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SUPPLEMENT ARTICLE

Systematic Review of Hospital Treatment Outcomes for Naturally Acquired and Bioterrorism-Related Anthrax, 1880–2018

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Background. *Bacillus anthracis* can cause anthrax and is a potential bioterrorism agent. The 2014 Centers for Disease Control and Prevention recommendations for medical countermeasures against anthrax were based on in vitro data and expert opinion. However, a century of previously uncompiled observational human data that often includes treatment and outcomes is available in the literature for analysis.

Methods. We reviewed treatment outcomes for patients hospitalized with anthrax. We stratified patients by meningitis status, route of infection, and systemic criteria, then analyzed survival by treatment type, including antimicrobials, antitoxin/antiserum, and steroids. Using logistic regression, we calculated odds ratios and 95% confidence intervals to compare survival between treatments. We also calculated hospital length of stay. Finally, we evaluated antimicrobial postexposure prophylaxis (PEPAbx) using data from a 1970 Russian-language article.

Results. We identified 965 anthrax patients reported from 1880 through 2018. After exclusions, 605 remained: 430 adults, 145 children, and 30 missing age. Survival was low for untreated patients and meningitis patients, regardless of treatment. Most patients with localized cutaneous or nonmeningitis systemic anthrax survived with 1 or more antimicrobials; patients with inhalation anthrax without meningitis fared better with at least 2. Bactericidal antimicrobials were effective for systemic anthrax; addition of a protein synthesis inhibitor(s) (PSI) to a bactericidal antimicrobial(s) did not improve survival. Likewise, addition of antitoxin/antiserum to antimicrobials did not improve survival. Mannitol improved survival for meningitis patients, but steroids did not. PEPAbx reduced risk of anthrax following exposure to *B. anthracis*.

Conclusions. Combination therapy appeared to be superior to monotherapy for inhalation anthrax without meningitis. For anthrax meningitis, neither monotherapy nor combination therapy were particularly effective; however, numbers were small. For localized cutaneous anthrax, monotherapy was sufficient. For *B. anthracis* exposures, PEPAbx was effective.

Keywords. anthrax; inhalation anthrax; anthrax meningitis; treatment; antitoxin/antiserum.

Bacillus anthracis, the causative agent of anthrax, is a category A bioterrorism agent because it is "…infective in low doses… suitable for mass production, storage, and weaponization; [and] stable during dissemination" [1]. It is one of the few biological agents that was released or used on civilians after more than 180 nations ratified or acceded to the international Biological Weapons Convention in 1972. A 1979 accidental release over a civilian population near a bioweapons facility in Sverdlovsk, in the former Soviet Union, led to at least 77 anthrax cases and 66 deaths [2]. In the early 1990s, it was manufactured into 50 bombs in Iraq [3]. In 2001, it was sent through the US Postal Service, resulting in 22 anthrax cases and 5 deaths [4].

Although these events were limited in scope, the World Health Organization has estimated that an anthrax spore release in a city of 5 million could cause up to 250 000 casualties with 100 000 deaths [5]. Given this threat, the US Department of Health and Human Services is tasked with stockpiling medical countermeasures and ensuring "timely and accurate recommended utilization guidelines" to protect the public against anthrax [6]. Recommendations for countermeasure use were last updated by the Centers for Disease Control and Prevention in 2014 in a trio of documents for postexposure prophylaxis and treatment of anthrax in adults [7], pregnant women [8], and children [9].

Because high-quality, prospective, controlled studies of anthrax treatment are lacking in humans, most anthrax countermeasures have been approved by the Food and Drug Administration based on the "Animal Rule," which allows

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animal models to be used to assess drug safety and efficacy [10]. However, almost 140 years of observational treatment and outcome data for patients with anthrax are available in the medical literature but had never been compiled for analysis. We performed a systematic review to assess outcomes by type of treatment for patients hospitalized with anthrax described in the English medical literature. We evaluated the effectiveness of different classes and combinations of antimicrobials and antitoxin/antiserum for treatment of localized cutaneous anthrax, systemic anthrax, and anthrax meningitis. We examined the use of nonantimicrobial therapeutic agents/measures in anthrax meningitis. Finally, we provide evidence for successful use of postexposure antimicrobials (PEPAbx) following exposure to *B. anthracis*.

METHODS

The search string, data sources, and case definitions used here were previously published [11]. The PRISMA diagram illustrated in Supplementary Figure 1 of Hendricks et al [12] shows how we identified anthrax cases who died or received ongoing medical care (ie, "hospitalized") in the English medical literature from 1880 through 2018. Anthrax determinations were based on diagnostic or environmental tests or epidemiological linkage. The "route of infection" (cutaneous, ingestion, and inhalation) was determined by inspecting a patient's first symptoms and epidemiological information. Injection anthrax patients were not analyzed separately but were included in broader categories such as systemic or meningitis as appropriate. Infections were categorized as "systemic" if patients had vital sign or white blood cell count abnormalities. We used the previously published case definition of systemic anthrax [11], in which patients who died were automatically deemed to have "systemic" illness. However, for analyses that evaluated survival of nonsystemic patients, patients who died were not automatically categorized into the systemic group.

Design

We analyzed survival by treatment type, including antimicrobials, antitoxin/antiserum, and steroids. Table 1 summarizes date ranges, populations, time frame of treatment receipt, and exclusions for each analysis. Timing of therapies was coded in the same manner as described in Hendricks et al [12]. Antimicrobials were grouped by both class (eg, penicillins, carbapenems, fluoroquinolones) and bactericidal vs protein synthesis inhibitor (PSI). Additionally, survival with mannitol and intrathecal/intraspinal treatments was analyzed for systemic anthrax meningitis cases. Sulfa drugs and cephalosporins were not considered anthrax-appropriate antimicrobial treatments and were therefore not counted when antimicrobials were summed. For analyses comparing monotherapy or combinations of antimicrobials and antitoxin/antiserum, patients were assigned to treatment regimens based on treatment received in the first 2 days of hospitalization. Single, dual, and triple refer to the number of classes, rather than the number of antimicrobials. Separate analyses were performed for the following antimicrobials: ≥1 bactericidal and no PSI, ≥1 PSI and no bactericidal, and ≥1 bactericidal and ≥1 PSI together, excluding those who also received antitoxin/antiserum. "No treatment" refers to patients who received no anthrax-appropriate antimicrobials or antitoxin/antiserum before or throughout hospitalization. Some analyses evaluated treatments received throughout hospitalization, including those focused on antitoxin/antiserum, mannitol, and intrathecal/intraspinal treatments. Except for analyses limited to meningitis patients, we only analyzed steroids administered in the first 2 days of hospitalization. Patients receiving steroids with no timing information available were always included. Time frames for analyses varied by therapy, generally starting when the treatment became available (Table 1). Analyses that included a "no treatment" comparison group included data from 1880 onward.

