

Anthrax meningoencephalitis

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Abstract—Objective: To review reported cases of anthrax meningoencephalitis and describe the clinical findings, diagnostic test results, treatment, and outcome over the past 50 years. **Methods:** Retrospective review of English language articles published since Haight's (1952) review. **Results:** Thirty-four core articles were identified, describing 70 patients with cutaneous (29%), gastrointestinal (17%), inhalational (39%), and unknown (16%) sources of infection. Clinical signs on presentation included fever, malaise, meningeal signs, hyperreflexia, and delirium, stupor, or coma. CSF analyses demonstrated hemorrhagic meningitis, with positive Gram's stains and CSF cultures. Many patients presented in extremis following a prodromal period of 1 to 6 days, and 75% died within 24 hours of presentation. Despite aggressive treatment in many cases, only 6% (4 of 70) survived, none of whom had pulmonary anthrax. Surviving patients generally had a cutaneous portal of entry, were younger, and had less severely abnormal initial CSF results than patients who died. Most of the survivors recovered fully. Pathologic findings included hemorrhagic meningitis, multifocal subarachnoid and intraparenchymal hemorrhages, vasculitis, and cerebral edema. **Conclusions:** Anthrax meningoencephalitis has a high case-fatality rate, even with aggressive antibiotic treatment and supportive therapy. Hemorrhagic meningitis should raise suspicion of anthrax infection, particularly if gram-positive rods are demonstrated on Gram's stain. Anthrax meningoencephalitis can develop from any primary focus, but survival appears to be most likely if meningoencephalitis develops from cutaneous anthrax. Treatment of surviving patients was generally begun before signs and symptoms of meningoencephalitis were present.

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In 1952, Haight reviewed the world literature on anthrax meningoencephalitis and added two cases of his own.¹ Several excellent recent reviews on clinical aspects of human anthrax infection have been published.^{2–6} The purpose of this report is to review reported cases of anthrax meningoencephalitis since Haight's report, to describe the clinical findings, diagnostic test results, treatment, and outcome over the past 50 years, and to compare these results with those in Haight's report.

Methods. English language articles on anthrax meningoencephalitis published since Haight's (1952) review¹ were identified by searching the Entrez-PubMed electronic database for articles published between January 1966 and January 2002 and by hand search of bibliographies of retrieved articles, previous reviews, monographs, and textbooks. Reports were selected if they provided patient-specific clinical information, with confirmation of meningoencephalitis, and either microbiological or pathologic confirmation of anthrax infection. In outbreaks with a single-source exposure (e.g., ingestion of contaminated meat), a case was considered confirmed if the clinical data supported anthrax infection and at least one of the affected

individuals had microbiological or pathologic confirmation. Data were abstracted using a standardized instrument.

The core articles in this series do not include reports^{7–10} without case-specific clinical information (17 cases), a report¹¹ without microbiological or pathologic confirmation (one case), a case¹² without lumbar puncture, postmortem, or other confirmation of leptomeningitis (one case), later reports of a case^{7,13} that had been reported earlier^{14,15} and cited by Haight¹ (one case), and reports^{16–26} written in languages other than English (i.e., French, German, Hungarian, Romanian, Spanish, Russian [eight additional cases]). Haight¹ omitted from his tallies the two new cases that he reported and a separate case with survival reported in 1948²⁷; for purposes of comparison with later cases reviewed here, these three cases were added to Haight's series of 70 cases.

Statistical comparisons of count data between Haight's series and the present one were made using χ^2 or Fisher's exact test (two-tailed). The nonparametric Mann–Whitney *U* test was used for comparison of age and CSF results between patients who survived and those who died. Microsoft Excel 2000 V9.0 for Windows spreadsheet program was used for data management and descriptive statistics. SPSS (Chicago, IL) PC+ V5.0 was used for analytic statistics.

Results. Seventy cases were identified from 34 reports^{12,28–59}; these reports form the core of this review. A number of cases or outbreaks were described in multiple

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reports, sometimes by several different authors. An outbreak of inhalational and cutaneous anthrax at a textile mill in Manchester, New Hampshire in 1957 was described in several reports by different authors.^{29,30,60,61} A clinical review in 1980³² included seven case reports of inhalational anthrax, and all three of the cases with anthrax meningoencephalitis had been previously reported.^{31,34,40} A number of reports in the American^{44,62-64} and Russian²⁴⁻²⁶ medical literature have described aspects of the anthrax outbreak that resulted from accidental release of anthrax spores in April, 1979 from a military bioweapons factory (Military Compound 19) in Sverdlovsk in the former Soviet Union (now Ekaterinburg, Russia). This outbreak resulted in at least 66 human deaths (among the 77 patients identified) in a narrow zone up to 4 kilometers downwind from the facility, as well as outbreaks of anthrax in livestock up to 50 kilometers downwind.⁶² Other reports and subsequent analyses indicate that the numbers of cases and deaths may have been significantly higher.^{6,65} Forty-two of these cases were autopsied, and 21 of the autopsied cases had anthrax meningoencephalitis.⁴⁴ In 1992, Russian President Boris Yeltsin confirmed that this outbreak was a result of "military developments,"⁶² and subsequent clinical and epidemiologic studies documented inhalational anthrax from a mixture of different *Bacillus anthracis* strains as the cause.^{44,62-64} Only one case of anthrax meningoencephalitis⁵⁹ has been identified among the 11 cases of inhalational anthrax in the September, 2001 bioterrorist anthrax outbreak in the United States.

