

Long-term Outcomes of Patients With Fungal Infections Associated With Contaminated Methylprednisolone Injections

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Background. The largest health care–associated infection outbreak in the United States occurred during 2012–2013. Following injection of contaminated methylprednisolone, 753 patients developed infection with a dematiaceous mold, *Exserohilum rostratum*. The long-term outcomes of these infections have not been described.

Methods. This retrospective cohort study of 440 of a total of 753 patients with proven or probable *Exserohilum* infection evaluated clinical and radiographic findings, antifungal therapy and associated adverse effects, and outcomes at 6 weeks, 3, 6, 9, and 12 months after diagnosis. Patients were grouped into 4 disease categories: meningitis with/without stroke, spinal or paraspinal infections, meningitis/stroke plus spinal/paraspinal infections, and osteoarticular infections.

Results. Among the 440 patients, 223 (51%) had spinal/paraspinal infection, 82 (19%) meningitis/stroke, 123 (28%) both, and 12 (3%) osteoarticular infection. Of 82 patients with meningitis/stroke, 18 (22%) died; among those surviving, 87% were cured at 12 months. Only 7 (3%) of 223 patients with spinal/paraspinal infection died, but at 12 months, 68% had persistent or worsening pain and only 47% were cured. For the 123 patients with both meningitis/stroke and spinal/paraspinal infection, 10 (8%) died, pain persisted in 72%, and 52% were cured at 12 months. Only 37% of those with osteoarticular infection were cured at 12 months. Adverse events from antifungal therapy were noted at 6 weeks in 71% of patients on voriconazole and 81% on amphotericin B.

Conclusions. Fungal infections related to contaminated methylprednisolone injections culminated in death in 8% of patients. Persistent pain and disability were seen at 12 months in most patients with spinal/paraspinal infections.

Keywords. amphotericin B; arachnoiditis; *Exserohilum rostratum*; meningitis; methylprednisolone; paraspinal infection; spinal infection; voriconazole.

In September 2012, the Centers for Disease Control and Prevention (CDC) and state public health partners investigated an outbreak of infections caused by the dematiaceous mold *Exserohilum rostratum* in patients who received injections, primarily epidural, of methylprednisolone acetate. All medications were produced by a single compounding pharmacy, the New England Compounding Center, and had been contaminated during the manufacturing process [1–4].

In this largest-ever health care–associated outbreak, 753 patients with fungal infections were reported and 64 (8%) patients died [5]. Initially, most patients experienced meningitis, sometimes involving stroke. However, after a few weeks, spinal and paraspinal infections became prominent [6–9]. Among the 753 patients, 325 (43%) had spinal/paraspinal infections, 241 (32%) had meningitis/stroke, 152 (20%) had both spinal/paraspinal infections and meningitis/stroke, 33 (4%) had a peripheral osteoarticular infection, and 2 had both spinal/paraspinal infection and peripheral osteoarticular infection [2, 3].

Initial treatment for most patients involved combination therapy with liposomal amphotericin B and voriconazole or voriconazole monotherapy [9]. Surgical debridement was recommended when feasible for spinal/paraspinal and osteoarticular infection. Most patients received antifungal treatment for 3–6 months, but others required longer therapy.

Preliminary results of follow-up of patients involved in the outbreak were briefly reported [5], but the long-term therapeutic approach, adverse events, and outcomes associated with

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Table 1. Categories of Infection

Meningitis with or without stroke: Signs or symptoms of meningitis with cerebrospinal fluid white blood cells $\geq 5/\mu\text{L}$ (accounting for the presence of red blood cells) and/or posterior circulation stroke without a cardioembolic source following epidural injection
Spinal/paraspinal infection: Abscess, phlegmon, soft tissue, or bony infection in the spinal or paraspinal structures at or near the site of epidural or paraspinal injection
Meningitis/stroke and spinal/paraspinal infection: Infection of both central nervous system and spinal/paraspinal tissues, usually with the latter occurring after the former
Nonvertebral osteoarticular infection: Osteomyelitis or worsening inflammatory arthritis following injection of a joint, bursa, or tendon insertion not contiguous with the spine

this outbreak have not been described in detail. The purpose of this study was to examine the clinical course and outcomes for patients who were affected by this outbreak. Outcomes in regard to resolution of the infection and functional status were sought, and adverse effects related to chronic treatment with antifungal agents were evaluated.