Exclusion criteria

Patients who were dead on hospital arrival, died on the first hospitalization day, or who lacked survival status or age and were not designated as an adult or child were excluded from analyses. Patients described by the authors Meselson and Andrews were also excluded as they lacked pertinent data [2, 13]. Exclusions for individual analyses are outlined in Table 1.

Statistical Analyses

Analyses were performed on adults (≥18 years old or those described in the publication as "adults") and children (<18 years old) separately (tables for children appear in the supplement). For all patients hospitalized for anthrax, we calculated the percent survival and hospital length of stay (LOS) by (1) antimicrobial treatment regimen with and without antitoxin/antiserum, (2) antitoxin/antiserum without antimicrobials, and (3) monotherapy or combination therapy with individual antimicrobial classes. We stratified by meningitis status, route of infection, and systemic criteria. Penicillins were analyzed as (1) a class, (2) beta-lactamase resistant or containing a beta-lactamase inhibitor, and (3) individually. We also calculated survival for patients with various complications, stratified by steroid use.

We calculated odds ratios (ORs) and 95% confidence intervals (CIs) comparing the odds of survival between different treatments using univariate and multivariable logistic regression. We compared survival between those receiving

1. bactericidal antimicrobial(s) alone vs no antimicrobial treatment,
2. PSI(s) alone vs no antimicrobial treatment,
3. bactericidal antimicrobial(s) alone vs PSI(s) alone,

Table 1. Time Frames, Populations, and Exclusions for Analyses by Type of Treatment

	Antimicrobials and Antitoxin/Antiserum		Antimicrobials Only			Antitoxin/Antiserum Only		Steroids		Mannitol	Intrathecal/ Intraspinal
	By Meningitis Status, Route of Infection and Systemic Criteria	LR	By Class and Individual Penicillins	LR Systemic Anthrax	LR Meningitis	LR all Anthrax	LR Meningitis	All anthrax With Various Complications	LR Meningitis	LR Meningitis	LR Meningitis
Table numbers[a]	2, S2a, S2b, 8, S8	4	3, S3a, S3b	4, S4	7, S7	5, S5	7, S7	6, S6	7, S7	7, S7	7, S7
Analytic time frame											
1880–2018	X (S2a)		X (S3a)								
1900–2018						X	X				
1940–2018	X (2, 8, S2b, S8)	X	X (3, S3b)	X	X						X
1950–2018								X	X		
1960–2018										X	
Population											
All anthrax (N = 965)	X		X			X		X			
Systemic anthrax		X		X							
Anthrax meningitis					X		X		X	X	X
Treatment time frame											
First two days of hospitalization	X	X	X	X	X			X			
Throughout hospitalization						X	X		X	X	X
Exclusions											
Cases from Meselson and Andrews	X	X	X	X	X	X	X	X	X	X	X
Dead on arrival	X	X	X	X	X	X	X	X	X	X	X
Died on day 1 of hospitalization	X	X	X	X	X	X	X	X	X	X	X
Lacking survival status	X	X	X	X	X	X	X	X	X	X	X
Cases given anthrax-appropriate antimicrobial treatment before hospitalization	X	X	X	X	X						
Cases with first antimicrobial or antitoxin/ antiserum after day 2 of hospitalization	X	X	X	X	X						
Cases with unclear treatment timing if they could not be classified into a treatment category	X	X	X	X	X						
Cases who received antitoxin/antiserum in first 2 days of hospitalization			X								
Cases who received antitoxin/antiserum at any point				X	X						
Patients given steroids before hospitalization or after day 2 of hospitalization. Patients that had steroids but no timing information were included.								X			

Abbreviation: LR, logistic regression.

[a]Table numbers in the supplement are preceded by the letter "S." Table numbers for analyses with multiple analytic time frames are notated in the corresponding row.

4. bactericidal antimicrobial(s) and PSI(s) vs bactericidal antimicrobial(s) alone,
5. bactericidal antimicrobial(s) and PSI(s) vs PSI(s) alone,
6. bactericidal antimicrobial(s) and PSI(s) vs bactericidal antimicrobial(s) or PSI(s) alone,
7. antimicrobial combination therapy vs monotherapy,
8. antimicrobial(s) and antitoxin/antiserum vs antimicrobial(s) alone,
9. steroids vs no steroids,
10. and antitoxin/antiserum vs no antitoxin/antiserum.

Only a few pediatric treatment regimens could be assessed because of the paucity of data.

In multivariable analyses, we controlled for age, sex, and 3 measures of illness severity: hypoxia (ventilated or intubated or respiratory rate > 30), shock (use of vasopressors or systolic blood pressure < 90 mmHg), and altered mental status. If there were too few observations to control for all 5 variables, variables were included in the model based on the smallest *P* values and/or the magnitude of the OR in univariate analysis. Backward elimination was performed; the final model and associated OR and CIs included control variables for which $P < .05$ plus the treatment regimen of interest. Logistic regression analyses involving antimicrobials alone, antimicrobials and antitoxin/antiserum, or steroids were restricted to patients with systemic anthrax, regardless of meningitis status. Analysis of antitoxin/antiserum compared with no antitoxin/antiserum included all patients hospitalized with anthrax. Outcomes for patients with systemic anthrax meningitis were assessed using univariate logistic regression for different antimicrobial treatments, steroids, mannitol, intrathecal/intraspinal treatment, and antitoxin/antiserum.

