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SUPPLEMENT ARTICLE

Risk Factors for Death or Meningitis in Adults Hospitalized for Cutaneous Anthrax, 1950–2018: A Systematic Review

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Background. Cutaneous anthrax accounts for approximately 95% of anthrax cases worldwide. About 24% of untreated patients die, and many cases are complicated by meningitis. Here, we explore clinical features of cutaneous disease associated with poor outcomes.

Methods. A systematic review identified 303 full-text articles published from 1950 through 2018 that met predefined inclusion criteria. Cases were abstracted, and descriptive analyses and univariate logistic regression were conducted to identify prognostic indicators for cutaneous anthrax.

Results. Of 182 included patients, 47 (25.8%) died. Previously reported independent predictors for death or meningitis that we confirmed included fever or chills; nausea or vomiting; headache; severe headache; nonheadache, nonmeningeal signs; leukocytosis; and bacteremia. Newly identified predictors included anxiety, abdominal pain, diastolic hypotension, skin trauma, thoracic edema, malignant pustule edema, lymphadenopathy, and evidence of coagulopathy (all with $P < .05$).

Conclusions. We identified patient presentations not previously associated with poor outcomes.

Keywords. anthrax; cutaneous; triage; mass casualty incident; with cutaneous anthrax.

Anthrax is a zoonotic infectious disease caused by the spore-forming bacterium *Bacillus anthracis*. Naturally occurring anthrax has a worldwide distribution and can infect humans through ingestion, inhalation, injection, or contact with infected animals or contaminated animal by-products [1–8]. Cutaneous anthrax accounts for more than 95% of cases worldwide [3].

Anthrax is also a major public health concern due to the historic use of *B. anthracis* spores as a biological weapon [2, 3, 9, 10]. Although aerosolized *B. anthracis* spores are best known as a precursor to highly fatal inhalation anthrax [11], cutaneous cases may also follow an aerosolization event. This was seen in both the 2001 bioterrorism incident in which half of all identified anthrax cases were estimated to be cutaneous [10] and the 1979 Sverdlovsk outbreak in which 18% of anthrax cases were cutaneous [12].

Patients with cutaneous anthrax commonly present with lesions that begin as a papule with surrounding vesicles, erythema, and marked edema; they may have a low-grade fever and regional lymphadenopathy [2, 3]. Over time, the papule will rupture, resulting in the hallmark depressed, black, necrotic lesion known as an eschar [2]. Although the incubation period ranges from a few hours to 17 days, more than 50% of lesions occur 2 to 7 days after *B. anthracis* first gains entry through the skin [4].

Historically, a quarter of the patients with cutaneous anthrax died before treatment options, such as antiserum and antimicrobials, became available. However, cutaneous anthrax can resolve spontaneously and usually has a mortality rate below 2% with antibiotic treatment [13]. Anthrax meningitis can complicate all forms of anthrax and has a mortality rate of 90% [2, 11]. Surprisingly, 30% to 50% of all anthrax meningitis cases are associated with cutaneous anthrax [2, 14], and most cutaneous anthrax deaths are from secondary anthrax meningitis [3, 13].

Previous reports (synthesized in Table 1) have suggested risk factors for inhalation anthrax and for meningitis, severe disease, or death across various forms of anthrax that include fever or chills; nausea or vomiting; headache; severe headache; shortness of breath; chest pain; hematemesis; hypothermia; tachypnea; neurologic signs; multiple lesions, lesions that involve the head, neck, or upper torso or that are large, surrounded by edema, or cross joints; and abnormal laboratory values [4, 11, 15–24]. Although not reported by the authors, an analysis of tabular data from Abramova et al showed that bacteremia was also a risk factor for meningitis [25]. Additionally, a delay in seeking care or onset of care during the fulminant phase have both been associated with higher risk of death. However, few studies have assessed risk factors for meningitis or death in cutaneous anthrax patients.

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Table 1. Known Risk Factors for Poor Prognoses for Patients With Anthrax From Any Route of Infection as Noted in Reviewed References