METHODS

Patients

This was a retrospective cohort study of a majority of patients who developed fungal infections following injection of contaminated methylprednisolone and who were cared for by physicians at 8 sites in 6 states (Indiana, Michigan, New Jersey, North Carolina, Tennessee, and Virginia).

Inclusion criteria were (1) exposure to a contaminated lot of methylprednisolone acetate; (2) symptoms compatible with meningitis with or without stroke, spinal/paraspinal infection, or osteoarticular infection; (3) laboratory or radiographic evidence of infection; (4) culture, histopathology, or polymerase chain reaction (PCR) evidence of fungal infection. Proven cases met all 4 criteria, and probable cases met the first 3 criteria but lacked confirmatory laboratory evidence of fungal infection.

Definitions

Cases were classified into 1 of 4 patient categories: meningitis with or without stroke, spinal/paraspinal infection, meningitis/stroke and spinal/paraspinal infection, and nonvertebral osteoarticular infection (Table 1). Disease in patients with spinal/paraspinal infection at or near the site of injection was further classified based on imaging (Table 2). Outcomes were defined based on clinical findings, radiographic evaluations, response to antifungal therapy, pain, and ability to perform activities of daily living (ADLs) (Table 3).

Data Collection

Retrospective medical chart reviews were performed at each institution. Data were entered into REDCap, a secure online database (Vanderbilt University, Nashville, TN, USA) at clinical visits corresponding with the following time points after diagnosis: 6 weeks, 3 months, 6 months, 9 months, and 12 months. Data were collected at 18 and 24 months on a subset of patients treated for longer than 12 months and those with a reported relapse. Demographic data, details of the injection of contaminated steroid, underlying medical conditions, symptoms and signs of infection, radiographic data, response to antifungal therapy, adverse effects of antifungal agents, quality of life assessments, and outcomes were collected. The institutional review board at each site and the CDC reviewed and approved the study protocol.

Data Analysis

We calculated descriptive statistics on demographic and clinical data. Survival functions for all-cause mortality and cumulative incidence of cure (defined in Table 3) of relapse-free patients in the 12-month cohort were estimated for a follow-up period of 450 days. The 450-day cutoff was chosen because <1% of patients had follow-up visits beyond 450 days and visit dates only roughly corresponded with the time points for later visits. The Kaplan-Meier method for all-cause mortality was used to estimate the survival function of relapse-free patients assuming no additional censoring occurred before 450 days. The cumulative incidence was used to estimate patients' time to cure, while accounting for the competing risk of all-cause mortality during the follow-up period [10]. A Cox proportional hazard model was used to calculate hazard ratio with 95% confidence intervals (CIs). Data cleaning and statistical analysis were performed in SAS, version 9.3 (SAS Institute Inc., Cary, NC, USA), and R, version 3.6.1 (R 2018).

Table 2. Classification of Spinal/Paraspinal Infection as Defined by Radiological Criteria

Arachnoiditis: Enhancement, thickening, or clumping of nerve roots and/or cauda equina
Epidural abscess/phlegmon: Epidural fluid collection with or without enhancement
Vertebral discitis/osteomyelitis/sacroiliac joint infection: Radiological changes indicating infection of vertebrae or sacroiliac joint
Other spinal/paraspinal infection: Fluid collection with or without enhancement in the paraspinal space or inflammatory changes, suggesting acute infection in facet joints