Data not identified by this systematic review were available on PEPAbx for Russians (1) exposed to anthrax-affected animals before 1965 and (2) who ingested *B. anthracis* contaminated meat from 1965 through 1967. Univariate logistic regression was used to calculate the OR and 95% CIs for not developing anthrax, using a 0.5 correction when needed, comparing penicillin monotherapy, penicillin plus benzacillin, and chlortetracycline to no treatment.

Analyses were performed in SAS version 9.4 (SAS Institute Inc, Cary, NC) and $P < .05$ was considered statistically significant.

RESULTS

This systematic review identified 965 patients who died or were hospitalized from anthrax. Exclusions included patients described by Meselson (n = 76) and Andrews (n = 140), those who were dead on arrival (n = 11), died on hospital day 1 (n = 124), and lacked survival status (n = 9); 605 patients remained (Supplementary Table 1), and 456 had their cases published from 1940 through 2018.

The 605 patients comprised 430 (71%) adults and 145 children; 30 were missing age. Sixty-seven adults and 15 children had meningitis. In adults without meningitis, routes of infection included 260 cutaneous (126 localized and 134 systemic), 18 ingestion, 36 inhalation, 48 injection, and 1 nasopharyngeal; systemic illness occurred in 63%. In children without meningitis, routes of infection included 114 cutaneous (84 localized and 30 systemic), 12 ingestion, 3 inhalation, and 1 nasopharyngeal; systemic illness occurred in 34%.

In general, anthrax survival was low for adults who received no treatment and for those with meningitis (Table 2 and Supplementary Table 2*A*). From 1940 through 2018 (Table 2), most adults with nonsystemic anthrax survived (≥97%) if they received any treatment; however, most (93%) had localized cutaneous anthrax. Survivorship was similarly high for adults with systemic cutaneous anthrax without meningitis if they received any treatment; only 1 adult in this category died.

Of adults with systemic anthrax without meningitis (45% of which had a cutaneous route), survivorship generally exceeded 70% if they received ≥1 antimicrobials with or without antitoxin/antiserum (Table 2). PSIs by themselves had the lowest survival (64%). Most (82%) adults survived if given combinations with ≥1 bactericidal and ≥1 PSI antimicrobial. Six of 9 (67%) adults given antitoxin/antiserum and ≥1 antimicrobials survived. Both adults given antitoxin/antiserum alone survived.

For children with localized cutaneous anthrax, all who were treated survived, and 1 of the 2 who went untreated died (Supplementary Table 2*B*). Survival occurred in 17 of 18 children with systemic cutaneous anthrax without meningitis who received any therapy. Children with ingestion anthrax fared better than adults, with a survival ≥80% regardless of treatment.

Table 3 describes survival for adults who received monotherapy (ie, 1 class of antimicrobial) vs combination therapy (ie, >1 class of antimicrobial) during their first 2 days of hospitalization by meningitis status, route, and systemic criteria for 1940 through 2018 (data from 1880-2018, Supplementary Table 3*A*). Monotherapy resulted in high survival (98%) for adults with localized cutaneous anthrax. Survival with penicillin monotherapy was 98% for adults with localized cutaneous anthrax and 89% for those with systemic illness without meningitis. However, patients with inhalation anthrax without meningitis fared poorly with monotherapy. Supplementary Table 3B describes monotherapy (and combination therapy) for specific penicillins.

For adults given combination therapy for localized cutaneous anthrax (Table 3), survivorship was 100%. For systemically ill adults without meningitis, overall survivorship with combination therapy was 73%, ranging from 71% to 86% with combinations including lincosamides, fluoroquinolones, macrolides, or penicillins. Though treatment data for adults with inhalation anthrax was sparse, combinations favored survival if they

Table 2. Survival for Adults Reported to be Hospitalized for Anthrax by Meningitis Status, Route of Infection, Systemic Criteria, and Treatment During First 2 Days of Hospitalization,[a] 1940–2018

	Without Meningitis												With Meningitis	
	Localized Cutaneous		Systemic Cutaneous		Ingestion		Inhalation		Nonsystemic[b,c]		Systemic[b,d]			
Treatment	(N = 93)		(N = 61)		(N = 16)		(N = 19)		(N = 100)		(N = 136)		(N = 46)	
None[e]	3/6	(50%)	1/2	(50%)	2/3	(67%)	0/2	(0%)	3/6	(50%)	4/9	(44%)	0/9	(0%)
1 Abx class[f]	61/62	(98%)	44/45	(98%)	5/8	(63%)	1/6	(17%)	62/64	(97%)	55/65	(85%)	3/14	(21%)
2 Abx classes	7/7	(100%)	8/8	(100%)	0/4	(0%)	4/4	(100%)	7/7	(100%)	14/19	(74%)	0/10	(0%)
≥3 Abx classes	8/8	(100%)	1/1	(100%)	0/1	(0%)	3/6	(50%)	13/13	(100%)	17/24	(71%)	3/8	(38%)
Antiserum[g]	…	…	2/2	(100%)	…	…	…	…	…	…	2/2	(100%)	0/1	(0%)
Antiserum and 1 Abx class	8/8	(100%)	…	…	…	…	…	…	8/8	(100%)	0/1	(0%)	1/2	(50%)
Antiserum and ≥2 Abx classes	1/1	(100%)	…	…	…	…	…	…	1/1	(100%)	6/8	(75%)	0/1	(0%)
Bactericidal(s)	60/61	(98%)	47/48	(98%)	5/11	(45%)	3/8	(38%)	61/63	(97%)	59/71	(83%)	4/18	(22%)
PSI(s)	11/11	(100%)	5/5	(100%)	0/1	(0%)	1/3	(33%)	11/11	(100%)	7/11	(64%)	0/2	(0%)
Bactericidal(s) and PSI(s)	6/6	(100%)	4/4	(100%)	0/1	(0%)	4/5	(80%)	11/11	(100%)	27/33	(82%)	3/13	(23%)

Abbreviations: Abx, antimicrobial; PSI, protein synthesis inhibitor.

