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Antimicrobial Treatment for Systemic Anthrax: Analysis of Cases from 1945–2014 Identified through Systematic Literature Review

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Abstract

Background—Systemic anthrax is associated with high mortality. Current national guidelines, developed for the individualized treatment of systemic anthrax, outline the use of combination intravenous antimicrobials for a minimum of two weeks; bactericidal and protein synthesis inhibitor antimicrobials for all cases of systemic anthrax; and at least 3 antimicrobials with good blood-brain barrier penetration for anthrax meningitis. However, in an anthrax mass casualty incident, large numbers of anthrax cases may create challenges in meeting antimicrobial needs.

Methods—To further inform our understanding of the role of antimicrobials in treating systemic anthrax, a systematic review of the English language literature was conducted to identify cases of systemic anthrax treated with antimicrobials for which a clinical outcome was recorded.

Results—A total of 149 cases of systemic anthrax were identified (cutaneous [n=59], gastrointestinal [n=28], inhalation [n=26], primary anthrax meningitis [n=19], multiple routes [n=9], and injection [n=8]). Among the identified 59 cases of cutaneous anthrax, 33 were complicated by meningitis (76% mortality), while 26 simply had evidence of the systemic inflammatory response syndrome (4% mortality); 21 of 26 (81%) of this latter group received monotherapy. Subsequent analysis regarding combination antimicrobial therapy was restricted to the remaining 123 cases of more severe anthrax (overall 67% mortality). Recipients of combination bactericidal and protein synthesis inhibitor therapy had a 45% survival versus 28% in the absence of combination therapy (p = 0.07). For meningitis cases (n=77), survival was greater for those receiving a total of ≥3 antimicrobials over the course of treatment (3 of 4; 75%), compared to receipt of 1 or 2 antimicrobials (12 of 73; 16%) (p = 0.02). Median parenteral antimicrobial duration was 14 days.

Conclusion—Combination bactericidal and protein synthesis inhibitor therapy may be appropriate in severe anthrax disease, particularly anthrax meningitis, in a mass casualty incident.

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Human Participation Protection

As a review of previously reported cases protocol approval was not needed for this work

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Introduction

In 2014 CDC published updated national guidelines on the clinical management of anthrax [1–3]. These practice guidelines outline the use of combination intravenous (IV) antimicrobials in the treatment of systemic anthrax. Treatment regimens are defined by clinical manifestations of disease and involve two sets of recommendations – one for treatment of individuals with confirmed, or suspected anthrax meningitis (or for instances where meningitis cannot be ruled out), and one for individuals in whom meningitis has been ruled out. Both recommendations call for intravenous treatment that includes at least one bactericidal agent combined with a protein synthesis inhibitor; in the setting of meningitis, the addition of a third, preferably bactericidal, antimicrobial agent is recommended [2]. Bactericidal agents with good blood-brain barrier penetration recommended for the treatment of suspected or confirmed anthrax meningitis include quinolones, carbapenems, and if the isolate is susceptible, β-lactams such as penicillin G and ampicillin [2].

Regarding protein synthesis inhibitors, options include linezolid as the preferred agent because of high central nervous system (CNS) concentrations while acceptable alternatives include clindamycin, rifampin and, if linezolid, clindamycin, and rifampin are unavailable, chloramphenicol. For non-meningitis, systemic anthrax (which includes inhalation anthrax and other forms of anthrax with systemic involvement), recommendations also include vancomycin as a potential bactericidal agent and doxycycline as an alternative protein synthesis inhibitor [2]. Combination intravenous antimicrobials are recommended for a minimum of two weeks for patients with systemic anthrax. This is consistent with findings from a systematic review of inhalation anthrax cases from the pre-antimicrobial era (1900) to 2005, where survivors were significantly more likely to have received a multi-drug antimicrobial regimen [4]. Cutaneous anthrax without systemic involvement historically is associated with a substantially lower mortality and thus oral monotherapy is considered adequate [2]. Combination antimicrobial therapy for cutaneous anthrax is recommended for cases with systemic signs or symptoms (e.g., systemic inflammatory response syndrome), or cutaneous disease involving the head/neck, or associated with significant edema [2]. These recommendations were developed as Best Practices recommendations for the treatment of an individual (or small number of) patient(s) [2] (herein referred to as Best Practices guidance). However, an anthrax mass casualty incident has the potential to produce hundreds of thousands of patients with systemic anthrax disease. Given that the current recommendations advise the use of multiple intravenous antimicrobials in the treatment of systemic anthrax, a mass casualty event involving large numbers of affected individuals could result in challenges in adequately meeting intravenous antimicrobial needs. As part of ongoing efforts to plan for large-scale bioterrorism events, CDC is developing clinical guidance for an anthrax mass casualty incident. To inform such guidance, a systematic review of antimicrobials utilized for the treatment of anthrax was conducted to summarize what is known about historical survival with combination antimicrobial treatment. This includes an assessment of the types and combinations of antimicrobials used to treat anthrax as well as information on the duration of anthrax treatment.