Table 3. Outcomes of Infection Associated With Injection of Contaminated Methylprednisolone

Cure: Improvement or resolution of symptoms and/or signs compared with baseline, defined as the date on which the diagnosis was established, no clinical evidence of active infection, and off antifungal therapy for at least 3 months

Improved: Improvement or resolution of symptoms and/or signs compared with baseline; may have clinical evidence of active infection; may or may not be off antifungal therapy

Stable: Little or no improvement of symptoms and/or signs as compared with baseline; may have clinical evidence of infection; may or may not be off antifungal therapy

Progression: Worsening symptoms and/or signs of infection compared with baseline

Relapse: Recurrent symptoms and/or signs occurring off antifungal therapy and radiographic or laboratory evidence to support the diagnosis of relapse

RESULTS

Patients and Disease Classification

Four hundred forty patients representing over half (58%) of the 753 patients were entered into the study. The median age (interquartile range [IQR]) was 65 (55–77) years; 58% (n = 257) were women, and most (n = 421, 96%) were non-Hispanic white. Of the 440 patients, 223 (51%) had spinal/paraspinal infection only, 123 (28%) had both spinal/paraspinal infection and meningitis/stroke, 82 (19%) had only meningitis/stroke, and 12 (3%) had nonvertebral osteoarticular infection only. The entire cohort had few underlying illnesses; the most common underlying illness was hypertension in 273 patients (62%), followed by hyperlipidemia in 202 (46%); underlying immunodeficiency was noted in only 26 (6%) patients (Table 4).

Proven infections were identified in 237 (54%) patients, and probable infections in 203 (46%). The majority of patients received care in Michigan (55%, n = 241). Patients with meningitis predominated at some sites, but at other sites most patients had spinal/paraspinal infections (Figure 1).

The median follow-up time (IQR) was 317 (219–365) days. At the 12-month follow-up, data were available for 328 (75%) of the 440 patients. This decrease was related to the loss of follow-up because patients were cured and off therapy, had died, or had moved. Data were available at 24 months for only 36 (8%) patients.

Meningitis and/or Stroke

Eighty-two patients developed meningitis and/or stroke; 64 (78%) had proven infection, and 18 (22%) had probable infection. Site of epidural injection was known for 71 (87%) patients (Table 4). Of the 82 patients, 73 (89%) had meningitis only, 2 (2%) had a stroke only, and 7 (9%) had both. At 6 months, 10 (16%) of 62 patients were in the hospital or had been hospitalized in the preceding 3 months, 2 (5%) were in long-term care facilities (LTCFs), and 3 (5%) were in long-term acute care hospitals (LTACHs).

Prominent symptoms at baseline were headache in 75 (91%), fever in 31 (38%), and decreased cognitive function in 23 (28%). Several patients had severe cognitive dysfunction. By 6 months, cognitive dysfunction was mild–moderate in 10 (16%) of 62

patients and severe in 1 patient, and at 12 months, 4 (11%) of 38 patients had persistent mild–moderate cognitive impairment. At the initial visit, 15 patients (18%) could not walk or needed assistive devices; by 6 and 12 months, 13 (21%) and 6 (16%) patients, respectively, still required assistance to ambulate. Four patients (5%) were aphasic at the initial visit, and 9 (11%) had mild to severe slurring of speech, which persisted for 3 (5%) patients at 6 months.

All patients received antifungal treatment, except for 2 who had stroke only and died soon after diagnosis (Table 5). Initial treatment was primarily with voriconazole. By the 12-month follow-up, only 2 patients remained on antifungal therapy.

Thirteen (16%) died by the 6-week follow-up and a total of 18 (22%) by the 6-month follow-up. Six (67%) of 9 patients who had a stroke died, 2 before therapy could be started, 3 by 2 weeks, and another by 6 months. Among the 38 patients for whom clinical status was known, 33 (87%) were considered cured at the 12-month follow-up (Table 6).