[a]Treatments in this table refer to antimicrobials, antitoxin/antiserum, or a combination of both. Each line is the number of patients that survived divided by the total number that received that treatment only (eg, "single antimicrobial" means that they received a single antimicrobial and they did not receive antitoxin/antiserum. "Bactericidal(s)" means that they received 1 or more bactericidal antimicrobial(s) but no protein synthesis inhibitor and no antitoxin/antiserum). Sulfa drugs and cephalosporins are not considered anthrax-appropriate antimicrobial treatment and therefore did not contribute to the count of antimicrobials in this table. Patients described by author Meselson (N = 76) were excluded because they lacked treatment data [2]. Additional exclusions included 1 patient who was dead on arrival, 65 who died on their first day of hospitalization, and 8 who lacked survival status. Thirteen patients had at least 1 antimicrobial other than a sulfa or cephalosporin before hospitalization and 8 patients had their first treatment after day 2 of hospitalization and were excluded from this table. A few patients had unclear treatment timing and could not be classified.

[b]Systemic refers to our definition published in "Identifying Meningitis During an Anthrax Mass Casualty Incident: Systemic Review of Systemic Anthrax Since 1880" except that we removed the qualification of "death" [11].

[c]Nonsystemic patients lacking meningitis consisted of the following: 93 cutaneous and 7 injection.

[d]Systemic patients lacking meningitis consisted of the following: 61 cutaneous, 16 ingestion, 19 inhalation, and 40 injection.

[e]"None" refers to no antimicrobials or antitoxin/antiserum given at all before or throughout hospitalization. This is the only category that is not restricted to the first 2 days of hospitalization.

[f]Antimicrobials are lumped into classes; therefore, having 1 antimicrobial refers to 1 class of antimicrobials, 2 antimicrobials refers to having 2 different classes of antimicrobials, etc.

[g]This includes both antiserum and antitoxin.

included aminoglycosides (2 of 3), fluoroquinolones (5 of 8), or macrolides (3 of 4).

Among adults with anthrax meningitis, survival was low with both monotherapy and combination therapy (Table 3). Two adults with anthrax meningitis who received combination therapy including rifamycin (N = 2) or lincosamides (N = 4) survived, as did 3 who received combination therapy with fluoroquinolones (N = 7). There were no survivors among adults who received combinations with aminoglycosides (N = 6) or amphenicols (N = 5).

Table 4 shows univariate and multivariable analyses comparing the odds of survival for adults with systemic anthrax by antimicrobial treatment regimens with and without antitoxin/antiserum. Final adjustments are displayed in the table, but no final multivariable models included age or sex. For both univariate and multivariable analyses, adults who received bactericidal antimicrobial(s) alone had higher odds of survival than untreated adults (adjusted OR [OR_{adj}], 6.12; 95% CI, 1.49–25.14). On univariate analysis, survival for the 12 adults who received PSI antimicrobial(s) alone did not differ from those who went untreated; the small numbers precluded a multivariable analysis. On multivariable analysis, treatment with bactericidal antimicrobial(s) alone was superior to treatment with PSI antimicrobial(s) alone (OR_{adj} 4.57; 95% CI, 1.02–20.47). Outcomes were not improved by adding PSIs to bactericidal antimicrobials (OR_{adj} 1.54; 95% CI, .52–4.50) or by adding bactericidal antimicrobials to PSI antimicrobials (OR_{adj} 3.60; 95% CI, .73–17.64). Adults who received combination therapy had odds of survival similar to those who received monotherapy, even after adjusting for severity. The addition of antitoxin/antiserum to antimicrobials did not improve survival before or after adjustment (OR_{adj} 1.31; 95% CI, .24–7.07).

Table 5 shows univariate and multivariable analyses for survival by antitoxin/antiserum receipt throughout hospitalization. The odds of survival for adults given antitoxin/antiserum did not differ from those who received no antitoxin/antiserum before (OR, 1.55; 95% CI, .94–2.58) or after adjustment for age, hypoxia, shock, and altered mental status (OR_{adj} 1.49; 95% CI, .73–3.05).

Supplementary Tables 4 and 5 show univariate analyses for survival by type of treatment in children. Only a benefit of bactericidal antimicrobial(s) vs no treatment was observed (OR, 6.33; 95% CI, 1.20–33.39).

Survival occurred in 71% of adults who did not receive steroids and 47% of those who did. Table 6 describes survival for adults who received steroids for various indications (ie, shock, meningitis, head/neck involvement, and extensive edema). The proportion of survivors favored the "no steroid" group for all indications except meningitis. On multivariable

Table 3. Survival for Adults Reported to be Hospitalized for Anthrax by Meningitis Status, Route of Infection, Systemic Criteria, and Antimicrobial Treatment During First 2 Days of Hospitalization,[a] 1940–2018

	Monotherapy				Combination Therapy			
	Without Meningitis				Without Meningitis			
Treatment	Localized Cutaneous	Inhalation	Systemic[b]	With Meningitis	Localized Cutaneous	Inhalation	Systemic[b]	With Meningitis
None[c]	3/6 (50%)	0/2 (0%)	4/9 (44%)	0/9 (0%)	3/6 (50%)	0/2 (0%)	4/9 (44%)	0/9 (0%)
Any	61/62 (98%)	1/6 (17%)	55/65 (85%)	3/14 (21%)	15/15 (100%)	7/10 (70%)	33/45 (73%)	3/18 (17%)
Aminoglycosides	…	…	1/1 (100%)	…	1/1 (100%)	2/3 (67%)	8/12 (67%)	0/6 (0%)
Amphenicols	3/3 (100%)	…	1/1 (100%)	…	…	…	…	0/5 (0%)
Carbapenems	…	…	…	…	…	1/1 (100%)	2/4 (50%)	0/1 (0%)
Fluoroquinolones	1/1 (100%)	…	…	…	12/12 (100%)	5/8 (63%)	24/32 (75%)	3/7 (43%)
Glycopeptides	…	…	…	…	…	0/1 (0%)	4/7 (57%)	0/3 (0%)
Lincosamides	…	…	2/2 (100%)	0/1 (0%)	3/3 (100%)	2/2 (100%)	18/21 (86%)	2/4 (50%)
Macrolides	…	1/2 (50%)	1/2 (50%)	…	…	3/4 (75%)	4/5 (80%)	1/2 (50%)
Metronidazole	…	…	0/2 (0%)	…	…	…	2/4 (50%)	0/1 (0%)
Oxazolidinone	…	…	…	…	…	…	…	0/1 (0%)
Rifamycins	…	…	…	…	…	2/4 (50%)	2/4 (50%)	2/2 (100%)
Streptogramins	…	…	…	…	7/7 (100%)	…	…	…
Tetracyclines	8/8 (100%)	0/1 (0%)	3/4 (75%)	0/1 (0%)	4/4 (100%)	1/1 (100%)	2/2 (100%)	0/3 (0%)
Penicillins (all)	49/50 (98%)	0/3 (0%)	47/53 (89%)	3/12 (25%)	13/13 (100%)	3/6 (50%)	22/31 (71%)	2/15 (13%)
Beta-lactamase resistant or with a beta lactamase inhibitor[d]	4/4 (100%)	0/1 (0%)	3/4 (75%)	…	3/3 (100%)	1/3 (33%)	17/21 (81%)	1/2 (50%)
Other[d]	45/46 (98%)	0/1 (0%)	40/44 (91%)	3/12 (25%)	11/11 (100%)	3/7 (43%)	24/33 (73%)	2/15 (13%)