	Predictors for		
Symptoms/Signs/Diagnostics	Inhalation Anthrax	Meningitis	Severe Illness/Death
Symptoms			
Fever ± chills		[11]	
Nausea/vomiting	[15] [16] [17]	[11]	
Sweats (diaphoresis)	[15] [17]		
Headache	[15]	[11]	[11]
Headache, severe		[11]	
Nonheadache, neurological symptoms	[16]		
Cough	[15]		[19]
Shortness of breath	[15] [16]		[19]
Chest pain	[15]		
Abdominal pain	[15]		
Cyanosis/pallor	[17]		
Signs			
Bleeding (hematemesis)		[11]	
Vital signs			
Hypothermia			[4]
Tachycardia	[18]		
Tachypnea		[11]	
Systolic hypotension			[4]
Skin/lesion description			
Large			[4] [20] [21] [22] [23]
Multiple			[4] [20] [21] [22] [23]
Including the head, neck, or upper torso			[4] [20] [21] [22] [23]
Surrounded by edema			[4]
Neurologic			
Altered mental status	[17]	[11]	[11]
Meningeal signs		[11]	
Nonheadache, nonmeningeal signs[a]		[11]	
Pulmonary			
Abnormal lung examination	[16]		
Fulminant		[11]	
Diagnostic test results			
Bacteremia			[2] [25][b]
Leukocytosis			[4] [11]
Hemoglobinemia	[17] [18]		[4]
Thrombocytopenia			[24]
Hyponatremia	[18]		[4]
Hypoalbuminemia	[18]		[4]
Elevated transaminases	[18]		[4]

[a]Nonheadache, nonmeningeal signs include seizure, cranial nerve signs, limb weakness, and papilledema.

[b]Based on risk ratio calculation using data from Table 1 in Abramova et al [25].

Because patients with meningitis require a different therapeutic approach, and other patients at increased risk of death may require additional in-hospital monitoring, it is important to identify clinical features associated with both meningitis and death. In a true mass-casualty incident, such prognostic information may allow limited resources to be directed to those patients most likely to benefit [26, 27]. To identify clinical characteristics that predict meningitis or death, we review all adult patients reported to be hospitalized for cutaneous anthrax from 1950 through 2018 described in English literature.

METHODS

Data Collection

A systematic review was performed to identify anthrax cases from the existing literature based on previously described search terms and case definitions [11]. Briefly, anthrax cases were identified from articles that included case reports, case series, and line lists. Cases were confirmed through diagnostic testing or epidemiological linkage to a confirmed case or environmental exposure. We restricted our analysis to hospitalized cases that resulted from a cutaneous route of infection in adults aged ≥18 years. To reduce the impacts of temporal trends and therapeutic advances on mortality, the analysis was further restricted to cases reported from 1950 through 2018.

Primary Outcomes

Death and meningitis were the primary outcomes assessed. We assessed overall mortality as well as mortality dichotomized into deaths that occurred up to 72 hours after hospitalization (early fatalities) and those that occurred after 72 hours (late fatalities). Suspect, probable, and confirmed anthrax meningitis cases were included in the analysis and were categorized based on previously described definitions [11].

Variable Definitions

Demographic and clinical characteristics were described for all adult patients. Case definitions for anthrax and meningitis have been previously described [11]. World Health Organization locational groupings were assigned based on each patient's country of origin, and age was categorized into 3 groups (18–45 years, 46–64 years, and ≥65 years). Descriptions of eschar locations were recorded and classified according to the number of lesions present, the presence of 1 or multiple lesions on the head or neck, and the presence of 1 or multiple lesions on or spanning a joint. Lesions described as malignant pustule edema were recorded as such. The jaw and neck were included in the definition of a joint. Skin trauma included reports of insect or other bites, lacerations, and other open wounds. Published lesion images were reviewed when available.

Clinical data were recoded as dichotomous variables where appropriate. Variable definitions and reference ranges for vital signs and laboratory values were classified according to the *New England Journal of Medicine* SI Unit Conversion Guide. "Anxiety" was defined as any description of anxiousness, apprehension, agitation, or restlessness. "Evidence of coagulopathy" was defined to include hematochezia, hematuria, retinal hemorrhage, petechial rash, hemoptysis, and subcutaneous

hemorrhage. "Nonheadache, nonmeningeal signs" included seizures, papilledema, and focal findings such as cranial nerve palsies and limb weakness. Hemoglobin and hematocrit values vary by sex and were stratified according to published reference ranges. Hemoconcentration was determined if either value fell above reference ranges. Bacteremia upon presentation was defined as a positive culture of *B. anthracis* from blood collected on day 1 of hospitalization, and overall bacteremia was defined as a positive culture of *B. anthracis* from blood collected at any point during hospitalization.

Clinical symptoms recorded on or before hospitalization were considered abnormal if outside published reference ranges. Similarly, vital signs and laboratory findings were considered abnormal if they fell outside reference ranges. Clinical symptoms were assumed to be absent if not reported. Vital signs were assumed to be normal if not reported in case reports or case series, but values were excluded from the analysis if not reported from line lists. Missing laboratory data were excluded if not reported.

Statistical Analyses

Frequencies and percentages were calculated for categorical variables overall and by outcome (died vs survived and meningitis vs no meningitis). Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using univariate logistic regression. Median, interquartile range (IQR), and range were calculated for overall length of hospital stay by fatality status and by meningitis status. Statistical significance was defined as $P < .05$, and all analyses were performed in SAS Version 9.4 (SAS Institute Inc, Cary, NC).