The systematic review was conducted to identify available data regarding: 1) combining a bactericidal antimicrobial with a protein synthesis inhibitor in the treatment of systemic

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anthrax disease, 2) the use of three antimicrobials for the treatment of anthrax meningitis, and 3) the duration of parenteral antimicrobial therapy for systemic anthrax.

Methods

Data Sources and Search Strategy

In collaboration with a CDC librarian, we conducted a systematic review of English literatures using the following twelve databases: Commonwealth Agricultural Bureaux (1973-), Cumulative Index to Nursing and Allied Health Literature (1981-), Defense Technical Information Center (1950-), EconLit (1886-), Embase (1988-), Federal Research in Progress (1930-), Global health (1910-), MEDLINE (1946-), National Technical Information Service (1964-), Web of Science (1980-), World Health Organization (1948-), and WorldCat (1967-). All databases were searched from inception through May 14, 2014 (See Figure 1 for search terms). Additional reports were identified through reference searching and consultation with subject-matter experts. Recognizing that all the studies were non-randomized and observational in nature, the quality of the primary data analyzed in this review is low [5].

Study Selection

We included author-reported cases of human anthrax that were treated with antimicrobials described in the Best Practices document [2] and for which a final outcome of survival was recorded. An initial review of titles and abstracts identified from the search strategy was conducted by two independent reviewers. Articles with a title or abstract containing information pertaining to human anthrax treated with antimicrobials were selected for full-text review. Four independent systematic reviewers then conducted full-text reviews to identify eligible studies based on clinical, epidemiologic, radiologic, pathologic, microbiologic, and other laboratory data provided in the report. Data abstraction was conducted in duplicate and decisions regarding inclusion of anthrax cases were adjudicated by a committee of clinical anthrax experts. We restricted reports of cutaneous anthrax to those that had evidence of systemic infection by systemic inflammatory response syndrome (SIRS) criteria [6, 7] or evidence of cutaneous anthrax complicated by anthrax meningitis.

Data Abstraction and Analysis

An Excel data abstraction tool was developed by the systematic reviewers. Data were collected for each individual for whom treatment was described. The following data elements were collected, when available: author, year of publication, and country of report; patient age and sex; type of anthrax, epidemiologic, clinical, pathologic and microbiologic features associated with diagnosis, evidence of systemic infection (fever, hypothermia, tachycardia, tachypnea, hypotension, leukocytosis or leukopenia based on age-specific thresholds as defined in [6, 7], and presence or absence of meningitis; antimicrobials used in treatment, mode of administration, antimicrobial class (bactericidal or protein synthesis inhibitor as defined in the Best Practices guidance [2]), total number of Best Practices [2] antimicrobials received during the course of treatment, combination treatment with bactericidal and protein synthesis inhibitor therapy (defined as any period during which there was concomitant receipt of a bactericidal agent and a protein synthesis inhibitor), and

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duration of parenteral (intravenous or intramuscular (IM) antimicrobial treatment; and outcome (lived or died). Meningitis status was classified as follows: confirmed case if cerebrospinal fluid (CSF) with gram positive bacilli or a positive CSF culture for *B. anthracis*; probable case if reported altered mental status, meningeal signs, focal neurologic deficits, coma, CSF pleocytosis, presence of CSF red blood cells, CSF xanthochromia or a bloody CSF profile. Due to the lack of human clinical trials and heterogeneity in treatment regimens, we did not perform a meta-analysis.

Descriptive epidemiology was performed on the final dataset using Excel (Microsoft, Redmond WA) and SAS 9.3 (Cary, NC) and, where relevant, statistical testing performed using Chi-square testing or Fisher's Exact Testing for small cell sizes.

