysis of 10 of these cases, the Centers for Disease Control and Prevention (CDC) issued diagnostic criteria for evaluating persons with possible IA [3]. The CDC criteria suggested that both a documented history of environmental or occupational exposure and clinical signs and symptoms of the disease were required for screening and treatment. Mayer et al. [1] retrospectively analyzed the 11 known cases of bioterrorism-related IA and applied the CDC criteria in an effort to determine whether these criteria would identify patients with IA. This analysis revealed that the CDC criteria would have selected 1 of the 11 anthrax cases for further diagnostic study or treatment. The CDC diagnostic criteria were revised to include a history of either environmental or occupational exposure and the presence of ⩾5 symptoms of the disease, plus fever and tachycardia (figure 1). These revised criteria would have selected 8 of the 11 anthrax cases for screening and treatment.

Hupert et al. [2] proposed a screening protocol entitled "Rapid Identification of Presumptive Cases of Inhalational Anthrax in the Setting of a Mass-Prophylaxis Campaign" (figure 2). In an effort to identify the utility of each of these screening protocols, we assessed their ability to identify patients with IA who presented to a large emergency department in which 2 documented cases of IA were successfully diagnosed and treated during the October–November 2001 outbreak in the Washington, D.C., area. We also assessed the total number of patients who would have been screened by these protocols, as well as the cost for such screening. Specifically, the questions we evaluated were: (1) Would applying each of these diagnostic approaches identify the patients with IA? (2) How many patients would be screened using each approach? (3) What are the financial charges of such screening?

METHODS

The research protocol was approved by the Inova Fairfax Hospital Institutional Review Board (Falls Church, VA). By consensus, we developed a list of emergency medicine diagnoses from the *International Classification of Disease, Ninth Revision* (ICD-9; table 1), that included all known symptoms and clinical presentations of acute pulmonary anthrax. With use of these IDC-9 diagnoses, we retrospectively reviewed emergency department patient records at Inova Fairfax Hospital for patients presenting from 20 October 2001 through 7 November 2001. This study period was the time period immediately after the

Received 23 June 2004; accepted 10 August 2004; electronically published 18 November 2004.

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Clinical Infectious Diseases 2004; 39:1842–7