Spinal/Paraspinal Infections

A total of 223 patients had localized infection (78 [35%] proven, 145 [65%] probable) at the site of injection, which was known for 216 (97%) patients (Table 4). At 6 months, 28 (14%) of 206 patients were in the hospital or had been hospitalized in the preceding 3 months, 6 (3%) were in LTCFs, and 7 (3%) were in LTACHs. At 12 months, 15 (10%) of 148 patients were in the hospital or had been hospitalized in the preceding 3 months, 1 (1%) was in an LTCE, and 5 (3%) were in LTACHs.

Pain was the prominent initial symptom, reported in 213 (96%) patients. By 6 months, pain levels were stable in 101 (49%) of 206 patients and had increased in 26 (13%). Pain was stable or had decreased at the 12-month follow-up in 124 (84%) of 148 patients but had increased in 15 (10%) patients.

Pain interfered with ADLs in 88 (39%) patients initially, 61 (30%) of 206 patients at 6 months, and 28 (19%) of 148 patients at 12 months. At 24 months, 7 (30%) of 23 patients were still not able to carry out ADLs. Initially, ambulation was impaired in 76 patients (33%), including 9 who were unable to walk. Of those 9 patients, 4 could not walk at 6 months, and 2 were still unable to walk at 24 months. Moderate impairment requiring use of a cane or walker was present at 6 months in

Table 4. Characteristics of Patients With Fungal Infections Following Contaminated Methylprednisolone Injections

Characteristic, No. (%)	Meningitis/Stroke (n = 82), No. (%)	Spinal/Paraspinal (n = 223), No. (%)	Spinal/Paraspinal and Meningitis/Stroke (n = 123), No. (%)	Osteoarticular (n = 12), No. (%)	Total (n = 440), No. (%)
Age, median (IQR), y	61 (50–77)	65 (55–75)	67 (55–75)	58 (53–65)	65 (55–75)
Sex					
Female	49 (60)	128 (57)	74 (60)	6 (50)	257 (58)
Race					
Caucasian	75 (92)	217 (97)	115 (96)	11 (92)	421 (96)
African American	6 (7)	5 (2)	4 (3)	0 (0)	15 (3)
Other	1 (1)	1 (0.4)	1 (1)	1 (8)	4 (1)
Treatment location (state)					
Indiana	18 (22)	18 (8)	9 (7)	0 (0)	45 (10)
Michigan	10 (12)	175 (78)	44 (36)	12 (100)	241 (55)
North Carolina	1 (1)	14 (6)	2 (2)	0 (0)	17 (4)
New Jersey	24 (29)	4 (2)	9 (7)	0 (0)	37 (8)
Tennessee	11 (13)	9 (4)	45 (37)	0 (0)	65 (15)
Virginia	18 (22)	3 (1)	14 (11)	0 (0)	35 (8)
Comorbidities					
Hypertension	50 (61)	132 (59)	80 (65)	9 (75)	273 (61)
Dyslipidemia	39 (46)	96 (43)	62 (50)	5 (42)	202 (46)
Diabetes mellitus	17 (21)	48 (21)	28 (23)	3 (25)	96 (22)
Coronary artery disease	11 (13)	37 (16)	14 (12)	4 (33)	66 (15)
Chronic kidney disease	7 (9)	20 (9)	6 (5)	1 (8)	34 (8)
Neurologic disease/chronic cognitive disorder	3 (4)	15 (7)	13 (11)	0 (0)	31 (7)
Underlying immunodeficiency	6 (7)	8 (4)	11 (9)	1 (8)	26 (6)
Cerebrovascular accident	5 (6)	11 (5)	6 (5)	0 (0)	22 (5)
Congestive heart failure	5 (6)	7 (3)	3 (3)	0 (0)	15 (3)
Chronic liver disease	1 (1)	0 (0)	4 (3)	0 (0)	5 (1)
Site of injection associated with infection					
Cervical	10 (12)	21 (9)	7 (6)	0 (0)	39 (9)
Thoracic	0 (0)	3 (1)	4 (3)	0 (0)	7 (2)
Lumbar	58 (71)	160 (72)	81 (66)	0 (0)	299 (68)
Sacral	6 (7)	37 (17)	2 (2)	0 (0)	45 (10)
Hip	0 (0)	0 (0)	0 (0)	4 (33)	5 (2)
Ankle	0 (0)	0 (0)	0 (0)	3 (25)	3 (1)
Shoulder	0 (0)	0 (0)	0 (0)	5 (42)	5 (1)
Unknown/missing	12 (13)	7 (3)	30 (24)	0 (0)	48 (11)