Results

One hundred forty-nine individual cases, identified in 98 articles (Figure 2; Appendix Table A), received an antimicrobial recommended in the Best Practices guidance [2]; had evidence of cutaneous disease (with systemic signs or symptoms and/or complicated by meningitis), GI anthrax, inhalation anthrax, injection anthrax, or primary anthrax meningitis (CNS disease without any other route of infection noted); and a defined outcome (survived or died). The cases were reported in the literature between 1945 and 2014. Over 80% of the cases were reported from the following 7 countries (from which ≥5 cases were reported): India (n=30), U.S. (n=27), Turkey (n=24), Iran (n=24), U.K. (n=9), Lebanon (n=6), and Zimbabwe (n=5). One hundred forty-five cases had recorded sex; 42 (29%) were female and 103 (71%) were male. Age was recorded in 145 cases; 111 (77%) were 18 years and older and 34 (23%) 17 years and younger. Appendix Table A presents the evidence table generated from this systematic review.

Types of anthrax

The most common types of anthrax were as follows: cutaneous (with systemic signs or symptoms and/or meningitis) (n=59, 40%), GI (n=28, 19%), inhalation anthrax (n=26, 17%), primary anthrax meningitis (n=19, 13%; probable n=4, confirmed n=15), multiple types, (n=9, 6%, such as GI and cutaneous, GI and inhalation, and GI and injection), and injection anthrax (n=8, 5%). Overall, 77 (52%) individuals had confirmed (n=53) or probable (n=24) anthrax meningitis (either as a complication following another route of infection or as primary CNS infection).

Thirty-three of the 59 individuals with a cutaneous route of infection met criteria for meningitis; of these, 25 died (76% mortality). Among the remaining 26 individuals with cutaneous anthrax who met SIRS criteria, 1 died (4% mortality). For the other frequently identified types of anthrax (n≥10 cases), mortality was reported to be 57%, 65%, and 89% for GI, inhalation, and primary anthrax meningitis, respectively (Table 1). Overall, 62 of 77 individuals (81%) with either probable or confirmed anthrax meningitis (either as a complication following another route of infection or as primary CNS infection) died. Among just those with confirmed anthrax meningitis, 47 of 53 individuals [89%] died.

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In addition to the substantially lower mortality rate of the 26 individuals with systemic cutaneous anthrax without reported meningitis, compared to the mortality for the other frequently identified forms of anthrax, 21 of 26 (81%) received single drug therapy and only 1 received overlapping bactericidal and protein synthesis inhibitor antimicrobial therapy. Given these observations, these individuals were not included in the subsequent analyses evaluating antimicrobial therapy and the remainder of the results focus on severe anthrax defined as all forms of anthrax other than cutaneous anthrax without secondary meningitis (i.e., cutaneous anthrax with secondary meningitis, inhalation, injection, GI anthrax, and primary anthrax meningitis).

Antimicrobial use and outcome for severe anthrax disease

Antimicrobial use, categorized as bactericidal or protein synthesis inhibitor therapy, was analyzed for the 123 remaining individuals, of whom 82 died (67% mortality). Among bactericidal agents, most cases received a penicillin class antimicrobial (n=108), followed by fluoroquinolones (n=27), vancomycin (n=8), or a carbapenem (n=4). For protein synthesis inhibitor therapy, the antimicrobials included chloramphenicol (n=20), clindamycin (n=20), rifampin (n=8), doxycycline (n=3), and linezolid (n=1).

In descending order, individuals received a total of 1 antimicrobial (n = 79, 64%), 2 antimicrobials (n = 22, 18%) or ≥ 3 antimicrobials (n=22, 18%) over their treatment course (Table 2). By class of antimicrobials, most single agent treatment consisted of a penicillin-class antimicrobial (74 of 79 individuals, 94%), with 42% of single agent therapy occurring among cases reported prior to 1990. Receipt of a single antimicrobial was associated with a 72% mortality.

To determine the association between survival and combined bactericidal and protein synthesis inhibitor therapy, survival for individuals who received (at any point in their treatment course and for any duration) overlapping therapy with a bactericidal agent and a protein synthesis inhibitor was compared to individuals who received at least one Best Practices [2] antimicrobial but never received overlapping bactericidal and protein synthesis inhibitor antimicrobials. Those receiving overlapping bactericidal and protein synthesis inhibitor therapy had a survival rate of 45% (17 of 38 patients) compared to those not receiving overlapping therapy (24 of 85 patients, 28%) ($p = 0.07$).