Of the 70 cases in this series, 54 (77%) were male, giving a male:female ratio of approximately 3:1, which was the ratio reported by Haight.¹ The age of cases ranged from 2 to 72 years (median 41), similar to the range of newborn to 71 years reported by Haight.¹ A probable source of exposure was reported in 49 cases (70%), of which 22 (31%) were exposed to weaponized anthrax spores as a result of the Sverdlovsk, Russia bioweapons release in 1979 (21 cases)⁴⁴ or the US outbreak of bioterrorism anthrax in 2001 (1 case),⁵⁹ 13 (19%) had direct exposure to livestock (usually occupational),^{12,36,39,41,43,45,46,49,50,56} 10 (14%) ingested contaminated meat,^{51-53,58} and four (6%) had exposure to livestock products (2 wool mill workers, 1 boy who skinned a goat, and 1 butcher).^{12,29,30,37} Additional possible sources of anthrax exposure included ritual head shaving⁴⁸ and insect bite⁴⁵; previous studies have suggested that shaving (with either contaminated animal hair brushes or instruments)⁶⁶ and blood-feeding insects⁶⁷ can be sources of anthrax transmission. A recent experimental study has established that blood-feeding insects can, in fact, transmit anthrax.⁶⁸

Portal of entry. Meningoencephalitis may develop with any type of anthrax, including cutaneous,^{1,8,12,33,35-37,39,42,45,48,52,54,56-58} gastrointestinal,^{28,51-53,55,58} and inhalational,^{29-32,34,40,44,59} but in some cases the portal of entry was not identified (table 1).^{1,35,38,39,43,46,50,69} Excluding the single case of in utero anthrax in Haight's series,¹ the distribution of portal of entry in the present series differed from that reported by Haight ($p = 0.02$), with a higher proportion of gastrointestinal and inhalational cases and a lower proportion of cutaneous cases in the present series (see table 1).

Clinical features. Anthrax meningoencephalitis presents with fever, headache, nausea, vomiting, and altered mentation (i.e., confusion or agitation) in association with

Table 1 Primary focus of anthrax in reported cases of anthrax meningoencephalitis

Primary focus	Haight 1952 (n = 73)	Lanska 2002 (n = 70)	Total (n = 143)
Cutaneous	39 (53)	20 (29)	59 (41)
Gastrointestinal	7 (10)*	12 (17)†	19 (13)‡
Inhalational	17 (23)*	27 (39)	44 (31)*
Maternal sepsis	1 (1)	0 (0)	1 (1)
None identified	9 (12)	11 (16)	20 (14)

Values are expressed as n (%).

* Includes one case mixed cutaneous.

† Includes four cases mixed cutaneous.

‡ Includes five cases mixed cutaneous.

symptoms related to the source of infection (e.g., cutaneous, gastrointestinal, or inhalational). Clinical signs include fever (38.3 °C to 41 °C), malaise, meningeal signs (i.e., nuchal rigidity, Kernig and Brudzinski signs), hyperreflexia (often with unilateral or bilateral Babinski signs), and confusion, delirium, stupor, or coma (table 2). Other less frequent findings include papilledema, cranial neuropathies, focal or generalized seizures, myoclonus, fascicula-

Table 2 Reported symptoms and signs during course of anthrax meningoencephalitis*

Symptom or sign	Value
Stupor or coma	38 (78)
Fever	35 (71)
Skin lesions	24 (49)
Headache	22 (45)
Nausea/vomiting	21 (43)
Seizures	20 (41)
Nuchal rigidity	18 (37)
Focal neurologic deficit	15 (31)
Confusion or agitation	13 (27)
Cranial neuropathies	13 (27)
Kernig or Brudzinski sign	11 (22)
Lateralizing long-tract signs	11 (22)
Malaise	7 (14)
Hyperreflexia	7 (14)
Respiratory symptoms	6 (12)
Decerebrate rigidity	4 (8)
Diaphoresis	3 (6)
Papilledema	3 (6)
Dizziness	2 (4)

Values are expressed as n (%).

* Because of variable and incomplete reporting of clinical features at onset, presentation, and over the course of the illness, the frequencies may be underestimates of the frequency with which these symptoms and signs occurred in these patients. These results are based on 49 cases and exclude the autopsy cases from the Sverdlovsk, Russia bioweapons anthrax outbreak from 1979.

Table 3 CSF analyses in anthrax meningoencephalitis*

Variable/value	n (%)	Variable/value	n (%)
Appearance		White cells, per mm ³	
Cloudy	15 (35)	<100	4 (9)
Bloody	12 (28)	100–999	3 (7)
Mixed	6 (14)	1000–9999	15 (35)
Clear	3 (7)	≥10,000	3 (7)
Unknown	7 (16)	Unknown	18 (42)
Glucose, mg/dL		Neutrophils, %	
<20	3 (7)	<50	0 (0)
20–40	13 (30)	50–79	3 (7)
>40	13 (30)	≥80	10 (23)
Unknown	14 (33)	Unknown	30 (70)
Protein, mg/dL		Gram-stain positive	
≤45	2 (5)	Yes	33 (77)
46–199	4 (9)	No	3 (7)
200–999	18 (42)	Unknown	7 (16)
≥1,000	8 (19)	CSF culture positive	
Unknown	11 (26)	Yes	35 (81)
Red cells, per mm ³		No	0 (0)
<100	4 (9)	Unknown	8 (19)
100–999	5 (12)		
1000–9999	5 (12)		
≥10,000	2 (5)		
Bloody, count not reported	12 (28)		
Unknown	15 (35)		

* These results are from the initial spinal taps for 43 cases with reported CSF results. Haight¹ did not summarize CSF results for his series, although he reported fairly detailed results from serial lumbar punctures in the two cases he reported. For the purpose of summarizing CSF results in anthrax meningitis, Haight's two cases from 1952¹ and two cases with survival from the late 1940s^{13,14,27} were included. For CSF glucose, two patients with normal values were coded as >40 mg/dL and one patient with a low CSF/blood ratio of glucose concentration (0.17) was coded as 20–40 mg/dL. Three patients had negative CSF Gram stains and CSF cultures were not done; diagnostic confirmation in these cases was based on antemortem or postmortem cultures of other tissues, histology, or, in one case, immunohistochemistry. Because of rounding, percentages for each variable may not sum to 100.

tions, generalized rigidity, lateralizing long-tract signs, and decerebrate posturing.

