

One-Year Health Assessment of Adult Survivors of *Bacillus anthracis* Infection

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IN 2001, BIOTERRORIST ACTIVITIES involving the US Postal Service infected 22 individuals with *Bacillus anthracis*.¹ Six survivors had manifested inhalational anthrax disease and 11 had cutaneous anthrax disease. Poorly defined and persistent health complaints among the survivors were reported in the news and by local health officials. However, long-term health problems had not been revealed in reports describing prior evaluations of persons infected by agricultural or industrial exposure to anthrax-contaminated animals or animal products.^{2,3}

Various exposures to traumatic events have been associated with medically unexplained somatic symptoms and poor physical functioning.⁴⁻⁹ Therefore, to better characterize the somatic symptoms, health status, and functional capacity of the bioterrorism-related anthrax survivors, we conducted a cross-sectional health assessment approximately 1 year after the onset of the infection.

METHODS

In collaboration with state and local public health agencies, a cross-sectional

Context Little is known about potential long-term health effects of bioterrorism-related *Bacillus anthracis* infection.

Objective To describe the relationship between anthrax infection and persistent somatic symptoms among adults surviving bioterrorism-related anthrax disease approximately 1 year after illness onset in 2001.

Design, Setting, and Participants Cross-sectional study of 15 of 16 adult survivors from September through December 2002 using a clinical interview, a medical review-of-system questionnaire, 2 standardized self-administered questionnaires, and a review of available medical records.

Main Outcome Measures Health complaints summarized by the body system affected and by symptom categories; psychological distress measured by the Revised 90-Item Symptom Checklist; and health-related quality-of-life indices by the Medical Outcomes Study 36-Item Short-Form Health Survey (version 2).

Results The anthrax survivors reported symptoms affecting multiple body systems, significantly greater overall psychological distress ($P < .001$), and significantly reduced health-related quality-of-life indices compared with US referent populations. Eight survivors (53%) had not returned to work since their infection. Comparing disease manifestations, inhalational survivors reported significantly lower overall physical health than cutaneous survivors (mean scores, 30 vs 41; $P = .02$). Available medical records could not explain the persisting health complaints.

Conclusion The anthrax survivors continued to report significant health problems and poor life adjustment 1 year after onset of bioterrorism-related anthrax disease.

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study was performed using in-person clinical interviews, 3 self-administered questionnaires, and a review of medical records. The goal of this study was to generate hypotheses about the relationship between the anthrax infection and persistent somatic symptoms by reviewing medical outcome data (ie, after the onset of the anthrax infection) and responses to health assessment instruments. Because of the unique sensitivities associated with collection of these data and concern about exploitation of the survivors' identities, we did not perform any additional physical or mental status examinations, laboratory testing, or diagnostic imaging, or collect additional data on conditions existing prior to the anthrax infection. The study protocol was approved by the Cen-

ters for Disease Control and Prevention's institutional review board and the New Jersey State institutional review board. Written informed consent was

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obtained from each participant prior to initiation of the health assessment and prior to obtaining medical records.

Study Population

Adults (>18 years) diagnosed as having confirmed or suspected bioterrorism-related anthrax and classified as manifesting either inhalational or cutaneous disease per the Centers for Disease Control and Prevention's case definition were eligible to participate.¹

Clinical Interview and Medical Review-of-Systems Questionnaire

A medical scientist from the Centers for Disease Control and Prevention conducted an in-person clinical interview with survivors, asking about current, persistent, or residual health complaints in a semistructured review-of-systems format and using a 5-point ordinal scale indicating how the health concern had affected the survivor's life (1 indicates not at all; 2, a little bit; 3, moderately; 4, quite a bit; 5, extremely). The interviews were conducted between September and December 2002, approximately 1 year after the onset of the infection. The survivors were also asked to complete a self-administered questionnaire asking about the presence and intensity of 25 predefined current (within recent 4 weeks) health complaints. Only those health complaints ranked as moderate, more extreme, or current were included in stratified analyses. Unique complaints were summarized by the body system affected and by symptom categories (ie, somatic or neurobehavioral) to minimize bias from potentially misclassifying or double counting.

Revised 90-Item Symptom Checklist

The Revised 90-Item Symptom Checklist (SCL-90-R) is a psychometrically and clinically validated and reliable self-reported measure of psychological symptoms.¹⁰ The Global Severity Index (GSI) is generated from all 90 questions and measures overall psychological distress. A raw score is rendered for each of 9 symptom dimensions and the

GSI. The scores for each of the SCL-90-R subscales were normalized to a referent population represented by a transformed mean (SD) score of 50 (10). This referent nonpatient population represents a stratified random sample from a diverse county in a large eastern state in the United States (n=974).¹⁰ Higher scores indicate greater psychological distress. We report the number of individuals with transformed scores of 63 or higher (used in clinical settings to trigger further psychiatric evaluation)¹⁰; transformed scores of 70 ($P \leq .05$); and transformed scores of 75 or higher ($P \leq .01$).