Table 3 provides detailed information regarding the type and number of antimicrobials received during course of treatment for the 77 patients with anthrax meningitis (confirmed and probable), stratified by mortality. In descending order, individuals received 1 antimicrobial (n = 54, 70%), 2 antimicrobials (n = 19, 25%) or ≥ 3 antimicrobials (n=4, 5%) over their treatment course. By class of antimicrobials, most single agent treatment consisted of a penicillin-class antimicrobial (51 of 54 individuals, 94%). Among these 77 patients, 75% (3 of 4 patients) of those receiving a total of ≥3 antimicrobials over the course of their treatment survived compared to 16% (12 of 73 patients) of those who received either a total of 1 or 2 antimicrobials over the course of their treatment ($p = 0.02$). Moreover, nineteen individuals with probable or confirmed meningitis received, for some duration, combination bactericidal and protein synthesis inhibitor antimicrobial therapy. Over the course of their

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treatment, four received a total of ≥3 antimicrobials (75% survival) and 15 received a total of 2 antimicrobials (7% survived) ($p = 0.02$).

Duration of Best Practices parenteral treatment

To determine how long to continue parenteral treatment, duration of Best Practices IV or IM antimicrobial therapy was assessed among those who survived anthrax. This information was recorded for 16 of 41 individuals. The median number of days of Best Practices IV or IM therapy was 14 days (range 0–30 days; 1 individual with anthrax meningitis received 10 days of cefaperazone/sulbactam + metronidazole (which would not count toward receipt of an IV or IM Best Practices antimicrobial [2]), followed by 60 days oral ciprofloxacin) [8]. For the subset of individuals that survived confirmed or probable anthrax meningitis, duration of Best Practices IV or IM antimicrobial therapy was recorded for 11 of 15 individuals and the median was 14 days (range 0–26 days).

Discussion

During an anthrax mass casualty incident, it is anticipated that individuals will present with inhalation anthrax from breathing in spores, cutaneous anthrax from physical contact with spores, and cases may be complicated by anthrax meningitis. Inhalation anthrax, anthrax meningitis, and cutaneous disease involving the head/neck or surrounded by significant edema have been reported to be associated with high mortality [4, 9, 10]. It is important to understand the role of combination antimicrobial regimens (in terms of number of agents and type of agents) for the treatment of systemic anthrax to ensure judicious and optimal use of antimicrobials during a mass casualty incident. On the other hand, for uncomplicated cutaneous anthrax, oral monotherapy should suffice and therefore this is less of a concern for mass event planning [2].

Before evaluating treatment regimens, we sought to understand the types of anthrax that have historically been most severe: inhalation anthrax and anthrax meningitis. In an earlier systematic review of inhalation anthrax [4], the overall mortality was 85%. Of note, that systematic review includes cases from 1900 through 2005, and thus includes inhalation anthrax cases from prior to the antimicrobial era. However, even among the 32 patients treated with antimicrobials, mortality remained high, at 75%. Consistent with these findings, our systematic review of anthrax cases treated with antimicrobials also found a high mortality: 70% among the 30 inhalation cases. Furthermore, in one review of 70 cases of anthrax meningoencephalitis, mortality was reported to be 94% [10]. In our systematic review, meningitis complicated 77 of 149 cases (52%) of systemic anthrax and 81% of these individuals died.

Combination bactericidal and protein synthesis inhibitor therapy may be appropriate in severe anthrax disease, particularly anthrax meningitis, as noted in the Best Practices guidelines [2]. In another systematic review focused on inhalation anthrax cases, including cases from the pre-antimicrobial era, previous investigators showed that receipt of a multi-drug regimen was associated with decreased mortality when compared to individuals that did not receive such treatment (which included single drug treatment as well as no antimicrobial treatment) [4]. In this review of antimicrobial therapy for systemic anthrax,

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our findings did not contradict current national guidelines, finding that among individuals treated with one or more Best Practices [2] antimicrobials for systemic anthrax, 45% of those receiving overlapping bactericidal-protein synthesis inhibitor therapy survived versus 28% of those without any overlapping bactericidal-protein synthesis inhibitor treatment. Much of anthrax pathogenesis is toxin mediated, thus the finding of an added benefit of protein synthesis inhibition is consistent with known mechanisms of disease. In vitro data confirm that a protein synthesis inhibitor (linezolid) is more effective than a bactericidal antimicrobial (ciprofloxacin) in attenuating *B. anthracis* toxin production [11]. In addition, the use of a protein synthesis inhibitor (clindamycin) has been shown to improve clinical outcomes of invasive group A streptococcal infections in humans, an infection that is known to be associated with bacterial toxin production [12].