CSF. Results of analyses of CSF were reported in some detail for 43 patients (table 3), eight of whom had serial lumbar punctures^{1,13,14,33,35,36,40,48} with up to six lumbar punctures in a single patient.^{13,14} Serial lumbar punctures were performed to monitor response to therapy and in some cases to administer intrathecal penicillin.^{1,13,14,27,33} In some cases, initial suspicion of anthrax meningoencephalitis was the result of CSF abnormalities. In the index case in the 2001 US bioterrorist outbreak, a diagnosis of anthrax was considered on the basis of CSF Gram's stain and ultimately confirmed by CSF culture.⁵⁹

CSF studies typically showed findings of hemorrhagic meningitis (see table 3). CSF in anthrax meningoencephalitis may appear cloudy, with yellowish or pinkish coloration, or may be grossly bloody; evolution across this spectrum has been reported in serial lumbar punctures in an individual patient.¹ The supernatant was frequently xanthochromic. Opening pressure was frequently elevated, with a range of 130 to 700 mm H₂O.⁴⁵ Hypoglycorrhachia was common, with CSF glucose in the range of 20 to 40

mg/dL, but occasionally less than 20 mg/dL. CSF protein concentration was generally elevated, with a range of 10 to 2800 mg/dL. CSF was frequently hemorrhagic, but early in the illness there may be no red blood cells.^{13,27,35,45} There was generally a CSF pleocytosis with from 0 to 10,000 white cells/mm³ with a predominance of polymorphonuclear leukocytes. There were many large gram-positive rods on Gram's stain, either singly or in short or long chains. CSF cultures from the initial lumbar puncture were always positive when tested, although some cases were confirmed instead by culture of swabs or fluid from skin lesions, other body fluids, or postmortem tissue samples.^{28–30,32,34,44,45} CSF may be sterile after several days of antibiotics.^{1,36} Serial lumbar punctures may document an evolution from cloudy to grossly bloody CSF, with increasing protein concentration, increasing numbers of red cells and polymorphonuclear leukocytes, and increasing predominance of polymorphonuclear leukocytes.^{1,13,14} Similar collective findings were reported in a recent series of 12 cases that did not provide case-specific results.⁹

Other diagnostic studies. Patients with anthrax meningoencephalitis generally have elevated white blood cell

counts with a left shift. The range of white cell counts in the current series was from 5,400 to 27,700, somewhat lower than the range of 10,000 to 80,000 reported by Haight.¹ Blood cultures were positive in 71% (i.e., 15/21) of cases for whom these were reported, nearly identical to the value of 70% reported by Haight.¹ Chest x-rays were often abnormal in patients with inhalational anthrax,^{32,34,40,59} and occasionally in patients with gastrointestinal⁵¹ or cutaneous disease.^{35,54} Chest x-ray findings included pleural effusion,^{32,34,40,51,59} hilar adenopathy,^{32,40} widened mediastinum,⁵⁹ infiltrates,³⁵ and soft tissue edema.⁵⁴

EEG results have rarely been reported, even though seizures are fairly common. In part, this reflects the moribund state of most of these patients. In one patient with reported myoclonus and fasciculations, EEG showed disorganized, low-amplitude, slow waves (1 to 7 Hz).³⁹

CT or MRI of the head in patients with anthrax meningoencephalitis may demonstrate focal intracerebral hemorrhage, subarachnoid hemorrhage, intraventricular hemorrhage, diffuse cerebral edema, and prominent leptomeningeal enhancement.^{54,58} Parenchymal cerebral enhancement has not been reported,⁵⁸ but its absence may simply reflect the paucity of neuroimaging studies in these patients. Abnormalities may progress rapidly on serial brain imaging studies.⁵⁴

Differential diagnosis. Hemorrhagic meningitis should raise suspicion of anthrax infection,^{3,6} particularly if gram-positive rods are demonstrated on Gram's stain. *Listeria monocytogenes*, the only common gram-positive rod causing meningitis, does not produce a hemorrhagic meningitis and is rarely seen on Gram's stain. Based on initial clinical diagnoses in reported cases, the differential diagnosis of anthrax meningoencephalitis may include subarachnoid and intracerebral hemorrhage, ischemic stroke, nonanthrax bacterial meningoencephalitis, herpes simplex virus encephalitis and other viral encephalitides, eclampsia, and cerebral malaria.

Treatment. Antianthrax treatment was reported in 39 patients.^{12,28-38,40,42,43,45-52,55-59} Of these, 19 (49%) received penicillin only^{28-32,35,38,42,45,48,49,52,56,58} (administered parenterally in all but one case),^{29,30} 19 (49%) received penicillin (or in one case ampicillin)⁵⁵ in combination with other antibiotic therapy,^{12,29,30,32-34,36,37,40,43,45-47,50,51,55,57,59} and one (3%) received antianthrax serum only.³³ Antibiotics used in conjunction with penicillin therapy included chloramphenicol (11 cases),^{33,36,43,45-47,50,57} streptomycin (7 cases),^{12,29,30,32,33,37,40,51} sulfonamides (4 cases),^{12,29,30,36,45,57} cefotaxime (2 cases),^{55,59} tetracyclines (1 case),³³ vancomycin (1 case),⁵⁹ and antianthrax serum (1 case).³³ Corticosteroids were administered in conjunction with antibiotics in ten cases (26%).^{33,36,42,43,45,48,52,57} In the Sverdlovsk inhalational anthrax outbreak in 1979, hospitalized patients were treated variously with penicillin, cephalosporin, chloramphenicol, antianthrax globulin, and corticosteroids,⁶² but case-specific treatments and outcomes were not reported in the English language literature either in general or for the 21 patients autopsied after dying with anthrax meningoencephalitis.^{44,62,63}