Medical Outcomes Study 36-Item Short-Form Health Survey

The Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36, version 2) is the second and current version of a psychometrically and clinically validated self-administered instrument used to measure general health-related quality of life.¹¹ The 36-item questionnaire assesses 2 summary scores and 8 health domains that are contained within the scores. The Physical Composite Score contains the health domains of physical functioning, role of physical functioning, bodily pain, and general health. The Mental Composite Score contains vitality, mental health, role of emotional functioning, and role of social functioning. Referent population scores were obtained from a national sample of 6742 US participants in 1998,¹¹ 30 patients hospitalized in intensive care units from 1994 to 1998,¹² and 341 persons with chronic illness (musculoskeletal complaints and hypertension) in 1989.¹¹ Lower scores indicate a reduced health-related quality of life.

Medical Evidence

We reviewed available medical records from evaluations conducted at least 2 months after the acute anthrax infection and focused on diagnostic evaluations for respiratory tract problems, fatigue, joint complaints, and cognitive problems. We did not perform any additional diagnostic evaluations;

therefore, the extent of diagnostic evaluation was determined within the context of each survivor's relationship with his/her personal clinician.

Statistical Analysis

Descriptive statistics were tabulated for demographic variables and stratified by clinical disease presentation. For continuous variables, the Shapiro-Wilk statistic was used to test for normality, followed by the *t* test for normally distributed data, and the Wilcoxon signed rank test otherwise. Bivariate analyses of categorical demographics (age, sex, work status, race/ethnicity, and type of anthrax disease) and outcome measures (GSI transformed score ≥ 63 on the SCL-90-R; Mental Composite Score and Physical Composite Score ≤ 30 on the SF-36) were conducted using the Fisher exact test of statistical significance ($P \leq .05$). The mean scores of the survivor groups were compared with referent populations ($P \leq .05$, 2-tailed). Statistical procedures were performed using SAS statistical software (version 8, SAS Institute Inc, Cary, NC).

RESULTS

Study Population

Fifteen of the 16 adult anthrax survivors (all 6 inhalational and 9 of 10 cutaneous) participated in this study.¹ At the time of the interview, 8 survivors (53%) had not returned to work since their infection; all were receiving psychiatric services at the time of the interview, 7 of whom had no reported prior treatment history. Inhalational survivors were significantly older (58 years) compared with cutaneous survivors (37 years; $P < .001$).

Clinical Interview and Medical Review-of-Systems Questionnaire

A similar proportion of inhalational and cutaneous survivors reported moderate to severe health complaints affecting multiple body systems: cardiopulmonary (100% inhalational vs 78% cutaneous), gastrointestinal tract (50% vs 67%), head and neck (83% vs 78%), muscular (50% vs 44%), orthopedic (83% vs 56%), constitutional (83% vs

78%), neurological (50% vs 56%), and psychiatric (83% vs 56%). Both survivor subgroups had a median of 6 body systems affected per survivor. No differences were detected when aggregating the affected systems into somatic and neurobehavioral symptom categories; survivors (inhalational vs cutaneous) reported a median of 5 (range, 1-7) vs 4 (range, 2-8) somatic symptoms and

1 (range, 1-2) vs 1 (range, 0-2) neurobehavioral complaints per person for a total of 36 vs 50 health complaints, respectively.

Revised 90-Item Symptom Checklist

Compared with the US referent population, the anthrax survivors reported significantly greater mean scores for

overall psychological distress (measured using the GSI) and in all 9 symptom dimensions ($P < .001$ to $P = .03$) (TABLE 1).

Nine survivors (3 inhalational and 6 cutaneous) had scores consistent with clinically relevant distress. Cutaneous survivors tended to have more psychological distress and higher scores on 67% of the symptom dimensions when compared with inhalational survivors; however, no statistically significant differences were found. Two inhalational and 4 cutaneous survivors had scores of 70 or higher on at least 4 of the 9 symptom dimensions. Depression, anxiety, obsessive-compulsive, and hostility were the most frequently reported symptoms.