While the Best Practices guidance [2] calls for combination triple antimicrobial therapy for meningitis, there was a paucity in our dataset of cases receiving 3 or more antimicrobials for meningitis. Among the subset of individuals with meningitis who received, for some period of time, combination bactericidal and protein synthesis inhibitor therapy, a higher percent survival was observed for those receiving 3 or more antimicrobials versus those receiving only 2 antimicrobials. These recommendations are consistent with a review of the management of anthrax meningoencephalitis by Sejvar and colleagues, in which they recommend the use of a fluoroquinolone coupled with 1 or 2 other antimicrobials with good CNS penetration [13]. Whether the improved outcomes associated with the use of three or more antimicrobials over the course of treatment relates to greater likelihood of at least one antimicrobial crossing the blood-brain barrier, versus a synergistic antimicrobial effect, or some other undefined factor, remains to be elucidated.

One limitation of these data relates to the fact the reports described in this manuscript were from the English literature only, though we did review nearly 6,700 titles and abstracts, conducted nearly 400 full text reviews, and the cases included in this analysis were from a very wide geographic distribution. In addition, several limitations in the available data impede our ability to know with certainty whether improved survival was due to combination antimicrobial therapy, advances in critical care medicine, or other confounding factors, such as shorter times to treatment or ancillary treatments such as intravenous fluid. As all the data was observational in nature, its quality could be considered, at best, low [5]. The reports we reviewed contained diverse and varying levels of information, requiring clinical interpretation. As noted, duration of treatment was not captured in a uniform manner, and this was the case with other treatment related variables, such as timing of antimicrobial therapy and route of administration. And, the definitions used for systemic anthrax and anthrax meningitis were based on interpretation of reported signs, symptoms, and epidemiologic, radiologic, pathologic and laboratory parameters. In addition, the data analyzed include cases spanning a 70-year period, during which antimicrobial options and intensive care have changed tremendously. The primary bactericidal antimicrobials recommended in the Best Practices guidance (fluoroquinolones) [2] were only used in 22% of the severe cases of anthrax. Another first-line antimicrobial class (carbapenems) was used in only 3% of cases. The most frequently used antimicrobials for severe illness were penicillins (88% of cases) and chloramphenicol (16% of cases), the latter of which is

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unlikely to be used in the current treatment of anthrax in the United States. In addition, these cases are heterogeneous, representing treatment in widely different locations, with differing health care capacities, and cases could have had widely varying severities of illness.

While data on total duration of parenteral therapy were sparse, they are consistent with the concept of a minimum of two weeks of intravenous therapy. Therapy beyond two weeks could not be evaluated.

The limitations and confounding factors described above must be taken into account when considering the results presented. And, as additional data become available regarding the use of newer, combination, and broader spectrum antimicrobial therapies, and in situations of severe antimicrobial shortages, treatment guideline developers may need to revisit whether fewer antimicrobials, perhaps used for a shorter time, could be effective for treating severe anthrax disease. These considerations are particularly relevant in the setting of a large-scale anthrax mass casualty incident when resource constraints may exist.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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The following search strategy was used in PubMed:

((((((((("woolsorter's disease") OR "woolsorter s disease") OR (("wool sorter s disease" OR "wool sorter's disease"))) OR wool sorters') OR "wool sorters' disease")) OR ((((((anthrax) OR "bacillus anthracis") OR "b. anthracis") OR "b anthracis")) OR (("Anthrax"[Mesh]) OR "Bacillus anthracis"[Mesh]))))) AND ((((((((((((("ciprofloxacin") OR "clindamycin") OR (("countermeasure" OR "countermeasures"))) OR (("counter measure" OR "counter measures"))) OR (("Crisis" AND "standards of care"))) OR "doxycycline") OR "imipenem") OR "penicillin") OR "penicillin g") OR "quinolones") OR "vancomycin")) OR (((((((("animal study") OR "animal studies") OR ("antibiotics" OR "antibiotic")) OR ("antimicrobial" or "antimicrobials" or "anti-microbial" or "anti-microbials")) OR ("antitoxin" or "antitoxins" or "anti-toxin" or "anti-toxins")) OR "chloramphenicol") OR "chloramphenical")) OR ((((((((((("Animals"[Mesh]) OR "Anti-Bacterial Agents"[Mesh]) OR "Anti-Infective Agents"[Mesh]) OR "Antitoxins"[Mesh]) OR "Ciprofloxacin"[Mesh]) OR "Clindamycin"[Mesh]) OR "Doxycycline"[Mesh]) OR "Imipenem"[Mesh]) OR "Penicillins"[Mesh]) OR "Penicillin G"[Mesh]) OR ("Quinolones"[Mesh] OR "4-Quinolones"[Mesh])) OR "Vancomycin"[Mesh])))).