Prognosis. Septicemia, toxic shock, and death rapidly follow development of anthrax meningoencephalitis in most cases. Many patients presented in extremis following a prodromal period of 1 to 6 days, and 75% died within 24 hours of presentation (i.e., 41/55 of cases for whom such

Table 4 Survival with anthrax meningoencephalitis in reported cases

Primary focus	Haight 1952	Lanska 2002	Total
Cutaneous	2/39 (5)	3/20 (15)	5/59 (8)
Gastrointestinal	0/7 (0)	1/12 (8)	1/19 (5)
Inhalational	0/17 (0)	0/27 (0)	0/44 (0)
Maternal sepsis	0/1 (0)		0/1 (0)
None identified	1/9 (11)	0/11 (0)	1/20 (5)
Total	3/73 (4)	4/70 (6)	7/143 (5)

Values are expressed as n (%).

Excluding the 21 inhalational cases from the Sverdlovsk autopsy series, estimated survival in the current series is 4/49 (8%) and in reported cases to date is 7/122 (6%).

information was available).^{28-35,38,39,41,44-47,49-52,69} Four patients (6%) in the present series survived,^{36,37,48,51} compared with three (4%) in the previous world literature, a difference that was not significant ($p = 0.71$) (table 4). Excluding the 21 cases of inhalational anthrax from the Sverdlovsk autopsy series,⁴⁴ estimated survival in the current series is four of 49 (8%) and in all reported cases to date is seven of 122 (6%); the difference in survival between this restricted group of deceased patients and the surviving patients was also not significant ($p = 0.44$). Reported additional cases of survival had no clinical information (two cases)⁷ or were not established microbiologically or pathologically as cases of anthrax (one case).¹¹ An additional recent series of 12 cases with no survivals did not report case-specific information.⁹

Survival appears to be most likely if meningoencephalitis develops as part of the course of cutaneous anthrax,^{36,37,48} but a single case with survival has been reported with gastrointestinal anthrax.⁵¹ In the current series, 15% of cutaneous cases survived, compared with 8% among gastrointestinal cases, none among inhalational cases, and none among unknown or unspecified cases (see table 3). The difference in survival of the cutaneous cases in the current series (15%) and Haight's series (5%) was not significant ($p = 0.32$). To date, in the world literature there are no reported cases of survival following anthrax meningoencephalitis associated with inhalational anthrax.

The seven surviving patients reported to date are summarized in table 5.^{13-15,27,36,37,48,51,70} Surviving patients were younger as a group than those in the present series who died (median age of surviving cases = 24 years, $n=7$; median age of cases who died = 45 years, $n = 66$; $p = 0.04$). If the comparison is restricted to cases in the current series only, the difference in age is greater (median age of surviving cases = 10.25 years, $n = 4$; $p = 0.003$). In general, initial CSF results from the surviving patients were either normal or were less severely abnormal compared to deceased patients. However, because of the small sample sizes for different CSF studies in the survival group, none of the individual contrasts was significant (glucose, $p = 0.41$; protein, $p = 0.12$; red cells, $p = 0.24$; white cells, $p = 0.08$).

Many reports and reviews failed to identify all of the previously reported cases with survival or misreported aspects of the cases they did review, resulting in incorrect conclusions about the agents that are potentially effective

Table 5 Patients with anthrax meningoencephalitis who survived

Variable	Patient no.						
	1	2	3	4	5	6	7
Reference no.	70	14	27	36	37	48	51
Year	1916	1947	1948	1972	1973	1989	1993
Age, y	24	57	51	8.5	12	25	6
Sex	F	M	M	F	M	M	M
Clinical type	Unknown	Cutaneous	Cutaneous	Cutaneous	Cutaneous	Cutaneous	Gastrointestinal
Treatment	None						
Antianthrax serum		X					
Penicillin		X	X	X	X	X	X
Chloramphenicol				I			
Streptomycin					X		X
Sulfonamide		X		I			
Corticosteroid				X		X	
Residual	L hemiparesis	None	None	None	None	RUE weakness	None

X = main therapy; I = initial therapy only; RUE = right upper extremity.

treatments. The treatments administered to surviving patients were, in fact, similar to those chosen in the entire group of patients in the current series. All of the patients received penicillin except the first case (Patient 1), who reportedly received no treatment (Bernd Remler, MD, personal communication, February 2002).⁷⁰ Only two of the patients received corticosteroids in addition to antibiotics (Patients 4 and 6).^{36,48} The only case with gastrointestinal anthrax (Patient 7) received the same treatment as his sister (aged 2 years), who died.⁵¹ Treatment of surviving patients was generally begun before the disease was clinically advanced. Three of the patients who survived (Patients 2 through 4) were receiving treatment for cutaneous anthrax (that included penicillin) before development of symptoms of meningoencephalitis.^{13-15,27,36} There is limited information on long-term outcomes among the survivors, but most were reported to have fully recovered,^{13-15,27,36,37,51} although two patients had residual focal weakness.^{48,70}

Autopsy findings. Autopsies were obtained in 40 of the 66 deceased patients (61%).^{28-32,34,35,38-40,43-45,47,55-57,59} This summary is restricted to pathologic findings in the central nervous system. Gross findings typically included cloudy and congested leptomeninges, with occasional obvious purulent exudate^{1,30,34,35,44,47} and with variable degrees of subarachnoid hemorrhage.^{1,28,29,31,35,39,40,44,45,55,57} In many cases subarachnoid hemorrhage was the dominant gross pathologic feature.^{1,28,29,31,35,39,40,44,45,55} The vascular congestion and extensive subarachnoid hemorrhage of the leptomeninges gave a dark red appearance on gross examination of the brain, a finding sometimes referred to as a "cardinal's cap."² Other common findings included intraventricular hemorrhage,^{29,39} intracerebral hematoma,^{1,39,56} multifocal small intraparenchymal cortical hemorrhages,^{39,40,47} or numerous petechial hemorrhages in cerebral parenchyma;^{28,64} zones of infarction in arterial, venous, or watershed distributions^{39,64}; and cerebral edema^{35,45,47,57} with tonsillar³⁵ or uncal herniation.⁴⁷