Abbreviation: IQR, interquartile range.

47 (23%) of 206 patients and at 12 months in 33 (22%) of 148 patients. Bowel and/or bladder dysfunction was present initially in 19 patients (8%) and persisted in 13 of 148 (9%) at 12 months.

All patients were treated with antifungal agents (Table 5). Initial antifungal therapy was voriconazole alone in 188 (84%) patients. Many patients had changes in their antifungal regimen because of adverse effects of voriconazole. A total of 118 patients (53%) underwent abscess drainage, a washout procedure, or debridement of the infected site. For 11 (9%) patients, multiple debridements were required, and 13 (11%) had a laminectomy.

Seven (3%) patients died. At 6 months, the status was known for 206 patients, of whom only 7 (3%) were reported as cured (Table 6). By 12 months, the status was known for 148 patients, of whom 70 (47%) were considered cured.

Meningitis/Stroke and Spinal/Paraspinal Infections

Both meningitis/stroke and spinal/paraspinal infections (92 [75%] proven, 31 [25%] probable) were reported in 123 patients. Only 10 (8%) patients had stroke without meningitis. In most patients, meningitis/stroke was the initial presenting infection, and then symptoms and signs of spinal/paraspinal involvement occurred, usually weeks later. Site of injection was documented for 93 (76%) patients (Table 4). At 6 months, 62 (58%) of 107 patients had been hospitalized in the preceding 3 months, 11 (10%) had been in LTCFs, and 10 (9%) had been in LTACHs. At 12 months, 39 (44%) of 89 patients had been hospitalized within the preceding 3 months, 4 (4%) were in LTCFs, and 3 (3%) were in LTACHs.

The symptoms and signs were similar to those demonstrated by patients in both of the preceding 2 groups. At the initial visit,

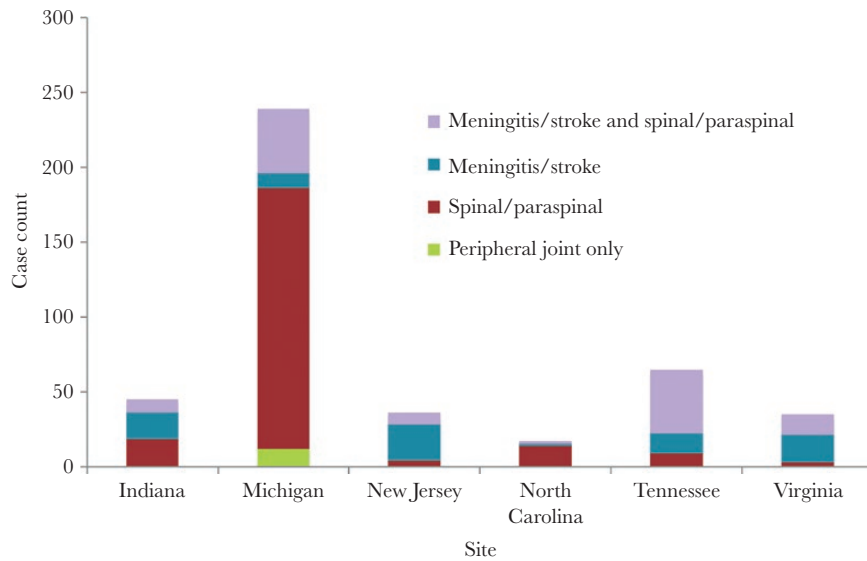


Figure 1. Types of infections and site of treatment in patients who received injections of contaminated methylprednisolone acetate.