[a]Each line is the number that survived divided by the total number that received that treatment. Patients described by author Meselson were excluded because they lacked treatment data [2]. Additional exclusions included patients who were dead on arrival, patients who died on their first day of hospitalization, patients who lacked survival status, and patients who received antitoxin/antiserum during the first 2 days of hospitalization. Sulfa drugs and cephalosporins are not considered anthrax-appropriate antimicrobial treatment and therefore did not contribute to the count of antimicrobials in this table. Patients who had at least 1 antimicrobial other than a sulfa or cephalosporin before hospitalization or had their first treatment (antimicrobial or antitoxin/antiserum) after day 2 of hospitalization were excluded from this table. A few patients had unclear treatment timing and could not be classified.

[b]Systemic refers to our definition published in "Identifying Meningitis During an Anthrax Mass Casualty Incident: Systemic Review of Systemic Anthrax Since 1880" except that we removed the qualification of "death" [11].

[c]"None" refers to no antimicrobials or antitoxin/antiserum given at all before or throughout hospitalization. This is the only category that is not restricted to the first 2 days of hospitalization.

[d]In the last 2 lines of the table, when splitting out beta-lactamase resistant or with beta-lactamase inhibitor and other penicillins, monotherapy means that patients just had penicillins from that specific category. Combination therapy means they could have also had a penicillin from the other category or any other antimicrobial class. Beta-lactamase resistant or with beta-lactamase inhibitor penicillins include ampicillin/sulbactam, Tazocin, Augmentin, flucloxacillin, and other beta lactam penicillin. The "other" penicillin category includes amoxicillin, ampicillin, penicillin, and benzyl/benzathine penicillin.

analysis for adults with systemic anthrax, the odds of survival for the steroid and no steroid groups did not differ after adjusting for age and severity (data not shown). Supplementary Table 6 describes children who received steroids for various indications. No benefit of steroids was demonstrated for children with head-and-neck involvement (96% survival in treated compared with 94% survival in untreated) or meningitis (1 of 3 treated children survived compared with 3 of 10 untreated).

Table 7 describes univariate analysis results for adults treated for systemic anthrax meningitis. There is no difference in the odds of survival for combination vs monotherapy, bactericidal antimicrobial(s) vs PSI(s), and bactericidal antimicrobial(s) and PSI(s) combination therapy vs either, by itself; however, only 3–6 anthrax meningitis survivors were available for analysis of antimicrobials after exclusions. Adults who received mannitol had higher odds of survival than their counterparts (OR, 24.00; 95% CI, 1.66–347.85). However, odds of survival were not higher for those who received steroids (OR, 6.00; 95% CI, .76–47.36) or antimicrobials administered intrathecally (OR, 7.80; 95% CI, .89–68.30). Survival for children and adolescents hospitalized for systemic anthrax meningitis by specified treatment is summarized in Supplementary Table 7.

Table 8 provides median LOS and interquartile intervals for adult anthrax survivors by treatment received during their first 2 days of hospitalization (pediatric data, Supplementary Table 8). Median stays for survivors were 11 days (interquartile range [IQR] 8, 16) for localized cutaneous anthrax; 16 days (IQR 10, 29) for systemic anthrax without meningitis; and 19 days (IQR 12, 32) for meningitis. For meningitis, the shortest median LOS was observed in the 3 survivors who received both bactericidal and PSI antimicrobials—10 days (IQR 8, 21).

Supplementary Tables 9 and 10 summarize data on PEPAbx from a 1970 Russian-language article [14]. Before 1965, 339 of 626 (54%) people went untreated after exposures to anthrax-affected animals (exposure route and antimicrobial administration route were not specified): 58 (17%) developed anthrax. In contrast, only 5 of 287 (1.7%) people who received PEPAbx developed anthrax. All 3 regimens reduced risk of anthrax: daily

Table 4. Survival for Adults Reported to be Hospitalized for Systemic Anthrax by Specified Treatment During First 2 Days of Hospitalization and Illness Severity Through Admission, 1940–2018[a]