Microscopic findings included hemorrhagic leptomeningitis,^{29,30,34,35,38-40,44,47,55,57,64} and associated necrotizing vas-

culitis,^{1,64} multifocal subarachnoid^{1,28-31,35,38-40,44,45,55,57,64} and intracerebral hemorrhage,^{1,28-30,38,39,47,56} multifocal cerebral infarction,^{39,64} and leptomeningeal and cerebral edema.^{35,39,44,45,47,57,64} The hemorrhagic leptomeningitis was associated with polymorphonuclear leukocytic inflammatory exudates,^{35,38,44,47,55-57,64} severe congestion of meningeal blood vessels,^{35,38,40,47,56} hemorrhagic infiltration^{35,44,45,56,64} or frank subarachnoid hemorrhage,^{1,28-31,35,38-40,44,45,55,57,64} aggregations of neutrophils and mononuclear phagocytes in and around meningeal vessels,^{35,38,40,47,64} and tracking of blood and inflammatory infiltrates along the Virchow-Robin (perivascular) spaces into the parenchyma.⁴⁷ The superficial cerebral cortex showed diffuse, perineuronal, and perivascular infiltration by neutrophils,^{35,39,47} severe vascular congestion,^{35,40} necrosis of blood vessel walls,^{35,39,47,56,64} recent thromboses,^{35,39,64} zones of ischemia,^{39,64} areas of hemorrhage,⁴⁷ and edema.^{35,39,44,45,47,57,64} Numerous large gram-positive rods in short chains were present in the leptomeninges and the subarachnoid and Virchow-Robin spaces,^{29-31,34,47,56} within and around meningeal and superficial cortical vessels and vessels in regions of hemorrhage,^{31,32,35,39,40,64} and within hemorrhagic lesions.^{31,32,47}

Discussion. Meningoencephalitis develops in, at most, 5% of cases of cutaneous anthrax^{14,28}; however, most cases of anthrax meningoencephalitis to date have developed from cutaneous anthrax because the vast majority of naturally acquired cases of anthrax are cutaneous.²⁸ Meningoencephalitis may occur in up to half of the cases in industrial or bioweapons outbreaks of inhalational anthrax^{8,29,30,32,44}; however, in the recent bioterrorist outbreak of anthrax in the United States, only the index case had meningitis among the 11 cases of confirmed or suspected inhalational anthrax identified.^{59,71-73} The relatively low frequency of meningitis among anthrax cases in the US bioterrorism outbreak may be misleading, though, as lumbar punctures were done in few cases and the

brain was not examined in some autopsies. Based on previous experience,⁴⁴ the potential exists for large numbers of cases of anthrax meningoencephalitis with further bioterrorist outbreaks or bioweapons dispersals. Meningoencephalitis may also occur with gastrointestinal anthrax or without a clinically apparent primary focus.

Current guidelines from the Centers for Disease Control indicate that ciprofloxacin or doxycycline should be included as essential components of initial therapy for anthrax infections of any portal of entry.^{72,74} It is important to treat anthrax meningoencephalitis with a polydrug antibiotic regimen, using antimicrobial agents that have good CSF penetration in meningitis and that provide good antibacterial coverage for *B. anthracis*. All six patients who survived after antibiotic treatment for anthrax meningoencephalitis were treated with penicillin. However, because of the presence of constitutive or inducible beta-lactamases in *B. anthracis* isolates from the recent US bioterrorist outbreak and expectations that beta-lactamase activity may be likely with bioengineered bioweapons agents, ampicillin or penicillin G alone are not recommended for initial therapy for anthrax meningoencephalitis prior to antibiotic sensitivity results from culture.^{72,74} Rifampin plus vancomycin would be a reasonable choice for addition to ciprofloxacin or doxycycline in the initial treatment of anthrax meningoencephalitis. Some infectious disease authorities recommend ciprofloxacin in preference to doxycycline, plus augmentation with chloramphenicol, rifampin, or penicillin for established or suspected anthrax meningoencephalitis.⁶ Aztreonam, trimethoprim-sulfamethoxazole, or third-generation cephalosporins should not be used because of natural resistance of *B. anthracis* strains to these antibiotics.

Bacterial toxins have long been felt to play a major role in anthrax meningoencephalitis because many effects of *B. anthracis* cannot be attributed to microscopically evident tissue changes.^{10,75} Virulence of *B. anthracis* requires an antiphagocytic capsule and two exotoxins. The two toxins are binary proteins composed of a binding protein and an enzymatically active protein.^{2,4,76} Among other actions, these toxins collectively produce local edema, impair neutrophil function, depress cerebral cortical electrical activity, depress central respiratory center activity, cause bleeding and destruction of the brain and vital organs in the chest, and induce cardiovascular collapse and shock.^{2,4,44,76-79}