A separate analysis was performed to assess the prognostic value of all clinical signs or symptoms noted throughout hospitalization (from initial presentation onward), though most data are not shown.

RESULTS

Patient Characteristics

The systematic review search strategy (Supplementary Figure 1) identified 182 adult patients hospitalized with cutaneous anthrax from 1950 through 2018. Of the 182 patients, about three quarters (72.9%) were male; 5 of the 49 females were pregnant (Table 2). The median age was 41 years (IQR, 32–52). Clinical signs and symptoms of all patients are described in Table 2. Death occurred in a quarter of the patients (n = 47), with 28 early fatalities (death within 72 hours of hospitalization) and 13 late fatalities (death after 72 hours of hospitalization; Supplementary Table 1). No data were available on time of death for 6 patients. Most patients lacked mention of any underlying conditions (n = 160, 87.9%); of the 22 patients who did have information, 18 (81.8%) were described as previously healthy and 4 (18.2%) had underlying conditions. One survivor had obesity and 1, renal failure. One fatality had hypertension and 1, alcoholic hepatitis.

Prognostic Indicators

Death

Table 2 describes clinical findings on presentation associated with mortality for adult cutaneous anthrax patients. Overall, death was more common among patients aged 46 to 64 years than those aged 18 to 45 years. It was also more common in those who lived in either South-East Asia or Africa compared with Europe. Lesions described as malignant pustules were associated with death, even after excluding 10 patients who showed signs of shock or were treated with vasopressors. The odds of death were significantly higher for patients with fever or chills, skin trauma, thoracic edema, anxiety, or headache. Four of 5 patients (80%) who presented with "anxiety" and 9 of 11 (81.8%) patients with headaches died.

Presenting with nausea or vomiting (OR, 48.3; 95% CI, 9.3–∞), diastolic hypotension (OR, 17.3; 95% CI, 1.2–∞), or evidence of coagulopathy (OR, 13.5; 95% CI, 1.3–681.7) had higher odds of death. All 10 patients with nausea or vomiting died. Five patients presented with evidence of coagulopathy and 4 died. The lone survivor was a female aged 20 years who lacked symptoms suggestive of meningitis, unlike the fatalities [28].

Odds of death were also significantly higher with nonheadache, nonmeningeal signs (OR, 113.8; 95% CI, 16.9–∞), and death occurred in 22 (95.7%) patients who experienced these. Finally, death was significantly associated with bacteremia at any point during hospitalization (OR, 55.4; 95% CI, 7.9–∞); 14 of 15 (93.3%) patients with bacteremia died, most within 72 hours of presentation (n = 11).

There were no significant associations between sex and fatality. Lesion characteristics were evaluated: neither the number of lesions nor their localization to the head, face, or neck; hands; or on or crossing a joint were associated with increased odds of mortality. Additionally, the following clinical findings previously noted as risk factors for anthrax mortality were not associated with overall death in this analysis: leukocytosis, neutrophilia, thrombocytopenia, hemoconcentration, hyponatremia, and hypoalbuminemia [15, 17, 18, 29].

Early and Late Fatality vs Survival

Similar prognostic trends were observed when deaths were stratified by either early or late fatality (Supplementary Table 1). The odds of early fatality were higher for patients with lymphadenopathy (OR, 3.9; 95% CI, 1.5–10.6) and leukocytosis (OR, 8.9; 95% CI, 1.6–∞). The odds of late fatality were higher for patients aged ≥45 years, as well as for those who presented with abdominal pain (OR, 26.8; 95% CI, 3.1–∞), though numbers were small.

Meningitis

Meningitis was identified in one fifth (n = 36) of patients. Risk factors for meningitis and death were similar (Table 3). Like death, meningitis was more common among patients aged 46–64 years

Table 2. Demographics and Clinical Findings on Presentation Associated With Overall Mortality Among Adults Hospitalized for Cutaneous Anthrax, 1950–2018