Treatment Comparison	Survived n (%), N	Died n (%), N	Univariate Analysis		Multivariable Analysis		Variables Included in Multivariable Analysis		
			OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	Hypoxia[b]	Shock[c]	AMS
Bactericidal(s) alone vs no antimicrobial treatment	60 (94%), 64	27 (61%), 44	9.44 (2.90–30.74)	<.01	6.12 (1.49–25.14)	.01	…	Y	Y
Protein synthesis inhibitor(s) alone vs no antimicrobial treatment	6 (60%), 10	6 (26%), 23	4.25 (.88–20.44)	.07	…	…	…	…	…
Bactericidal(s) alone vs protein synthesis inhibitor(s) alone	60 (91%), 66	27 (82%), 33	2.22 (.66–7.52)	.20	4.57 (1.02–20.47)	.047	…	Y	Y
Bactericidal(s) and protein synthesis Inhibitor(s) vs bactericidal(s) alone	26 (30%), 86	14 (34%), 41	0.84 (.38–1.85)	.66	1.54 (.52–4.50)	.43	Y	Y	Y
Bactericidal(s) and protein synthesis inhibitor(s) vs protein synthesis inhibitor(s) alone	26 (81%), 32	14 (70%), 20	1.86 (.50–6.85)	.35	3.60 (.73–17.64)	.11	Y	…	…
Bactericidal(s) and protein synthesis inhibitor(s) vs bactericidal(s) alone or protein synthesis inhibitor(s) alone	26 (28%), 92	14 (30%), 47	0.93 (.43–2.01)	.85	1.89 (.67–5.31)	.23	Y	Y	Y
Antimicrobial combination therapy vs monotherapy[d]	31 (36%), 87	25 (53%), 47	0.49 (.24–1.00)	.051	0.88 (.33–2.35)	.80	Y	Y	Y
Antimicrobial(s) and antitoxin/antiserum vs antimicrobial(s) alone	7 (7%), 100	5 (9%), 55	0.75 (.23–2.49)	.64	1.31 (.24–7.07)	.75	Y	Y	Y

Abbreviations: AMS, altered mental status; CI, confidence interval; OR, odds ratio; Y, yes.

[a]Patients are only included in each row if they received the specified treatment. Patients are considered to have the specified treatment if given in the first 2 days of hospitalization. Patients are classified as having no antimicrobial treatment if they did not receive any antimicrobials throughout hospitalization. Patients were excluded from analysis if they were dead on arrival, died on day 1 of hospitalization, or lacked survival status. Additional exclusions included patients who were given anthrax-appropriate antimicrobial treatment before hospitalization. Sulfa drugs and cephalosporins are not considered anthrax-appropriate antimicrobial treatment and therefore did not contribute to the count of antimicrobials in this table. Patients who were given antitoxin/antiserum at any time in the course of their treatment were excluded except when comparing antimicrobial(s) and antitoxin/antiserum to antimicrobial(s) alone. Patients described by the author Meselson were excluded because they lacked sign, symptom, and treatment data [2].

[b]Ventilated or intubated or respiratory rate > 30.

[c]Vasopressors or systolic blood pressure < 90 mmHg.

[d]Included 1 anthrax meningitis patient who did not meet our definition of systemic.

penicillin for 3 days, 1 dose of penicillin plus 1 dose of intramuscular penicillin, and chlortetracycline for 3 days. From 1965 through 1967, another 407 people were given these same PEPAbx regimens for *B. anthracis*–contaminated meat exposures. None were infected in any of the 3 groups.

DISCUSSION & CONCLUSION

This retrospective review of more than a century of English-language publications analyzed treatment outcomes for patients hospitalized for various types of anthrax. Table 9 summarizes the major findings of this review. Both adults and children with localized anthrax, most of whom had only cutaneous illness, almost always survived with treatment, including monotherapy. Patients with systemic illness had lower survival than those with localized illness. Survival among systemically ill adults without meningitis depended on route of infection and treatment type: 16 adults with inhalation anthrax had higher survival with combination therapy and did poorly with monotherapy, supporting prior findings by Holty et al [15], whereas all 16 adults with ingestion anthrax had poor survival, whether treated or not. Most children (10 of 12 [83%])

Table 5. Survival for Adults Reported to be Hospitalized for Anthrax by Antitoxin/Antiserum Receipt Throughout Hospitalization and Illness Severity Through Admission, 1900–2018[a]

	Survived n (%), N	Died n (%), N	Univariate Analysis		Multivariable Analysis		Variables Included in Multivariable Analysis			
			OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	Age	Hypoxia[b]	Shock[c]	AMS
Antitoxin/antiserum vs no antitoxin/antiserum	84 (28%), 298	25 (20%), 124	1.55 (.94–2.58)	.09	1.49 (.73–3.05)	0.27	Y	Y	Y	Y

Abbreviations: AMS, altered mental status; CI, confidence interval; OR, odds ratio; Y, yes.

[a]Patients were excluded from analysis if they were dead on arrival, died on day 1 of hospitalization, or lacked survival status. Patients described by the authors Meselson and Andrews were excluded because they lacked sign, symptom, and treatment data [2, 13]. Patients included in this analysis could have received other treatment, including antimicrobials.

[b]Ventilated or intubated or respiratory rate > 30.

[c]Vasopressors or systolic blood pressure <90 mm Hg.

Table 6. Survival for Adults Reported to be Hospitalized for All Types of Anthrax With Various Complications by Steroid Use, 1950–2018[a]

	Steroids		No Steroids	
Indication for Steroid Use	Survived/Total With steroids	(%)	Survived/Total Without Steroids	(%)
Shock (N = 19)[b]	0/2	(0)	6/17	(35)
Meningitis, both primary and secondary (N = 44)[c]	1/5	(20)	3/39	(8)
Head or neck involvement (N = 52)[d]	4/7	(57)	38/45	(84)
Edema involving > 1 extremity (N = 37)[e]	4/8	(50)	24/29	(83)

[a]Excluded patients that were dead on arrival, died on day 1 of hospitalization, or lacked survival status. Excluded patients that were given steroids before hospitalization or after day 2 of hospitalization. Patients that had steroids but no timing information were included. Patients from the author Meselson were excluded because they lacked sign, symptom, and treatment data [2].

[b]These include the following routes of infection: 6 cutaneous, 7 injection, 3 inhalation, and 3 ingestion.

[c]These include the following routes of infection: 18 cutaneous, 9 inhalation, 10 primary meningitis, 5 injection, and 2 ingestion. Patients are classified as (1) primary meningitis if they met criteria for meningitis [11] but lacked a discernable route of infection, and (2) secondary meningitis if they met criteria for meningitis and had another route of primary infection.

[d]These include the following routes of infection: 45 cutaneous, 5 ingestion, and 2 injection.

[e]These include the following routes of infection: 24 cutaneous, 10 injection, and 3 ingestion.