Search terms included antimicrobials and antitoxin because we were simultaneously conducting a systematic review on antimicrobial and antitoxin treatment for systemic anthrax.

Figure 1.
Search Strategy

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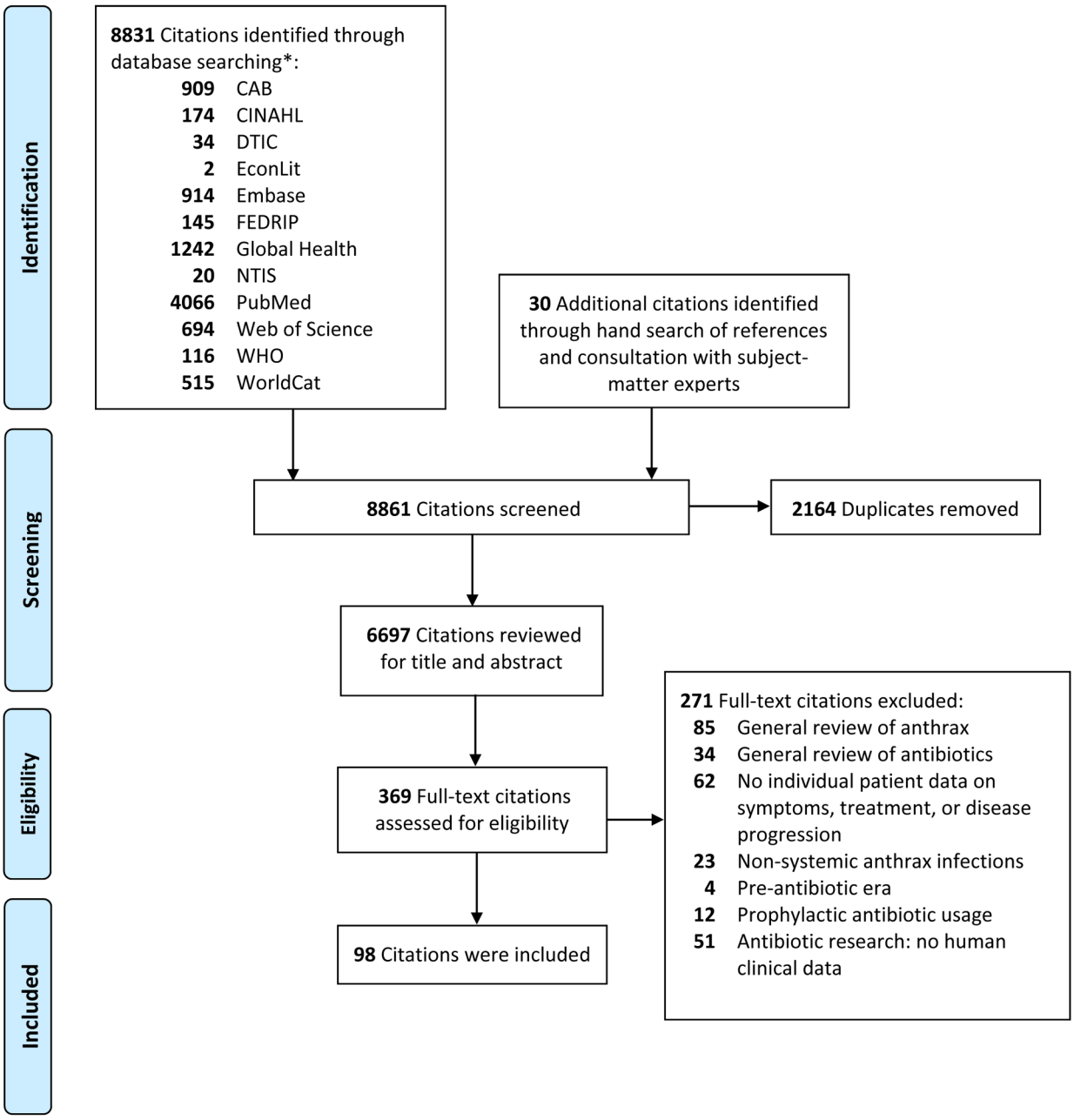

Figure 2.