	Total		Died		Survived			
Characteristic	n (%)		n (%)		n (%)		Odds Ratio (95% Confidence Interval)	*P* Value
Overall	182 (100)		47 (25.8)		135 (74.2)			
Demographics								
Age, years								
18–45	108 (60.3)	179	19 (40.4)	47	89 (67.4)	132	Reference	-
46–64	64 (35.8)	179	24 (51.1)	47	40 (30.3)	132	2.8 (1.3–6.1)	<.01
65+	7 (3.9)	179	4 (8.5)	47	3 (2.3)	132	6.1 (1.0–45.2)	.06
Sex								
Male	132 (72.9)	181	38 (80.9)	47	94 (70.1)	134	1.8 (.8–4.6)	.2
Female	49 (27.1)	181	9 (19.1)	47	40 (29.9)	134	Reference	-
Pregnant	5 (10.2)	49	2 (22.2)	9	3 (7.5)	40	3.4 (.2–36.0)	.4
Not pregnant	44 (89.8)	49	7 (77.8)	9	37 (92.5)	40	Reference	-
Geographic location[1]								
European Region	85 (46.7)	182	11 (23.4)	47	74 (54.8)	135	Reference	-
Eastern Mediterranean Region	27 (14.8)	182	4 (8.5)	47	23 (17.0)	135	1.2 (.2–4.4)	1.0
Region of the Americas	22 (12.1)	182	6 (12.8)	47	16 (11.9)	135	2.5 (.7–8.8)	.2
Western Pacific Region	9 (4.9)	182	3 (6.4)	47	6 (4.4)	135	3.3 (.5–18.5)	.3
South-East Asia Region	27 (14.8)	182	15 (31.9)	47	12 (7.8)	135	8.2 (2.8–25.4)	<.0001
African Region	12 (7.0)	182	8 (17.0)	47	4 (3.0)	135	12.9 (2.9–68.9)	<.001
Clinical findings								
Symptoms								
Fever or chills	87 (48.6)	179	34 (73.9)	46	53 (39.8)	133	4.2 (1.9–9.9)	.0001
Anxiety	5 (2.8)	180	4 (8.7)	46	1 (0.7)	134	12.5 (1.2–628.3)	.03
Headache	11 (6.1)	179	9 (19.1)	47	2 (1.5)	132	15.1 (3.0–149.5)	<.001
Severe headache	2 (1.1)	181	2 (4.3)	47	0 (0)	134	7.0 (.8–∞)	.07
Abdominal pain	2 (1.1)	182	2 (4.3)	47	0 (0)	135	7.1 (.8–∞)	.07
Vomiting, emesis, nausea	10 (18)	180	10 (21.3)	47	0 (0)	133	48.3 (9.3–∞)	<.001
Vital signs								
Fever (>38°C)	31 (54.4)	57	11 (73.3)	15	20 (47.6)	42	3.0 (.7–14.9)	.2
Tachycardia (>90 bpm)	14 (58.3)	24	6 (66.7)	9	8 (53.3)	15	1.7 (.2–14.7)	.8
Systolic hypotension (<90 mm Hg)	6 (33.3)	18	4 (57.1)	7	2 (18.2)	11	5.3 (.5–90.1)	.2
Diastolic hypotension (<60 mm Hg)	6 (35.3)	17	5 (71.4)	7	1 (10.0)	10	17.3 (1.2–∞)	.04
Skin								
Lymphadenopathy	33 (18.2)	181	12 (25.5)	47	21 (15.7)	134	1.8 (.8–4.4)	.2
Lesion characteristics								
Eschar number								
1	142 (82.6)	172	32 (80.0)	40	110 (83.3)	132	Reference	-
2+	30 (17.4)	172	8 (20.0)	40	22 (16.7)	132	1.2 (.4–3.3)	.8
Head or neck lesion	63 (34.6)	172	11 (27.5)	40	52 (39.4)	132	0.6 (.3–1.4)	.3
Head or neck edema	57 (31.7)	180	10 (21.7)	46	47 (35.1)	134	0.6 (.2–1.2)	.2
On or crossing a joint	79 (45.9)	172	20 (50.0)	40	59 (44.7)	132	1.2 (.6–2.7)	.7
Skin trauma	15 (8.2)	182	7 (14.9)	47	8 (5.9)	135	3.7 (1.1–12.9)	.03
Thoracic edema	19 (10.4)	182	10 (21.3)	47	9 (6.7)	135	3.8 (1.3–11.3)	.02
Malignant pustule edema	28 (16.5)	170	12 (32.4)	37	16 (12.0)	133	3.5 (1.3–9.0)	.01
Neurologic								
Nonheadache, nonmeningeal signs	23 (12.6)	182	22 (46.8)	47	1 (0.7)	135	113.8 (16.9–∞)	<.0001
Other								
Evidence of coagulopathy	5 (2.7)	182	4 (8.5)	47	1 (0.7)	135	13.5 (1.3–681.7)	.03
Diagnostic test results								
Leukocytosis ($>12\times10^3/\mu L$)	42 (23.1)	87	6 (60.0)	10	36 (46.8)	77	1.7 (.4–8.9)	.7
Thrombocytopenia ($<130\times10^3/mm^3$)	2 (1.1)	7	1 (50.0)	2	1 (20.0)	5	3.2 (–391.0)	1.0
Hemoconcentration	6 (3.3)	25	1 (14.3)	7	5 (27.8)	18	0.4 (–5.5)	.9

Table 2. Continued

Characteristic	Total n (%)		Died n (%)		Survived n (%)		Odds Ratio (95% Confidence Interval)	*P* Value
Complications								
Bacteremia								
At presentation	2 (1.1)	182	1 (2.1)	47	1 (0.7)	135	2.9 (.1–230.3)	.9
Throughout hospitalization	15 (8.2)	182	14 (29.8)	47	1 (0.7)	135	55.4 (7.9–∞)	<.000

n = 182.