Although antitoxin was used early in the 20th century to treat anthrax alone or in combination with penicillin,¹³⁻¹⁵ it has not been available in recent decades to US civilian populations. Conceptually, antianthrax serum may augment the effect of antibiotics by helping to neutralize the anthrax toxins, which are not inactivated by antibiotics. However, there are no documented cases of successful treatment of anthrax meningitis with antianthrax serum alone. Haight incorrectly stated that a case reported

by Czyhlarz in 1916⁷⁰ had been cured by treatment with antianthrax serum, when in fact a full translation indicates that the patient received no treatment (Bernd Remler, MD, personal communication, February, 2002; see supplementary document); this error has been promulgated by numerous subsequent authors and has been a source of incorrect conclusions regarding potentially effective therapy for anthrax meningoencephalitis in recent reviews. Czyhlarz⁷⁰ also presented unpublished second-hand information on another patient who purportedly recovered from anthrax meningoencephalitis without treatment. In light of subsequent experience with this disease, it is hard to interpret or credit either of these reports. Available experimental data⁸⁰ do not indicate a significant treatment effect of antianthrax serum beyond that of penicillin. Nevertheless, antianthrax immune globulin, derived from the blood of soldiers who have received the anthrax vaccine, is being added to the US bioterrorism treatment stockpile and is being considered as a potential experimental anthrax treatment in the event of further bioterrorism anthrax cases.^{6,81}

Corticosteroids have been recommended as an adjunctive agent in the treatment of meningitis in children.⁸² Use of corticosteroids in adults with meningitis is controversial, but steroids have been recommended for consideration as adjunctive agents without any age restriction in anthrax meningitis.⁷² If corticosteroids are used in conjunction with vancomycin therapy, antibiotic dosing may need to be modified because CSF vancomycin levels may be decreased by corticosteroids, contributing to treatment failure.⁸²⁻⁸⁶

In addition to antibiotic management, patients with anthrax meningoencephalitis may require aggressive intensive care measures. Seizures, increased intracranial pressure, subarachnoid and intracerebral hemorrhage, electrolyte disturbances, hypotension, shock, and disseminated intravascular coagulation may develop as complications of this infection. Despite aggressive treatment, the prognosis for survival with anthrax meningoencephalitis is very poor.

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References

1. Haight TH. Anthrax meningitis: review of literature and report of two cases with autopsies. *Am J Med Sci* 1952;224:57-69.
2. Dixon TC, Meselson M, Guillemin J, Hanna PC. Anthrax. *N Engl J Med* 1999;341:815-826.