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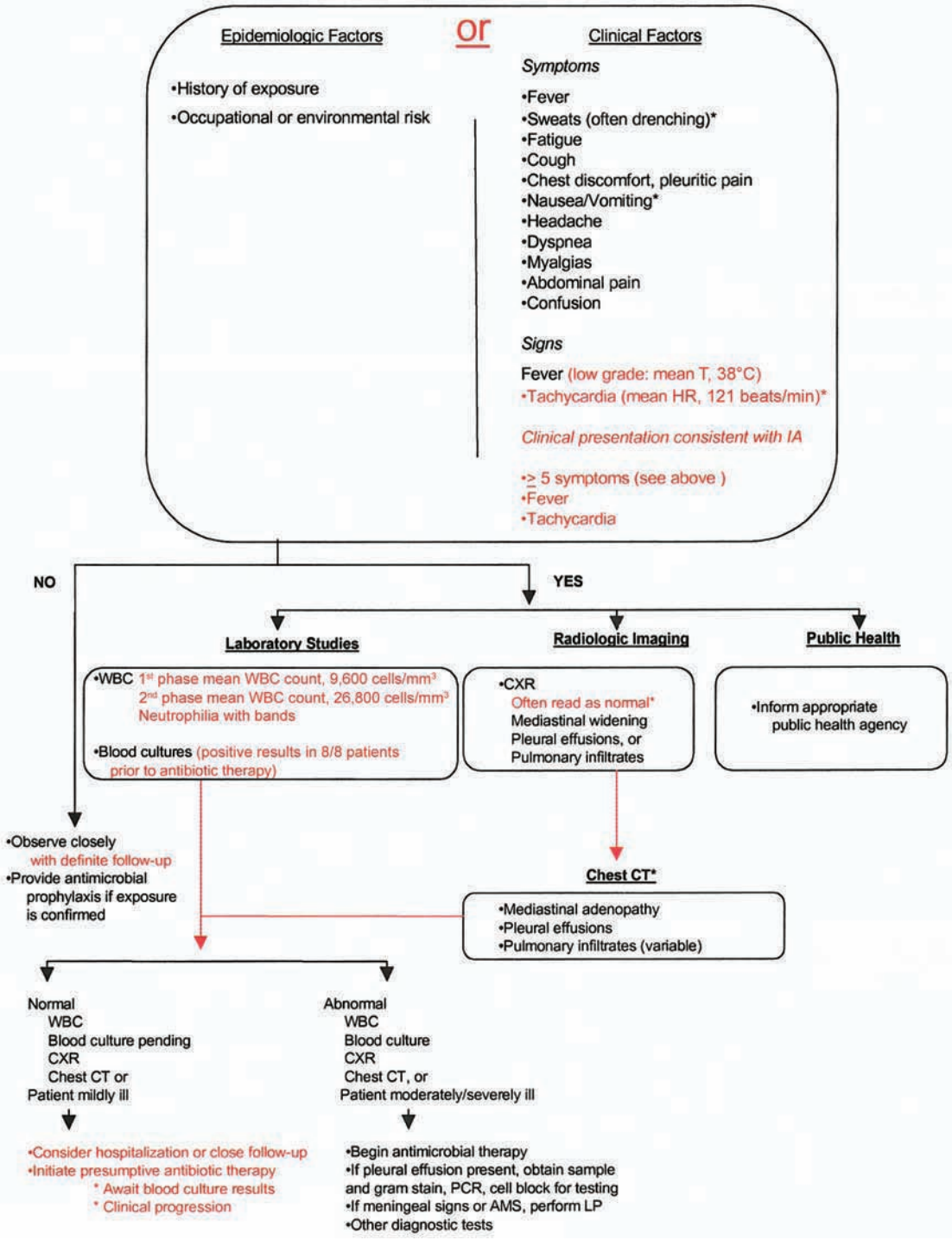

Figure 1. Revisions to the Centers for Disease Control and Prevention interim guidelines. AMS, altered mental status; CXR, chest radiograph; HR, heart rate; IA, inhalational anthrax; LP, lumbar puncture; T, temperature. *Feature not previously known to be associated with IA. Adapted and expanded from [2].

distribution of anthrax-contaminated letters through the US Postal Service and the diagnosis of IA in 5 patients who worked and resided in the Washington, D.C., metropolitan area. The Inova Fairfax Hospital emergency department is a level I trauma center, comprising an annual census of 72,000 adult and pediatric patients. We extracted data from those patient records that were identified by the screening process and entered these data into an Excel spreadsheet (Microsoft Excel 1997).

Table 2 lists the data extracted from each patient record. Clinical data were assumed to be present if they were listed in