Medical Outcomes Study 36-Item Short Form

TABLE 2 illustrates that the anthrax survivors had significantly lower mean scores than the 1998 referent population of healthy individuals for all health domains ($P < .001$). Inhalational survivors scored significantly below cutaneous survivors on physical functioning (measures of 27 vs 56; $P = .01$) and role of physical functioning (23 vs 57; $P = .02$), and on the summary Physical Composite Score ($P = .02$). Inhalational survivors tended to score below

Table 1. Psychological Symptom Dimension Scores for Anthrax Survivors

| SCL-90-R Symptom Dimension | Type of Anthrax Manifestation or Disease | | Total (n = 15)* |
|--|--|-------------------|-----------------|
| | Inhalational (n = 6) | Cutaneous (n = 9) | |
| | Mean (SD)† | | |
| Somatization | 62 (10) | 62 (12) | 62 (11) |
| Obsessive-compulsive | 67 (10) | 64 (15) | 65 (13) |
| Interpersonal sensitivity | 55 (11) | 63 (11) | 60 (11) |
| Depression | 65 (6) | 68 (12) | 67 (10) |
| Anxiety | 61 (12) | 66 (16) | 64 (15) |
| Hostility | 51 (12) | 66 (15) | 60 (16) |
| Phobic anxiety | 54 (11) | 61 (14) | 58 (13) |
| Paranoid ideation | 55 (8) | 63 (15) | 60 (13) |
| Psychoticism | 65 (9) | 62 (8) | 63 (8) |
| Global Severity Index | 64 (7) | 68 (14) | 66 (11) |
| | No. (%) | | |
| Global Severity Index (clinical cut-off score) | | | |
| ≥63‡ | 3 (50) | 6 (67) | 9 (60) |
| ≥75§ | 0 | 4 (44) | 4 (27) |

Abbreviation: SCL-90-R, 90-Item Symptom Checklist, Revised.
 *All dimensions are statistically different from the referent population.
 †Normalized and standardized to the referent population to yield a mean (SD) of 50 (10).
 ‡Not statistically different from the referent population ($P = .19$), but score indicates psychiatric evaluation warranted.
 §Statistically different score from the referent population mean ($P = .01$).

Table 2. SF-36 Health Domain Scores for Anthrax Survivors*

| SF-36 Health Domain | US Healthy Referent Population in 1998 ¹¹ (n = 6742) | Anthrax Survivor Group† (n = 15) | Inhalational Survivors‡ (n = 6) | Cutaneous (n = 9) | Hospitalized ICU Patients With Sepsis ^{12§} (n = 30) | Patients With Chronic Illness ¹¹ (n = 341) |
|-------------------------------|---|----------------------------------|---------------------------------|-------------------|---|---|
| Physical Composite Score | 50 (10) | 37 (8)¶ | 30 (8)¶ | 41 (4) | 37 (12) | NA |
| Physical functioning | 83 (24) | 44 (24)¶ | 27 (23)¶ | 56 (11) | 48 (33) | 68 (26)¶ |
| Role of physical functioning | 83 (26) | 43 (30)¶ | 23 (30)¶ | 57 (22) | 45 (43) | 56 (41) |
| Bodily pain | 71 (24) | 31 (10)¶ | 28 (12) | 34 (8) | 67 (27)¶ | 67 (24)¶ |
| General health | 71 (21) | 37 (7)¶ | 38 (8) | 37 (7) | 56 (20)¶ | 60 (20)¶ |
| Mental Composite Score | 50 (10) | 28 (10)¶ | 30 (10) | 27 (10) | 50 (11)¶ | NA |
| Vitality | 58 (20) | 23 (16)¶ | 24 (19) | 22 (14) | 47 (24)¶ | 57 (22)¶ |
| Mental health | 75 (18) | 39 (17)¶ | 43 (15) | 36 (18) | 70 (22)¶ | 78 (18)¶ |
| Role of emotional functioning | 87 (21) | 42 (29)¶ | 34 (37) | 47 (23) | 76 (37)¶ | 73 (38)¶ |
| Role of social functioning | 84 (23) | 31 (14)¶ | 23 (12) | 37 (12) | 66 (32)¶ | 87 (20)¶ |

Abbreviations: ICU, intensive care unit; NA, data not applicable; SF-36, Medical Outcomes Study 36-Item Short-Form Health Survey (version 2).
 *Values are expressed as mean (SD).
 †Compared with US healthy referent population.
 ‡Compared with cutaneous survivors.
 §Compared with inhalational survivors.
 ||Chronic illness is musculoskeletal complaint and hypertension.¹¹ Compared with cutaneous survivors.
 ¶ $P = .05$ for statistical significance (2-tailed test).