[a]Geographic locations of countries based on the World Health Organization classification system.

[b]Skin trauma is defined as the presence of insect or other bites, lacerations, or other open wounds.

[c]Cases demonstrating symptoms of shock or treatment with vasopressors excluded (n = 10).

[d]Nonheadache, nonmeningeal signs include seizure, cranial nerve signs, limb weakness, and papilledema.

[e]Hemoconcentration defined by sex-specific elevations in hemoglobin (male, 14.0–18.0 g/dL; female, 11.5–15.5 g/dL) or hematocrit (male, 39%–49%; female, 33%–43%) values.

than among those who were younger. It was also more common in those who lived in either South-East Asia or Africa compared with Europe. Odds of developing meningitis were significantly higher for patients who presented with fever or chills, lymphadenopathy, thoracic edema, malignant pustule edema, headache (OR, 22.9; 95% CI, 4.4–229.0), severe headache (OR, 10.0; 95% CI, 1.2–∞), or abdominal pain (OR, 10.0; 95% CI, 1.2–∞). Patients who presented with evidence of coagulopathy (OR, 20.2; 95% CI, 1.9–∞), nausea or vomiting (OR, 73.4; 95% CI, 14.6–∞), or nonheadache, nonmeningeal signs (OR, 333.0; 95% CI, 68.4–∞) also had higher odds of meningitis. Finally, meningitis was strongly associated with detection of bacteremia at any point during hospitalization (OR, 23.2; 95% CI, 5.7–137.2).

Prognostic Indicators Noted During Hospitalization

Patients noted to have altered mental status during hospitalization had higher odds of meningitis (OR, 97.2; 95% CI, 22.3–895.6), early fatality (OR, 18.3; 95% CI, 6.3–61.9), late fatality (OR, 8.0; 95% CI, 2.1–34.4), and overall fatality (OR, 11.9; 95% CI, 5.2–28.4). Patients noted to have shortness of breath during hospitalization had higher odds of late mortality (OR, 7.6; 95% CI, 1.03–46.2).

Hospitalization Data

Data for the hospitalization length of stay were available for 79 patients, of whom 42 died. The median length of stay was 14 days (IQR, 10–18) for survivors, 2 days (IQR, 1–4) for fatalities, and 1 day (IQR, 1–2) for patients with meningitis. Limited data were available regarding treatments provided during hospitalization. All 6 patients who required mechanical ventilation died, and 4 of 5 patients who required vasopressors died. Data regarding antimicrobial therapy for these patients is published in another article in the supplement [30].

DISCUSSION

Cutaneous anthrax is the most common form of anthrax, and death can occur in up to 24% of patients without treatment. A wide-area release of *B. anthracis* spores could result in significant cutaneous exposure, so it is important to characterize clinical findings associated with poor outcomes to guide treatment. This review details 182 hospitalized adult cutaneous anthrax patients described in the English-language literature from 1950 through 2018 and identifies prognostic indicators of meningitis and death. Children were not evaluated due to low sample size [11].

Table 4 summarizes clinical features of cutaneous anthrax significantly associated with death or meningitis. Most deaths occurred within 72 hours of hospital presentation, and adults aged 45 to 64 years were more likely to develop meningitis or die compared with their younger counterparts. Adults aged ≥45 years were also more likely than their younger counterparts to die after 72 hours, suggesting they may need more monitoring during hospitalization. Risk factors for meningitis or death in patients with anthrax from various routes of infection suggested by other authors that we confirm for cutaneous anthrax in adults include fever or chills; nausea or vomiting; headache; severe headache; nonheadache, nonmeningeal signs; leukocytosis; and bacteremia (Table 1) [4, 11, 19, 25].

Bacteremia was documented in half the inhalation anthrax autopsies from the 1979 Sverdlovsk outbreak, and hematogenous spread to both the gastrointestinal tract and the nervous system was proposed [25]. A χ^2 analysis we performed on data from Table 1 of Abramova et al confirmed an apparent association between bacteremia and meningitis (data not shown). Our analysis describes a similar finding among adults with cutaneous anthrax. As bacteremia predicts both meningitis and death, blood cultures should be obtained in patients with cutaneous anthrax whenever possible to guide therapy and optimize patient outcomes.