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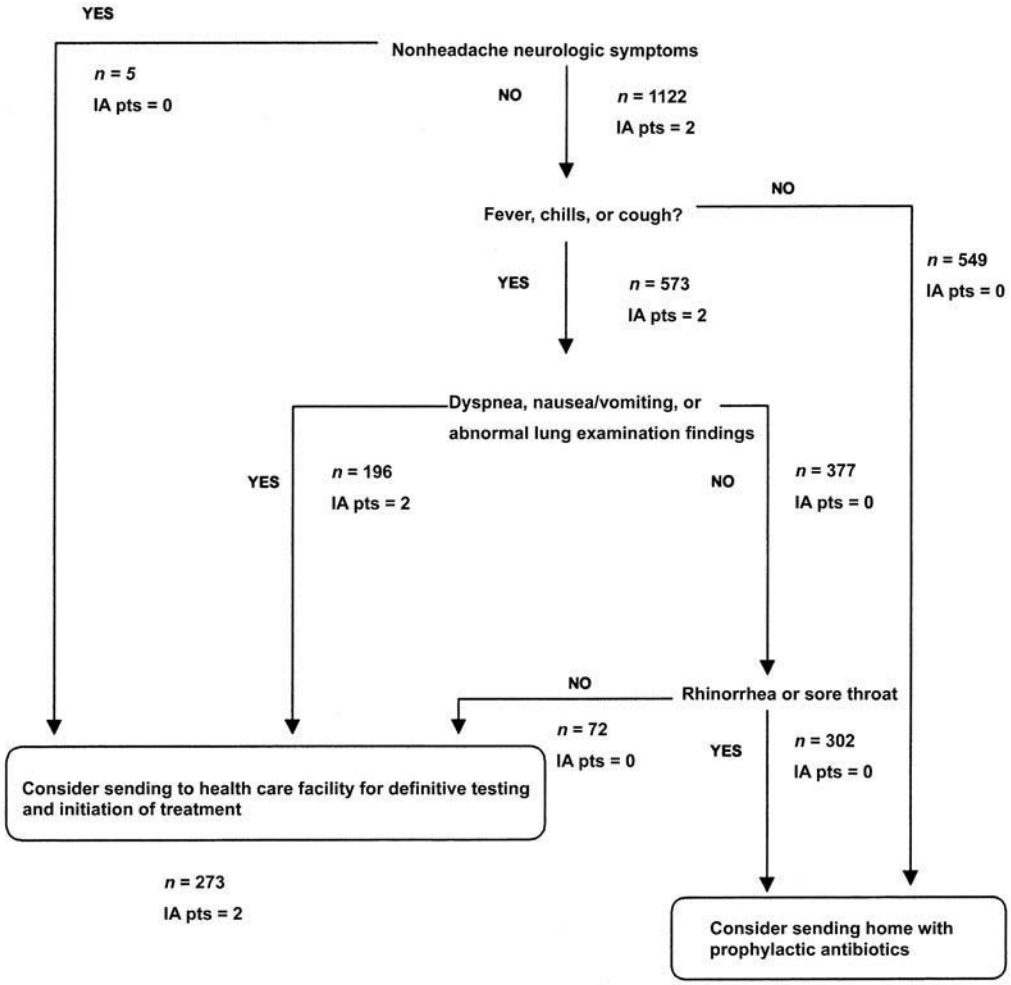

Figure 2. The Cornell protocol [2] applied to 1127 patients with symptoms of and/or exposure to inhalational anthrax (IA) presenting to emergency departments and evaluated during the 2001 bioterrorism-related outbreak of IA. IA pts, number of patients with documented inhalational anthrax; *n,* number of patients with symptoms of and/or exposure to IA.

the triage note, vital signs, patient history and physical examination results, or nursing notes, including fever (temperature, ⩾38°C) or tachycardia (heart rate, ⩾100 beats/min or greater than local age-defined limits for children). The percentages of subjects with each clinical symptom (table 2) were calculated from the total number of audited charts, not the total emergency department census for that time period.

Table 3 lists the data extracted from each patient record. The proposed revision of clinical criteria [3] defined a patient as eligible for pulmonary anthrax screening if he or she had either (1) a history of exposure to either a known or a suspected anthrax source, (2) a high-risk occupation (e.g., postal worker or Senate staff), or (3) fever and tachycardia and ⩾5 clinical symptoms (table 3).

We defined charges for anthrax screening as those associated with 1 complete blood cell count with manual differential, 1 set of aerobic and anaerobic blood cultures, and 1 posterior-anterior (with lateral) chest radiograph per patient. We did not include charges for chest CT, because these studies were performed only if chest radiograph findings or other clinical data strongly suggested IA. Charges for antibiotic prophylaxis were calculated by assuming that all patients who were identified by the screening protocols would be treated with generic doxycycline for 10 days or until blood culture results were confirmed to be negative. Drug charges were taken from *Red Book 2002: Drug Topics* [4]. Charges included hospital and professional fees. Charges were calculated using local values in 2003 US dollars. Descriptive statistics and 95% CIs were calculated. Data were analyzed using Minitab software, version 13.32 (Minitab).

RESULTS

During the study period, the daily emergency department census averaged 27% more than the mean daily emergency department census prior to the bioterrorism events of 2001. The total emergency department census during the study period

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Table 1. *International Classification of Disease, Ninth Revision* (ICD-9), codes used to identify for review the records of patients presenting to emergency departments with possible cases of inhalational anthrax.