Table 7. Survival for Adults Reported to be Hospitalized for Systemic Anthrax Meningitis by Specified Treatment[a]

	Survived n (%), N	Died n (%), N	OR (95% CI)	*P* Value
Antimicrobials[b]				
Combination therapy vs	3 (60), 5	14 (56), 25	1.18 (.17–8.33)	.87
monotherapy	2 (40), 5	11 (44), 25	Reference	
Bactericidal(s) alone vs	3 (100), 3	14 (88), 16	0.46 (.05–inf)	1.00
PSI(s) alone	0 (0), 3	2 (13), 16	Reference	
Bactericidal(s) and PSI(s) vs	3 (50), 6	9 (36), 25	1.78 (.30–10.72)	.53
bactericidal(s) alone or PSI(s) alone	3 (50), 6	16 (64), 25	Reference	
Steroids[c]				
Yes	2 (40), 5	4 (10), 40	6.00 (.76–47.36)	.09
No	3 (60), 5	36 (90), 40	Reference	
Mannitol[d]				
Yes	2 (40), 5	1 (3), 37	24.00 (1.66–347.85)	.02
No	3 (60), 5	36 (97), 37	Reference	
Intrathecal/intraspinal[e]				
Yes	2 (29), 7	2 (5), 41	7.80 (.89–68.30)	.06
No	5 (71), 7	39 (95), 41	Reference	
Antitoxin/antiserum[f]				
Yes	1 (14), 7	8 (14), 57	1.02 (.11–9.64)	.99
No	6 (86), 7	49 (86), 57	Reference	

Abbreviations: CI, confidence interval; OR, odds ratio; PSI, protein synthesis inhibitor(s).

[a]Patients were excluded from analysis if they were dead on arrival, died on day 1 of hospitalization, or lacked survival status. Patients described by the authors Meselson and Andrews were excluded because they lacked sign, symptom, and treatment data [2, 13].

[b]Patients are considered to have the specified antimicrobial treatment if given in the first 2 days of hospitalization. Patients were excluded if they were given anthrax-appropriate antimicrobial treatment before hospitalization or if they were given antitoxin/antiserum at any time in the course of their treatment. Sulfa drugs and cephalosporins are not considered anthrax-appropriate antimicrobial treatment and therefore did not contribute to the count of antimicrobials in this table. Only included patients who were described in medical literature from 1940 through 2018.

[c]Only included patients in medical literature from 1950 through 2018.

[d]Only included patients in medical literature from 1960 through 2018.

[e]Only included patients in medical literature from 1940 through 2018.

[f]Only included patients in medical literature from 1900 through 2018.

reported to have ingestion anthrax survived, whether treated or not.

These data on survival with ingestion anthrax are notably different than published outbreak summaries, which suggest (1) better prognosis for promptly treated patients but (2) higher mortality in untreated children. For instance, there were 134 survivors among Ugandan patients with ingestion anthrax treated with penicillin plus tetracycline. However, 9 children died before treatment was implemented [16]. Ingestion anthrax is likely underdiagnosed given the vast number of pathogens causing gastroenteritis. Unlike cutaneous anthrax (which presents with an obvious lesion) and inhalation anthrax (which often presents with characteristic radiological findings), ingestion anthrax is characterized by nausea, vomiting, and abdominal pain, with or without bloody diarrhea–symptoms seen with most enteric pathogens. Our inclusion criteria may therefore be overly specific and resulting analyses may not represent the true survival rate for this condition.

For systemically ill adults with or without meningitis, ≥1 bactericidal antimicrobials were superior to ≥1 PSI antimicrobials; adding an antitoxin/antiserum to antimicrobials did not improve survival. Of the 62 adults (8 survivors and 54 fatalities) with meningitis in our study, survival rates were highest among those who received antimicrobial combinations including fluroquinolones, lincosamides, or rifamycin. The latter finding agrees with recommendations made by Lanska et al [17]. Fluroquinolones, lincosamides, and rifamycin all have high central nervous system penetration and were previously recommended by the Centers for Disease Control and Prevention for anthrax meningitis [7]. However, there were no survivors among the 6 adults who received aminoglycosides or the 5 who received amphenicols.

Regarding the utility of steroids, our current data set did not have enough cases to show their use significantly contributed to adult survival for meningitis (2 of 5 survivors received steroids). However, we are aware of 2 additional adult meningitis survivors outside the time frame for our systematic review who received steroids, as well as mannitol: the survivor described in our supplement [18] and a survivor described by Popescu et al [19]. Adding in these 2 survivors from after 2018 would make steroid use statistically significant, assuming the 2 cases met all inclusion criteria and no fatal cases who received steroids were published after 2018.

Table 8. Hospital Length of Stay for Adult Survivors Reported to be Hospitalized for Anthrax by Meningitis Status, Route of Infection, Systemic Criteria, and Treatment During First 2 Days of Hospitalization[a], 1940–2018

	Localized Cutaneous[b,c] (N = 93 [89 Survivors])		Systemic (Without Meningitis)[b,d] (N = 136 [106 Survivors])		With Meningitis (N = 46 [8 Survivors])	
	Length of Stay		Length of Stay		Length of Stay	
Treatment	Median (N)	IQR	Median (N)	IQR	Median (N)	IQR
None[e]	6 (1)	…	9 (3)	8–12	- (-)	…
1 Abx class[f]	11 (28)	8–14	14 (27)	8–20	43 (3)	14–56
2 Abx classes	23 (3)	5–31	28 (9)	18–61	- (-)	…
≥3 Abx classes	10 (2)	6–14	19 (14)	11–30	16 (3)	8–21
Antiserum[g]	- (-)	…	14 (1)	…	- (-)	…
Antiserum and 1 Abx class	17 (8)	15–22	- (-)	…	21 (1)	…
Antiserum and ≥ 2 Abx classes	- (-)	…	38 (5)	31–42	- (-)	…
Bactericidal(s)	11 (25)	8–14	15 (31)	9–22	30 (4)	15–50
PSI(s)	12 (4)	8–16	18 (2)	12–23	- (-)	…
Bactericidal(s) and PSI(s)	10 (4)	6–19	17 (22)	13–31	10 (3)	8–21

Abbreviations: Abx, antimicrobial; IQR, interquartile range; PSI, protein synthesis inhibitor(s).