Patients with cutaneous anthrax in need of supportive care on presentation were at increased risk of death. These findings are consistent with those of Holty et al, who noted that 97% of fulminant phase patients died, regardless of their treatment [19].

New prognostic indicators that we identified for death or meningitis in cutaneous anthrax include anxiety, abdominal

Table 3. Demographics and Clinical Findings on Presentation Associated With Meningitis Among Adults Hospitalized for Cutaneous Anthrax, 1950–2018

Characteristic	Total		Meningitis		No Meningitis		Odds Ratio (95% Confidence Interval)	*P* Value
	n (%)		n (%)		n (%)			
Overall	182 (100)		36 (19.8)		146 (80.2)			
Demographics								
Age, years								
18–45	108 (60.3)	179	14 (38.9)	36	94 (65.7)	143	Reference	
46–64	64 (35.8)	179	21 (58.3)	36	43 (30.1)	143	3.3 (1.4–7.6)	<.01
65+	7 (3.9)	179	1 (2.8)	36	6 (4.2)	143	1.1 (0–10.4)	1.0
Sex								
Male	132 (72.9)	181	29 (80.6)	36	103 (71.0)	145	1.7 (.7–4.9)	.3
Female	49 (27.1)	181	7 (19.4)	36	42 (29.0)	145	Reference	
Pregnant	5 (10.2)	49	2 (28.6)	7	3 (7.1)	42	4.9 (.3–55.9)	.3
Not pregnant	44 (89.8)	49	5 (71.4)	7	39 (92.9)	42	Reference	
Geographic location[a]								
European Region	85 (46.7)	182	9 (19.4)	36	76 (52.1)	146	Reference	
Eastern Mediterranean Region	27 (14.8)	182	3 (8.3)	36	24 (16.4)	146	1.1 (.2–4.7)	1.0
Region of the Americas	22 (12.1)	182	2 (5.6)	36	20 (13.7)	146	0.8 (.1–4.6)	1.0
Western Pacific Region	9 (4.9)	182	3 (8.3)	36	6 (4.1)	146	4.1 (.6–23.9)	.2
South-East Asia Region	27 (14.8)	182	13 (36.1)	36	14 (9.6)	146	7.6 (3.5–24.8)	<.001
African Region	12 (6.6)	182	6 (16.7)	36	6 (4.1)	146	8.1 (1.8–38.5)	<.01
Clinical findings								
Symptoms								
Fever or chills	87 (48.6)	179	26 (74.3)	35	61 (42.4)	144	3.9 (1.6–10.2)	.001
Anxiety	5 (2.8)	180	2 (5.7)	35	3 (2.1)	145	2.8 (.2–25.9)	.5
Headache	11 (6.1)	179	9 (19.4)	36	2 (1.4)	143	22.9 (4.4–229.0)	<.0001
Severe headache	2 (1.1)	181	2 (5.6)	36	0 (0)	145	10.0 (1.2–∞)	.04
Abdominal pain	2 (1.1)	182	2 (5.6)	36	0 (0)	146	10.0 (1.2–∞)	.04
Vomiting, emesis, nausea	10 (18)	180	10 (27.8)	36	0 (0)	144	73.4 (14.6–∞)	<.0001
Vital signs								
Fever (>38°C)	31 (54.4)	57	9 (75.0)	12	22 (48.9)	45	3.1 (.7–20.0)	.2
Tachycardia (>90 bpm)	14 (7.7)	24	6 (75.0)	8	8 (50.0)	16	2.9 (.4–37.6)	.5
Systolic hypotension (<90 mm Hg)	6 (3.3)	18	3 (50.0)	6	3 (25.0)	12	2.8 (.2–36.4)	.6
Diastolic hypotension (<60 mm Hg)	6 (3.3)	17	4 (66.7)	6	2 (18.2)	11	7.6 (.6–151.7)	.1
Skin								
Lymphadenopathy	33 (18.2)	181	12 (33.3)	36	21 (14.5)	145	2.9 (1.2–7.3)	.02
Lesion characteristics								
Eschar number								
1	141 (82.0)	172	29 (67.7)	31	136 (96.5)	141	Reference	
2+	31 (18.0)	172	2 (6.5)	31	5 (3.5)	141	1.2 (.3–3.4)	.9
Head or neck lesion	63 (36.0)	172	8 (25.8)	31	55 (39.0)	141	0.6 (.2–1.4)	.2
Head or neck edema	57 (31.7)	180	7 (20.0)	35	50 (34.5)	145	0.5 (.2–1.2)	.1
On or crossing a joint	79 (45.9)	172	17 (54.8)	31	62 (44.0)	141	1.5 (.7–3.7)	.4
Skin trauma[b]	15 (8.2)	182	6 (16.7)	36	9 (6.2)	146	3.0 (.8–10.4)	.1
Thoracic edema	19 (10.4)	182	8 (22.2)	36	11 (7.5)	146	3.5 (1.1–10.5)	.03
Malignant pustule edema[c]	28 (16.5)	170	12 (41.4)	29	16 (11.3)	141	5.4 (2.0–14.8)	<.001
Neurologic								
Nonheadache, nonmeningeal signs[d]	23 (12.6)	182	23 (63.9)	36	0 (0)	146	333.0 (68.4–∞)	<.0001
Other								
Evidence of coagulopathies	5 (2.8)	178	4 (12.5)	32	1 (0.7)	146	20.2 (1.9–∞)	<.01
Diagnostic test results								
Leukocytosis (>12 × 10^3/μL)	42 (48.3)	87	6 (75.0)	8	36 (45.6)	79	3.5 (.6–37.9)	.2
Thrombocytopenia (<130 × 10^3/mm^3)	2 (28.6)	7	1 (50.0)	2	1 (20.0)	5	3.2 (–391.0)	1.0
Hemoconcentration[e]	6 (24.0)	25	1 (20.0)	5	5 (25.0)	20	0.4 (–5.5)	.9
Complications								
Bacteremia								
At presentation	2 (1.1)	182	1 (2.8)	36	1 (0.7)	146	4.1 (.1–327.4)	.7
Throughout hospitalization	15 (8.2)	182	12 (33.3)	36	3 (2.1)	146	23.2 (5.7–137.2)	<.0001
Outcomes								
Fatal	47 (25.8)	182	35 (97.2)	36	12 (8.2)	146	363.5 (52.7–∞)	<.0001