Diagnosis	Code
Anthrax, Pulmonary	022.1
Anthrax NOS	022.9
Septicemia NOS	038.9
Meningitis, Viral NOS	047.9
Infection, Viral NOS	079.99
Meningitis NOS	322.9
Pharyngitis, Acute	462
Croup	464.4
Infect Up RSprt MLT Sites, Acute NOS	465.9
Bronchitis, Acute	466.0
Bronchio Acute D/T Oth Infct Organism	466.19
Sinusitis, Chronic NOS	473.9
Abscess, Peritonsillar	475
Disease, Nasal Cavity and Sinus NEC	478.1
Pneumonia, Organism NOS	486
Influenza with respiratory manifestations NEC	487.1
Bronchitis NOS	490
Bronchitis, Obstructive Chronic with Exacerbation	491.21
Emphysema NEC	492.8
Asthma NOS without Status Asthmaticus	493.90
Gastroenteritis/Colitis Noninfectious NEC	558.9
Syncope and Collapse	780.2
Fever	780.6
Malaise and Fatigue NEC	780.79
Headache	784.0
Shortness of Breath	786.05
Wheezing	786.07
Abnormality, Respiratory	786.09
Hemoptysis	786.3
Cough	786.2
Pain, Chest NOS	786.50
Painful Respiration	786.52
Pain, Chest NEC	786.59
Hiccough	786.8
Symp Inv Respiratory Syst/Chest NEC	786.9
Nausea and Vomiting	787.01
Nausea Alone	787.02
Vomiting Alone	787.03
Diarrhea NOS	787.91
Pain, Abdominal, Site NOS	789.00
Pain, Abdominal, Right Upper Quadrant	789.01
Pain, Abdominal, Left Upper Quadrant	789.02
Pain, Abdominal, Right Lower Quadrant	789.03
Pain, Abdominal, Left Lower Quadrant	789.04
Pain, Abdominal, Periumbilic	789.05
Pain, Abdominal, Epigastric	789.06
Pain, Abdominal, Site NEC	789.09

was 4259 patients. Of these, 1127 patients (26.5%; 95% CI, 25.1%–27.8%) had ICD-9 codes consistent with any signs or clinical presentations of IA. Each of these charts was reviewed under both of the screening protocols. The mean patient age was 35.1 years (95% CI, 33.5–36.7 years). A total of 513 (45.5%) of the patient records were for male patients (95% CI, 42.7%–48.4%). Two (0.2%) of the patients received a diagnosis of acute pulmonary anthrax (95% CI, 0.02%–0.6%). Table 2 shows the number of patient charts that listed each of 6 different clinical symptoms and shows the associated screening charges. Four patients (0.4%; 95% CI, 0.1%–0.9%) had ⩾5 clinical symptoms and fever and tachycardia (2 of these patients had pulmonary anthrax). Two hundred fifty patients (22.2%; 95% CI, 19.8%–24.7%) had high-risk occupations (i.e., they were either postal workers or senate staff). Nine patients (0.8%; 95% CI, 0.4%–1.5%) had a history of exposure to anthrax or a suspected anthrax substance. Eight of the 9 individuals who had a history of anthrax exposure were also members of the high occupational risk group. Of the subjects with occupational risk for pulmonary anthrax (i.e., postal workers and senate staff employees), 11 had ⩾4 clinical symptoms, and 239 had <4 clinical symptoms.

Of the 1127 patients, 4 (0.4%; 95% CI, 0.1%–0.9%) had ⩾5 symptoms of IA plus fever and tachycardia, including both of the patients with documented IA disease. Using the revised CDC criteria to screen and treat these patients would have resulted in charges of $1900. Twenty-nine patients (2.6%; 95% CI, 1.7%–1.7%) who had ⩾5 symptoms did not have fever and tachycardia. Screening and treating these patients would have resulted in charges of $13,325. The protocol suggested by Hupert et al. [2] would result in 273 (24%; 95% CI, 22%–27%) of 1127 patients being screened and treated, including both of the patients with IA. The cost of this screening would have been $126,025 (table 4).