the cutaneous survivors on role of social functioning ($P = .06$). For the other 5 health domains and the summary mental health index, inhalational and cutaneous survivors were statistically indistinguishable ($P = .31$ to $P = .84$). Inhalational survivors scored significantly lower than patients surviving sepsis and intensive medical care on all of the domains in the Mental Composite Score, bodily pain, and general health.¹² Cutaneous survivors scored significantly below persons with chronic illness on all domains except the role of physical functioning.¹¹

Medical Records

Thirteen of the survivors (87%) submitted their medical records for review. We looked for evidence from physical examinations and diagnostic evaluations to explain respiratory tract problems (eg, chronic cough, dyspnea on exertion), fatigue, joint complaints (eg, swelling, pain), and cognitive impairment (eg, memory problems). These were the most prevalent symptoms. Specifically, we reviewed the records for pulmonary functioning tests, computed tomographic scans of the chest, and measures of resting oxygen saturation to explain respiratory tract symptoms; anemia and thyroid functioning to explain complaints of fatigue; erythrocyte sedimentation rate, C-reactive protein, antinuclear antibodies, rheumatoid factor, and radiographs of affected joints to explain joint symptoms; and thyroid function tests, brain imaging, and vitamin B₁₂ to explain cognitive problems.

Of the 12 survivors who reported moderate to severe respiratory tract symptoms, we received the medical records for 10, which included results for 13 diagnostic tests among 5 survivors. Mild abnormalities on pulmonary function tests were detected for 3 of these survivors (all had been infected with inhalational anthrax). Two had mild reductions in oxygen-diffusing capacity and 1 of these had additional mild and reversible obstructive findings. Another survivor had mild restrictive and mild obstructive findings. Computed

tomographic scans of the chest for all 3 of these survivors had been normalized, with resolution of both the mediastinal lymphadenopathy and the pleural effusions. Another survivor (infected with inhalational anthrax) was unable to tolerate the pulmonary function testing procedure and a computed tomographic scan of the chest was not performed.

Medical records were available for 6 of the 8 survivors (5 infected with inhalational anthrax and 3 with cutaneous anthrax) who reported moderate to severe joint complaints, decreased physical functioning, and prolonged work absence. Among these 6 survivors, 11 diagnostic tests, including radiographs and serological markers for autoimmune or inflammatory conditions, were unremarkable. Blood cell counts and thyroid functioning were in the normal range. Two inhalational anthrax survivors had further workups for cognitive complaints; however, magnetic resonance imaging of the brain detected no abnormalities.

COMMENT

We found that many of the anthrax-infected survivors continued to report significant health problems, psychological distress, poor life adjustment, and a loss of functional capacity 1 year after the onset of infection. This is similar to findings reported after exposure to other types of traumatic events and highlights the importance of measuring these dimensions as standard practice.^{4-9,13} Many factors may contribute to the distress variance reported by the anthrax survivors, including differences in exposure characteristics, sociocultural and occupational considerations, and perceived inequities of case management.

We used published studies of long-term sequelae of infectious disease and chronic conditions to provide a context with which to interpret our findings; in comparison, the anthrax survivors had a poorer life adjustment (Table 2). Studies of persons surviving Lyme disease, legionnaires disease, adult respiratory distress syn-

drome, and sepsis have also described persistent and medically unexplained health complaints and poor life adjustment.^{12,14-17} Posttraumatic stress disorder has been postulated as a mediator of the poor health outcomes and unresolved health conditions after traumatic exposures.^{9,13,16,17} Friedman and Schnurr¹³ contend that persons with posttraumatic stress disorder may be more prone to develop medical illness due to increased cardiovascular reactivity, disturbed sleep physiology, and adrenergic dysregulation. Medically unexplained physical symptoms can arise from many sources, including physical or mental disorders or psychosocial distress, and may be affected by individual appraisal of such symptoms.⁹ Health care service use patterns and the patient-clinician relationship may also influence the expression, persistence, and severity of medically unexplained symptoms.

Our findings support those of other studies in the United States in which terrorism has led to significant chronic physical and mental health problems.^{9,18-20} Standard assessment of terrorism survivors should include medically unexplained health complaints and psychiatric comorbidity, such as symptoms of posttraumatic stress disorder, depression, and anxiety disorders.^{9,13,20,21} Psychiatric and medical systems of care and rehabilitation should be coordinated to minimize functional impairment and improve health-related quality of life.

Author Contributions: Drs Reissman and Perkins had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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An attack upon systematic thought is treason to civilization.
—Alfred North Whitehead (1861-1947)