n = 182.

[a]Geographic regions of countries based on World Health Organization classification system.

[b]Skin trauma is defined as the presence of insect or other bites, lacerations, or other open wounds.

[c]Cases demonstrating symptoms of shock or treatment with vasopressors excluded (n = 10).

[d]Nonheadache, nonmeningeal signs include seizure, cranial nerve signs, limb weakness, papilledema.

[e]Hemoconcentration defined by sex-specific elevations in hemoglobin (male, 14.0–18.0 g/dL; female, 11.5–15.5 g/dL) or hematocrit (male, 39%–49%; female, 33%–43%) values.

Table 4. Odds Ratios With 95% Confidence Intervals for Demographics, Symptoms, and Signs Associated With Fatality or Meningitis for Adults With Cutaneous Anthrax

	Fatality			
Characteristic	Overall	Early	Late	Meningitis
Demographics				
Age 46–64 vs ≤45, years	2.8 (1.3–6.1)		21.8 (2.9–∞)	3.3 (1.4–7.6)
Age 65+ vs ≤45, years			49.7 (2.1–∞)	
South East Asia vs Europe	8.2 (2.8–25.4)	16.5 (4.6–70.2)		7.6 (3.5–24.8)
Africa vs Europe	12.9 (2.9–68.9)	10.5 (1.2–84.7)		8.1 (1.8–38.5)
Clinical findings on presentation				
Symptoms				
Fever/chills[a]	4.2 (1.9–9.9)	3.7 (1.5–10.6)	4.5 (1.1–26.9)	3.9 (1.6–10.2)
Anxiety	12.5 (1.2–628.3)	15.5 (1.2–843.8)		
Headache[a]	6.1 (1.7–24.5)	5.6 (1.2–26.3)		9.2 (2.5–37.9)
Severe headache[a]				10.0 (1.2–∞)
Abdominal pain			26.8 (3.1–∞)	10.0 (1.2–∞)
Nausea/vomiting[a]	48.3 (9.3–∞)	46.7 (8.5–∞)	45.7 (6.7–∞)	73.4 (14.6–∞)
Vital signs				
Diastolic hypotension	17.3 (1.2–∞)	29.2 (1.6–∞)		
Skin				
Lymphadenopathy		3.9 (1.5–10.6)		2.9 (1.2–7.3)
Trauma	3.7 (1.1–12.9)	4.9 (1.2–19.0)		
Thoracic edema	3.8 (1.3–11.3)	4.6 (1.3–15.7)		3.5 (1.1–10.5)
Malignant pustule edema	3.5 (1.3–9.0)	3.9 (1.2–11.7)	7.4 (1.2–42.5)	5.4 (2.0–14.8)
Neurologic				
Nonheadache, nonmeningeal signs[a]	113.8 (16.9–∞)	221.9 (29.9–∞)	37.0 (2.8–∞)	333.0 (68.4–∞)
Other				
Evidence of coagulopathy	13.5 (1.3–681.7)	24.7 (2.3–∞)		20.2 (1.9–∞)
Diagnostic test results				
Leukocytosis[a]		8.9 (1.6–∞)		
Bacteremia (throughout hospitalization)[a]	55.4 (7.9–∞)	82.5 (10.9–∞)	37.6 (2.8–∞)	23.2 (5.7–137.2)