DISCUSSION

Because the spectre of bioterrorism moved from a possibility to a reality in the fall of 2001, many voices have called for a proactive approach to providing clinical guidelines for the diagnosis and treatment of IA, as well as of other agents that

Table 2. Number of patients presenting to emergency departments with clinical symptoms referable to acute pulmonary anthrax, with associated charges.

No. of symptoms	No. of patients screened	Percentage of patients screened (95% CI) (n = 1127)	Associated charges, US$
⩾6	4	0.4 (0.1–0.9)	1,699.96
⩾5	29	2.6 (1.7–3.7)	8,924.79
⩾4	71	6.3 (4.9–7.9)	30,174.29
⩾3	240	21.3 (18.9–23.8)	101,997.60
⩾2	681	60.4 (57.4–63.3)	289,418.19
⩾1	1047	92.9 (91.3–94.3)	444,964.53

NOTE. Each patient screened was assumed to receive 1 complete blood cell count, 1 posterior-anterior and lateral chest radiograph, 1 set of blood cultures, and a 10-day course of generic doxycycline (100 mg b.i.d.).

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Table 3. Clinical data extracted from emergency department records from 20 October 2001 through November 2001.

Age
Sex
Occupation
Presence of fever
Presence of tachycardia
History of exposure to a known or suspected anthrax substance
Clinical symptoms of fever, sweats, fatigue, cough, chest discomfort, nausea, vomiting, headache, dyspnea, myalgias, abdominal pain, or confusion
Clinical diagnosis
Presence of abnormal findings of a lung examination

could potentially be used in a bioterrorist attack [1–7]. The study by Danzig [6] calls specifically for the development of such guidelines, as well as for the development of training scenarios for responding to outbreaks involving agents that might potentially be used in future bioterrorist attacks. Fortunately, as the 2001 outbreak showed, IA is a serious but treatable disease if it is detected and treated early in its course.

The development of screening and treatment protocols increases in importance when one considers the phenomenon of "reload," as delineated by Danzig [6] in a penetrating and insightful study commissioned by the National Defense University for the Department of Defense. Reload refers to the likely ability of attackers using biological weapons to avoid detection and "stockpile or replenish resources that permit repeated attack" [6, p. 2]. Thus, although making a kilogram of weaponized anthrax in the 1–5 micron range presents certain technical challenges, as Danzig indicates, "it is not a significant challenge for a terrorist organization that can make a kilogram to make 10 or 100 kilograms" [6, p. 2]. The phenomenon of reload thus raises the unpleasant but distinct possibility of large-scale atmospheric distribution of anthrax spores in multiple cities, either simultaneously or sequentially. Without planning scenarios and screening and treatment protocols, the surge capacity of the health care system (and of emergency departments, in particular) would be overwhelmed. Simply stated, given the phenomenon of reload, without effective screening and treatment protocols, our health care system would go quickly from "reload" to "overload." Our study evaluated existing screening and treatment protocols for patients who had possibly been exposed to IA by comparing them with a population of patients seen at one of the primary treatment facilities for patients with IA in the Washington, D.C., area after the October 2001 bioterrorism-related outbreak.

The criteria proposed by Mayer et al. [1] (the Inova Fairfax protocol) and by Hupert et al. [2] (the Cornell protocol) were each attempts to provide clear and concise screening mechanisms for the large number of patients likely to present for diagnosis and therapy after a bioterrorism-related outbreak. In an attempt to clarify the utility and cost of using the Inova Fairfax and Cornell protocols to screen and identify patients for treatment after possible exposure to *Bacillus anthracis*, we assessed the ability of these protocols to identify cases of IA in a busy emergency department during the 2 weeks following initial identification of patients with IA in the Washington, D.C., area. Both protocols identified the documented cases of IA seen at our institution, but the Inova Fairfax criteria would have screened only 4 patients at a cost of $1900, whereas the Cornell criteria would have screened 273 patients at a cost of $126,025. In the editorial accompanying the Cornell protocol, Sox [8] noted that "If a bioterrorism attack occurs in the meantime, we have a triage algorithm that seems safe, but is probably inefficient" (p. 1). Our study supports that statement, because 26% of patients with possible signs or symptoms of IA would have been screened by the Cornell protocol, compared with the ~0.5% of patients who would have been screened by the Inova Fairfax screening guidelines.