Flow Diagram of Search Strategy

* Commonwealth Agricultural Bureaux (CAB), Cumulative Index to Nursing and Allied Health Literature (CINAHL), Defense Technical Information Center (DTIC), Federal Research in Progress (FEDRIP), National Technical Information Service (NTIS), World Health Organization (WHO)

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Table 1

Systemic anthrax by type, stratified by presence of meningitis, and mortality, published literature, 1945–2014.

Type	Total	With Meningitis		Without Meningitis	
		Lived N (%)	Died N (%)	Lived N (%)	Died N (%)
Cutaneous	59	8 (24)	25 (76)	25 (96)	1 (4)
GI	28	2 (25)	6 (75)	10 (50)	10 (50)
Inhalation	26	2 (15)	11 (85)	7 (54)	6 (46)
Injection	8	1 (50)	1 (50)	6 (100)	0 (0)
Multiple*	9	0 (0)	2 (100)	3 (43)	4 (57)
Primary Meningitis	19	2 (11)	17 (89)	na	na

* multiple includes: GI and cutaneous, GI and inhalation, and GI and injection;

na = not applicable

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Table 2

Type and number of antimicrobials received during course of treatment for severe anthrax, stratified by mortality (n=123)

	Number of antimicrobials used during treatment						
	1	2	3	4	5	6	7
received treatment with:	***L/**D**	**L/D**	**L/D**	**L/D**	**L/D**	**L/D**	**L/D**
penicillin, ampicillin, or amoxicillin (n = 108)	19/55	3/19	6/1	1/1	0/0	1/1	1/0
ciprofloxacin, moxifloxacin, or levofloxacin (n = 27)	2/2	1/1	9/3	3/2	1/0	1/1	1/0
clindamycin (n = 20)	0/0	0/2	9/2	1/2	1/0	1/1	1/0
chloramphenicol (n = 20)	1/0	2/16	1/0	0/0	0/0	0/0	0/0
vancomycin (n = 8)	0/0	0/0	2/0	2/1	1/0	0/1	1/0
rifampin (n = 8)	0/0	0/0	2/2	2/1	1/0	0/0	0/0
meropenem, imipenem, or doripenem (n = 4)	0/0	0/0	0/1	0/0	1/0	1/0	1/0
doxycycline (n = 3)	0/0	0/0	0/0	1/0	0/0	0/1	1/0
linezolid (n = 1)	0/0	0/0	0/0	0/0	0/0	0/0	1/0

* L=Lived,

** D=Died

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Table 3

Type and number of antimicrobials received during course of treatment for anthrax meningitis (confirmed and probable), stratified by mortality (n=77)

	Number of antimicrobials used during treatment						
	1	2	3	4	5	6	7
received treatment with:	*** L/** D**	**L/D**	**L/D**	**L/D**	**L/D**	**L/D**	**L/D**
penicillin, ampicillin, or amoxicillin (n = 74)	8/43	2/17	1/0	1/0	0/0	1/1	0/0
ciprofloxacin, moxifloxacin, or levofloxacin (n = 6)	1/1	1/0	0/0	1/0	0/0	1/1	0/0
clindamycin (n = 4)	0/0	0/2	0/0	0/0	0/0	1/1	0/0
chloramphenicol (n = 18)	1/0	1/15	1/0	0/0	0/0	0/0	0/0
vancomycin (n = 2)	0/0	0/0	0/0	1/0	0/0	0/1	0/0
rifampin (n = 1)	0/0	0/0	0/0	1/0	0/0	0/0	0/0
meropenem, imipenem, or doripenem (n = 1)	0/0	0/0	0/0	0/0	0/0	1/0	0/0
doxycycline (n = 1)	0/0	0/0	0/0	0/0	0/0	0/1	0/0
linezolid (n = 0)	0/0	0/0	0/0	0/0	0/0	0/0	0/0

* L=Lived,

** D=Died