[a]Previously reported as risk factors in other studies.

pain, diastolic hypotension, skin trauma, thoracic edema, malignant pustule edema, lymphadenopathy, and evidence of coagulopathy. A number of these newly identified risk factors are consistent with the known pathophysiology of anthrax. The anxiety displayed by some patients might stem from an increase in cyclic adenosine monophosphate (cAMP) caused by edema toxin (ET), as cAMP serves as a second messenger for "fight-or-flight" catecholamines such as epinephrine [31]. Additionally, challenge studies in rodents have suggested that ET and lethal toxin (LT) induce hypotension (ie, vascular shock) [32], which is a poor prognostic indicator for any illness. This would support findings from Booth et al and Sweeney et al that anthrax is resistant to supportive measures once the disease has progressed to shock [24, 33].

Skin trauma may be a risk factor because it influences dose-response, allowing a larger dose of *B. anthracis* than would be possible in the absence of trauma. The increased odds of fatality and meningitis with thoracic edema and malignant pustule edema may stem from pathologic changes induced by anthrax endotoxins [2, 34]. ET and LT are responsible for hemorrhage, impaired water homeostasis and edema, vasodilation, and hypotension [2, 10, 33]. The presence of lymphadenopathy may suggest that the cutaneous anthrax infection is no longer localized. We could not confirm previous reports that lesion number, location, or characteristics were important prognostic indicators [2, 4, 20, 22, 23, 35]. Previous studies by Eurich [36] and Hughes et al [37] suggested lesions located on or crossing joints might promote drainage of lymph from regional lymph nodes and lead to bacteremia or sepsis, but we could not confirm the prognostic value of these types of lesions.

Evidence of coagulopathy was also newly identified as a risk factor for death and meningitis and is consistent with the activity of ET [32]. In addition to causing bleeding, ET may disrupt endothelial integrity and LT may promote invasion and penetration of the blood brain barrier, together leading to central nervous system colonization [38].

Our findings should be interpreted in light of some limitations. In our study, we only evaluated risk factors for death and meningitis among adults with cutaneous anthrax. One risk factor, malignant pustule edema, does not appear to have a standard definition. It is possible that these same risk factors

may not apply to systemic anthrax from other routes of infection. All data collected for this review were limited to existing English-language indexed literature, and our interpretations were dependent upon the quality of published data, which may have varied in completeness or accuracy. The high representation of case reports and case series may have produced publication bias in our findings, as such reports may focus on more complicated or severe cutaneous anthrax cases and leave out common presentations. Reporting bias was possible. Specifically, preferential publication in English literature of only the most severe cases from Africa and Southeast Asia may have skewed the univariate results for mortality. Thus, the regional analyses should be interpreted with caution. Multiple prognostic indicators were evaluated among cutaneous anthrax patients, but the small sample size prohibited the use of multivariable analyses and limited our ability to understand which risk factors were most important. Even so, the number of included patients is the largest sample size used in a study evaluating outcomes among hospitalized cutaneous anthrax patients across all geographic locations.

CONCLUSIONS

In this study, we describe a retrospective cohort of adult cutaneous anthrax cases reported from 1950 through 2018 and identify clinical characteristics associated with poor outcomes. We confirm several previously identified risk factors for poor patient outcomes, such as severe headache, nonheadache, nonmeningeal signs, and bacteremia. We add several new risk factors to the known list. Anxiety, diastolic hypotension, and skin trauma heralded death, and lymphadenopathy was associated with meningitis. Thoracic edema, malignant pustule edema, abdominal pain, and evidence of coagulopathy were prognostic indicators for both death and meningitis.

Many of the risk factors identified in this study are hallmarks of disease severity and should always be recognized by physicians as poor prognostic indicators, especially during triage for a mass-casualty incident. Others, such as those newly identified, may be less commonly appreciated and could be important early indicators of severe complications such as meningitis. Regardless, information on risk factors for poor outcomes can guide healthcare professionals to perform diagnostic tests that optimize patient outcomes and prompt earlier diagnosis and treatment for meningitis. It may also help health providers improve the outcomes of patients with cutaneous anthrax in resource-poor areas or following a mass casualty incident related to a wide-area release of *B. anthracis* spores.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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