Using a simple checklist of IA symptoms offers several advantages over the 3-tier algorithm. First, a checklist approach assures that each of the recognized symptoms of IA is assessed in each patient, and, therefore, it better fits the concepts of syndromic surveillance. Second, the checklist approach avoids the necessity of an algorithm with multiple branch-points and instead focuses on the simple issue of labeling each patient as having or not having ⩾5 symptoms plus fever and tachycardia. Third, this analysis indicates that the Inova Fairfax criteria are more accurate and cost-effective than the 3-tier algorithm, be-

Table 4. Comparison of screening guidelines in terms of the total number and percentages of patients screened for inhalational anthrax (IA) and the associated charges.

Screening guideline	Identified patients with IA	No. of patients screened	Percentage of patients screened (95% CI)	Associated charges, US$
Inova Fairfax protocol [1]	Yes	4	0.4 (0.1–0.9)	1900
Cornell protocol [2]	Yes	273	24 (21.7–26.9)	126,025
Presence of ⩾3 clinical symptoms	Yes	240	21.3 (18.9–23.8)	102,000
Possible occupational and/or environmental exposure	Yes	250	22 (20–25)	106,250

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cause only 2 additional patients would have been screened if fever and tachycardia had been included among the symptoms, and only 27 additional patients would have been screened if fever and tachycardia had been deleted completely from the list of clinical factors. In contrast, the Cornell protocol would have resulted in 271 patients being screened who did not have the disease, with charges of $126,025.

Although the primary purpose of our study was not to address the effect of occupational or environmental exposure on screening and treatment, we did find that 250 (22%) of the 1127 patients evaluated were either postal employees or worked in the Hart Senate Office Building (i.e., the site of the anthrax-laden letter addressed to Senator Daschle.) Of these patients, 239 had $\leqslant$4 clinical symptoms of IA. However, 2 postal employees had $\geqslant$5 symptoms plus fever and tachycardia and had PCR-confirmed diagnoses of IA. In this admittedly limited sample, these data suggest that the use of occupation alone as a screening condition would have performed similarly to use of either the Cornell protocol or the criterion of $\geqslant$3 clinical symptoms of IA.

This study, like most, is subject to certain limitations. First, although it assesses the accuracy and cost among the population presenting to a specific emergency department, it is possible that these results may not apply to other populations. Second, because a rigorous patient questionnaire was not used proactively in the evaluation of patients with potential IA, it is possible that patients who appeared to be less seriously ill were questioned less extensively and may, in fact, have had more symptoms of IA than were captured in the medical record. If such questionnaires had been used, there might well have been more patients identified with $\geqslant$5 symptoms of IA, thereby increasing the percentage of patients screened. This screening approach (i.e., use of the tachycardia and fever criteria) should not be applied to patients with a heart block or a pacemaker, those who have received β-blockers, or those who have ingested antipyretics within 6 h before presentation. Finally, we do not know whether the criteria of $\geqslant$5 symptoms plus fever and tachycardia would apply in other outbreaks involving different strains of *B. anthracis*.

Notwithstanding these limitations, this study supports the concept that patients who may have been exposed to anthrax spores during this bioterrorism-related outbreak could have been safely screened for diagnosis and treatment on the basis of the presence or absence of $\geqslant$5 clinical symptoms of IA plus the presence of fever (temperature, $\geqslant$38°C) and tachycardia. This study also suggests that the proactive development of similar screening and treatment protocols that might be used in responding to a bioterrorism attack should be developed and disseminated to primary care physicians and emergency department physicians, as suggested by Danzig [6] and others.

Acknowledgments

Potential conflicts of interest. All authors: no conflicts.

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