3. Inglesby TV, Henderson DA, Bartlett JG, et al. Anthrax as a biological weapon: medical and public health management. *JAMA* 1999;281:1735-1745.
4. Swartz MN. Recognition and management of anthrax: an update. *N Engl J Med* 2001;345:1621-1626.
5. Jernigan JA, Stephens DS, Ashford DA, et al. Bioterrorism-related inhalational anthrax: the first 10 cases reported in the United States. *Emerg Infect Dis* 2001;7:933-944.
6. Inglesby TV, O'Toole T, Henderson DA, et al. Anthrax as a biological weapon, 2002: updated recommendations for management. *JAMA* 2002;287:2236-2252.
7. Miller JK. Human anthrax in New York State. *NY State J Med* 1961;61:2046-2053.
8. Brachman PS. Human anthrax in the United States. *Antimicrob Agents Chemother* 1965;5:111-114.
9. Kumar A, Kanungo R, Bhattacharya S, Badrinath S, Dutta TK, Swaminathan RP. Human anthrax in India: urgent need for effective prevention. *J Commun Dis* 2000;32:240-246.
10. Dutz W, Kohout E. Anthrax. *Pathol Annu* 1971;6:2009-2248.
11. Trivedy JR. Case of anthrax meningitis survival. *Cent Afr J Med* 1981;27:166.
12. Roberts CJ, Chambers PG. An outbreak of anthrax in the Mondoro Tribal Trust lands. *Cent Afr J Med* 1975;21:73-76.
13. Kindler D. Recovery from anthrax meningitis. *Ind Med Surg* 1952;21:487-488.
14. Shanahan RH, Griffin JR, Von Auersperg AP. Anthrax meningitis: report of a case of internal anthrax with recovery. *Am J Clin Pathol* 1947;17:719-722.
15. Griffin JR, Shanahan RH, DeAngelis CE. Treatment of cutaneous anthrax with penicillin. *NY State J Med* 1948;48:1718-1721.
16. Boudin G, Lauras A, Vaillant C. Etat de mal épileptique révélateur d'une méningite charbonneuse: étude anatomoclinique. *Bull Mem Soc Med Hop Paris* 1964;115:183-187.
17. Rapun Pac JL, Ull Laita M. Meningitis carbuncosa. *Arch Neurol (Madr)* 1972;35:143-148.
18. Baltiev A, Besleaga E, Cucuoreanu G, Obreja E. Meningoencefalita carbunoasa la un copil cu pustula cutanata necaracteristica. *Rev Med Chir Soc Med Nat Iasi* 1973;77:885-888.
19. Beer K. Milzbrandmeningitis. *Path Microbiol* 1973;39:12-13.
20. Bach I, Simon L, Bán E, Tóth L, Kovács M. Haemorrhagiás meningitisés apoplexia anthrax sepsisben. *Orv Hetil* 1978;119:1797-1799.
21. Marandian MH, Kamali A. Méningite charbonneuse: un cas en apparence primitif. *Nouv Presse Med* 1981;10:1747-1748.
22. Dürst UN, Bartenstein J, Bühlmann H, Wüst J, Spiegel MV. Anthraxmeningitis. *Schweiz Med Wochenschr* 1986;116:1222-1228.
23. Gonzalez A, Rodriguez E, Castillo M, Ortega I, Ramirez E, Fajardo J. Lesión necrótica en mentón en paciente con síndrome meníngeo. *Enferm Infecc Microbiol Clin* 1997;15:163-164.
24. Abramova AA, Grinberg LM. [Pathology of anthrax sepsis according to materials of the infectious outbreak in 1979 in Sverdlovsk (macroscopic changes)]. *Arkh Patol* 1993;55:12-17.
25. Abramova AA, Grinberg LM. [Pathology of anthrax sepsis according to materials of infectious outbreak in 1979 in Sverdlovsk (microscopic changes)]. *Arkh Patol* 1993;55:18-23.
26. Grinberg LM, Abramova AA. [Pathology of anthrax sepsis according to materials of the infectious outbreak in 1979 in Sverdlovsk (various aspects of morpho-, patho- and thanatogenesis).] *Arkh Patol* 1993;55:23-26.
27. Weinstein L, Oliver CS. The treatment of human anthrax with penicillin. *Am Pract* 1948;2:533-538.
28. Raper AB. Anthrax meningo-encephalitis. *East Afr Med J* 1953;30:399-401.
29. Albrink WS, Brooks SM, Biron RE, Kopel M. Human inhalational anthrax: a report of three fatal cases. *Am J Pathol* 1960;36:457-468.
30. Plotkin SA, Brachman PS, Utell M, Bumford FH, Atchison MM. An epidemic of inhalation anthrax, the first in the twentieth century: I. Clinical features. *Am J Med* 1960;29:992-1001.
31. Brachman PS, Pagano JS, Albrink WS. Two cases of fatal inhalation anthrax, one associated with sarcoidosis. *N Engl J Med* 1961;265:203-208.
32. Brachman PS. Inhalation anthrax. *Ann NY Acad Sci* 1980;353:83-93.
33. Vita A, Secu A, Cucuoreanu G, Leibovici M, Bejanariu C, Cuju G. Considerations on 3 cases of meningo-encephalitis due to anthrax bacilli. *Rom Med Rev* 1961;5:36-39.
34. LaForce FM, Bumford FH, Freely JC, Stokes SL, Snow DB. Epidemiologic study of a fatal case of inhalation anthrax. *Arch Environ Health* 1969;18:798-805.
35. Rangel RA, González DA. Bacillus anthracis meningitis. *Neurology* 1975;25:525-530.
36. Tahernia AC, Hashemi G. Survival in anthrax meningitis. *Pediatrics* 1972;50:329-333.
37. Tengio FU. Anthrax meningitis: report of two cases. *East Afr Med J* 1973;50:337-339.
38. Viratchai C. Anthrax gastro-enteritis and meningitis. *J Med Assoc Thai* 1974;57:147-150.
39. Pluot N, Vital C, Aubertin J, Croix JC, Pire JC, Poisot D. Anthrax meningitis: report of two cases with autopsies. *Acta Neuropathol (Berl)* 1976;36:339-345.
40. Suffin SC, Carnes WH, Kaufman AF. Inhalation anthrax in a home craftsman. *Hum Pathol* 1978;9:594-597.
41. Al-Dulaimy SB, Al-Allaf GA. Anthrax meningitis. *Trans R Soc Trop Med Hyg* 1978;72:315.
42. Manios S, Kavaliotis I. Anthrax in children: a long forgotten, potentially fatal condition. *Scand J Infect Dis* 1979;11:203-206.
43. Koshi G, Lalitha MK, Daniel J, Chacko A, Pulimood BM. Anthrax meningitis, a rare clinical entity. *J Assoc Physicians India* 1981;29:59-62.
44. Abramova FA, Grinberg LM, Tampolskaya OV, Walker DH. Pathology of inhalational anthrax in 42 cases from the Sverdlovsk outbreak of 1979. *Proc Natl Acad Sci USA* 1993;90:2291-2294.
45. Levy L, Baker N, Meyer MP, Crosland P, Hampton J. Anthrax meningitis in Zimbabwe. *Cent Afr J Med* 1981;27:101-104.
46. Bhat P, Pereira P, Mohan N. Primary anthrax meningitis: a case report. *Neurol India* 1983;31:71-73.
47. Chandramukhi A, Shankar P, Rao TV, Sundararajan S, Swamy HS. Acute leptomeningitis due to *Bacillus anthracis*: a case report. *Trop Geogr Med* 1983;35:79-82.
48. Khanna N, Gokul BN, Ravikumar R, et al. Successfully treated primary anthrax meningitis. *Indian J Pathol Microbiol* 1989;32:315-317.
49. Kanungo R, Sujatha S, Das AK, Rao RS. Anthrax meningitis: a clinical enigma. *Indian J Med Microbiol* 1990;6:149-151.
50. Bharathmoorthy, Chakravarthy I, Swaminathan RP, et al. Haemorrhagic meningitis due to *Bacillus anthracis*. *J Assoc Physicians India* 1992;40:134-135.
51. Tabatabaie P, Syadati A. *Bacillus anthracis* as a cause of bacterial meningitis. *Pediatr Infect Dis* 1993;12:1035-1037.
52. George S, Mathai D, Balraj V, Lalitha MK, John TJ. An outbreak of anthrax meningoencephalitis. *Trans R Soc Trop Med Hyg* 1994;88:206-207.
53. Berthier M, Fauchère J-L, Perrin J, Grignon B, Oriot D. Fulminant meningitis due to *Bacillus anthracis* in 11-year-old girl during Ramadan. *Lancet* 1996;347:828.
54. Domínguez E, Bustos C, Garcia M, Recio S. Anthrax meningoencephalitis: radiologic findings. *AJR Am J Roentgenol* 1997;169:317.
55. Kwong KL, Que TL, Wong SN, So KT. Fatal meningoencephalitis due to *Bacillus anthracis*. *J Paediatr Child Health* 1997;33:539-541.
56. Garcia AG, Jimenez RR. *Bacillus anthracis* meningitis. *N Engl J Med* 1999;341:814.
57. Ringertz SH, Hoiby EA, Jensenius M, et al. Injectional anthrax in a heroin skin-popper. *Lancet* 2000;346:1574-1575.
58. Kim HJ, Jun WB, Lee SH, Rho MH. CT and MR findings of anthrax meningoencephalitis: report of two cases and review of the literature. *AJNR Am J Neuroradiol* 2001;22:1303-1305.
59. Bush LM, Abrams BH, Heall A, Johnson CC. Index case of fatal inhalational anthrax due to bioterrorism in the United States. *N Engl J Med* 2001;345:1607-1610.
60. Brachman PS, Plotkin SA, Bumford FH, Atchison MM. An epidemic of inhalation anthrax: the first in the twentieth century: II. Epidemiology. *Am J Hygiene* 1960;72:6-23.
61. Belluck P. Anthrax outbreak of '57 felled a mill but yielded answers. *New York Times* October 27, 2001:B8.
62. Meselson M, Guillemin J, Hugh-Jones M, et al. The Sverdlovsk anthrax outbreak of 1979. *Science* 1994;266:1202-1208.