[a]Treatments in this table refer to antimicrobials, antitoxin/antiserum, or a combination of both. Each line is the length of hospital stay for survivors on that treatment only (eg, "single antimicrobial" means that they received a single antimicrobial and they did not receive antitoxin/antiserum. "Bactericidal(s)" means that they received 1 or more bactericidal antimicrobial(s) but no protein synthesis inhibitor and no antitoxin/antiserum). Sulfa drugs and cephalosporins are not considered anthrax-appropriate antimicrobial treatment and therefore did not contribute to the count of antimicrobials in this table. Patients described by author Meselson (N = 24) were excluded because they lacked treatment data [2]. Additional exclusions included 63 patients who died on their first day of hospitalization and 8 who lacked survival status. Thirteen patients had at least 1 antimicrobial other than a sulfa or cephalosporin before hospitalization and 7 patients had their first treatment after day 2 of hospitalization and were excluded from this table. A few patients had unclear treatment timing and could not be classified.

[b]Systemic refers to our definition published in "Identifying Meningitis During an Anthrax Mass Casualty Incident: Systemic Review of Systemic Anthrax Since 1880" except that we removed the qualification of "death" [11].

[c]One localized cutaneous patient had possible meningitis and was excluded from these columns. This 1 patient had antimicrobial monotherapy (a bactericidal) and lived. The length of hospital stay for this patient was 14 days.

[d]Systemic patients lacking meningitis consisted of the following: 61 cutaneous, 16 ingestion, 19 inhalation, and 40 injection.

[e]"None" refers to no antimicrobials or antitoxin/antiserum given at all before or throughout hospitalization. This is the only category that is not restricted to the first 2 days of hospitalization.

[f]Antimicrobials are lumped into classes; therefore, having 1 antimicrobial refers to 1 class of antimicrobials, 2 antimicrobials refers to having 2 different classes of antimicrobials, etc.

[g]This includes both antiserum and antitoxin.

Adults with meningitis who received mannitol were more likely to survive than nonrecipients. Because of hemorrhage and infection, patients with meningitis may have rapid onset of cerebral edema. Hyperosmolar therapy, such as mannitol or hypertonic saline, might reduce swelling and herniation and improve chances of survival [20].

Overall, hospital LOS appeared similar for adults with localized cutaneous illness, systemic illness without meningitis, and meningitis. However, direct comparisons between LOS for patients with meningitis and those with localized or systemic infections are likely to be biased. Those with mild disease, treated relatively early, might have had shorter LOS and avoided long-term neurologic complications, including intracranial tissue necrosis, abscess formation, stroke, and hemorrhage. Long-term neurologic complications with extended rehabilitation may be additional costs that should be evaluated in patients with anthrax meningitis.

Finally, a 1970 Russian-language article [14] translated to English for the systematic review described in Kennedy et al [21] documents human PEPAbx following known *B. anthracis* exposures. This article has not previously been published in English literature and appears to have predated consensus on PEPAbx in the former Soviet Union (present-day Russia). The Soviet Union appears to have enacted a highly effective PEPAbx policy around 1965: everyone exposed to *B. anthracis* after that date was effectively prophylaxed.

Our retrospective review of publications from many countries over 138 years has several limitations. We limited our search to English-language articles; reports of cases in other languages may have provided additional evidence on effective therapies. The data were extracted from case reports, case series, and line lists. Details were not always provided regarding pertinent negatives, prehospital duration of illness, vasopressors, mechanical ventilation, treatment regimens, and outcomes. A high degree of variability in medical care standards across the globe was present over the 138 years covered by our review. The most dramatic or successfully treated cases may have been preferentially published, which could lead to unrepresentative conclusions—particularly for mortality and LOS. Analyses regarding antimicrobial effectiveness were restricted to the 1940s and later; temporal changes in medical care standards could have favored survival with the newer antimicrobials. Survival for those who received monotherapy and combination therapy should not be directly compared: physicians may have prescribed combination therapy, rather than monotherapy, to the sicker patients, and more sophisticated methods for analytically adjusting for severity (eg, acute physiology and chronic

Table 9. Summary of Findings From This Anthrax Treatment Systematic Review

Patient scenario	Recommendation
Dermal or ingestion exposure to Bacillus anthracis	Postexposure prophylaxis has been shown to reduce risk of anthrax
Localized cutaneous anthrax	Antimicrobial monotherapy is highly effective. Penicillin may be used as monotherapy if susceptibilities are known
Systemic anthrax without meningitis	Treatment with ≥1 bactericidal antimicrobials, with or without a protein synthesis inhibitor, is effective
Inhalation anthrax without meningitis	Combination therapy improves survival
Systemic anthrax, regardless of meningitis status	Treatment with ≥1 bactericidal antimicrobials is preferable to treatment with ≥1 protein synthesis inhibitors
	Addition of antitoxin/antiserum to antimicrobial treatment has not been shown to improve or decrease survival
Any type of anthrax	Steroids for nonmeningitis indications have not been shown to improve or decrease survival
Anthrax meningitis	Mannitol appears to improve survival
	Steroids might improve survival

evaluation [APACHE] II) could not be used because the data were not available. Although this is the largest compilation of hospitalized anthrax cases to date, most were cutaneous. Combinations of some drug classes appeared more successful than others; however, these finding should be interpreted cautiously. Observational data cannot provide the quality of evidence that would be provided by prospective, controlled studies comparing different therapies.

Information on current cases of anthrax should continue to be gathered for future efforts to analyze treatment efficacies. Well-designed animal-model treatment studies could determine whether some combinations of antimicrobial classes are associated with higher survival than others. Currently, treatment studies for anthrax meningitis in animal models are almost nonexistent. Future anthrax meningitis studies in primates would be the most applicable to humans, using defined inoculation with *B. anthracis* spores, with optimal antibiotic and adjunctive therapy regimens to achieve the best neurologic outcomes.

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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