63. Jackson PJ, Hugh-Jones ME, Adair DM, et al. PCR analysis of tissue samples from the 1979 Sverdlovsk anthrax victims: the presence of multiple *Bacillus anthracis* strains in different victims. *Proc Natl Acad Sci USA* 1998;95:1224–1229.
64. Grinberg LM, Abramova FA, Yampolskaya OV, Walker DH, Smith JH. Quantitative pathology of inhalational anthrax I: Quantitative microscopic findings. *Mod Pathol* 2001;14:482–495.
65. Brookmeyer R, Blades N, Hugh-Jones M, Henderson D. The statistical analysis of truncated data: application to the Sverdlovsk anthrax outbreak. *Biostatistics* 2001;2:233–247.
66. Knott FA. A note on anthrax infection by shaving brushes. *Lancet* 1923;1:227–228.
67. Bradaric N, Punda-Polic V. Cutaneous anthrax due to penicillin-resistant *Bacillus anthracis* transmitted by an insect bite. *Lancet* 1992;340:306–307.
68. Turell MJ, Knudson GB. Mechanical transmission of *Bacillus anthracis* by stable flies (*Stomoxys calcitrans*) and mosquitoes (*Aedes aegypti* and *Aedes taeniorhynchus*). *Infect Immun* 1987;55:1859–1861.
69. Drake DJ. Meningitic anthrax. *Cent Afr J Med* 1971;17:97–98.
70. Czyhlarz EV. Beitrag zur Lehre von der Milzbrandmeningitis. *Wein Klin Wochenschr* 1916;29:768–769.
71. Centers for Disease Control. Investigation of anthrax associated with intentional exposure and interim public health guidelines, October 2001. *MMWR Morb Mortal Wkly Rep* 2001;50:889–893.
72. Centers for Disease Control. Update: investigation of bioterrorism-related anthrax and interim guidelines for exposure management and antimicrobial therapy, October 2001. *MMWR Morb Mortal Wkly Rep* 2001;50:909–919.
73. Centers for Disease Control. Investigation of bioterrorism-related anthrax and interim guidelines for clinical evaluation of persons with possible anthrax. *MMWR Morb Mortal Wkly Rep* 2001;50:941–948.
74. Centers for Disease Control. Updated recommendations for antimicrobial prophylaxis among asymptomatic pregnant women after exposure to *Bacillus anthracis*. *MMWR Morb Mortal Wkly Rep* 2001;50:960.
75. Bonventure PF, Sueoka W, True CW, Klein F, Lincoln R. Attempts to implicate the central nervous system as a primary site of action for *Bacillus anthracis* lethal toxin. *Fed Proc* 1967;26:1549–1553.
76. Friedlander AM. Anthrax. In: Sidell FR, Takafuji ET, Franz DR, eds. *Textbook of military medicine: medical aspects of chemical and biological warfare*. Washington, DC: Office of the Surgeon General, 1997:467–478.
77. Vick JA, Lincoln RE, Klein F, Mahlandt BG, Walker JS, Fish DC. Neurological and physiological responses of the primate to anthrax toxin. *J Infect Dis* 1968;118:85–96.
78. Klein F, Lincoln RE, Dobbs JP, Mahlandt BG, Remmele NS, Walker JS. Neurological and physiological responses of the primate to anthrax infection. *J Infect Dis* 1968;118:97–103.
79. Remmele NS, Klein F, Vick JA, Walker JS, Mahlandt BG, Lincoln RE. Anthrax toxin: primary site of action. *J Infect Dis* 1968;118:104–113.
80. Doganay M, Hanagasi R, Zora A. [Evaluation of penicillin alone and penicillin combined with anti-anthrax serum in experimental anthrax in mice.] *Mikrobiyol Bul* 1985;19:57–64.
81. Associated Press. Government may offer anthrax treatment. *New York Times* January 7, 2002.
82. Davis LE. Acute bacterial meningitis. In: Johnson RT, Griffin JW, eds. *Current therapy in neurologic disease*. 5th ed. St. Louis: Mosby, 1997:120–127.
83. Viladrich PF, Gudiol F, Liñares J, et al. Evaluation of vancomycin for therapy of adult pneumococcal meningitis. *Antimicrob Agents Chemother* 1991;35:2467–2472.
84. París M, Hickey SM, Uscher MI, Shelton S, Olsen KD, McCracken GH Jr. Effect of dexamethasone on therapy of experimental penicillin- and cephalosporin-resistant pneumococcal meningitis. *Antimicrob Agents Chemother* 1994;38:1320–1324.
85. Cabellos C, Martinez-Lacasa J, Martos A, et al. Influence of dexamethasone on efficacy of ceftriaxone and vancomycin therapy in experimental pneumococcal meningitis. *Antimicrob Agents Chemother* 1995;39:2158–2160.
86. Ahmed A, Jafri H, Lutsar I, et al. Pharmacodynamics of vancomycin for the treatment of experimental penicillin- and cephalosporin-resistant pneumococcal meningitis. *Antimicrob Agents Chemother* 1999;43:876–881.