54 patients (44%) had fever and 23 patients (19%) had cognitive impairment. At 6 months, 28 (26%) of 107 patients were cognitively impaired. At the initial visit, pain was present in 120 patients (98%). By 6 months, pain was unchanged or worse in 73 (68%) of 107 patients, and at the 12-month follow-up, 64 (72%) of 89 patients continued to have unchanged or worsening pain. In 33 (28%) patients, pain interfered with ability to complete ADLs, and this continued for 8 patients at 6 months and for 3 patients at 12 months.

Initially, 11 (9%) patients had slurring of speech, and 22 (18%) had problems with bowel and/or bladder function. Thirty-seven (30%) patients had difficulty ambulating, including 5 who could not walk at all. The ability to ambulate worsened by 6 months, when 52 (49%) of 107 patients had difficulty walking. At 12 months, 29 (33%) of 89 patients still had difficulty walking, and 1 patient was unable to walk.

Treatment with antifungal agents was given to 121 (98%) patients; 2 patients died following a stroke before treatment

Table 5. Antifungal Treatment for 4 Patient Categories of Infection Over Time

Category of Disease	Initial, ^a No. (%)	3 Months, ^a No. (%)	6 Months, ^a No. (%)	12 Months, ^a No. (%)
Meningitis/stroke (No. of patients)	(82)	(66)	(62)	(38)
Voriconazole	81 (99)	56 (85)	42 (68)	2 (5)
Amphotericin B	32 (39)	4 (6)	2 (3)	—
Itraconazole	3 (4)	5 (8)	5 (8)	—
Posaconazole	2 (2)	2 (3)	1 (2)	1 (3)
Spinal/paraspinal (No. of patients)	(223)	(210)	(206)	(148)
Voriconazole	192 (86)	199 (95)	171 (83)	25 (17)
Amphotericin B	35 (16)	9 (4)	12 (6)	3 (2)
Itraconazole	4 (2)	20 (10)	65 (32)	37 (25)
Posaconazole	—	—	2 (1)	7 (5)
Meningitis/stroke and spinal/paraspinal (No. of patients)	(123)	(114)	(107)	(89)^b
Voriconazole	113 (92)	105 (92)	96 (90)	13 (15)
Amphotericin B	42 (34)	41 (36)	15 (14)	6 (7)
Itraconazole	—	6 (5)	23 (21)	15 (17)
Posaconazole	8 (7)	4 (4)	3 (3)	2 (2)
Osteoarticular infection (No. of patients)	(12)	(12)	(11)	(8)
Voriconazole	12 (100)	7 (64)	7 (58)	—
Itraconazole	—	5 (45)	7 (58)	4 (50)
Posaconazole	—	—	1 (8)	—

^aNumbers listed are greater than the total number of patients in each category because many patients received several antifungal agents either in combination or sequentially.

^bOne patient received isavuconazole.

Table 6. Outcomes at 6 and 12 Months for Each of 4 Patient Categories of Infection

Category of Disease	Cure, No. (%)	Improved, No. (%)	Stable, No. (%)	Progression, No. (%)
Meningitis/stroke (n = 82)^a				
6 mo (n = 62)	9 (15)	47 (76)	7 (11)	1 (2)
12 mo (n = 38)	33 (87)	3 (8)	1 (3)	0
Spinal/paraspinal (n = 223)^b				
6 mo (n = 206)	7 (3)	149 (72)	39 (19)	12 (6)
12 mo (n = 148)	70 (47)	57 (39)	15 (10)	3 (2)
Meningitis/stroke and spinal/paraspinal (n = 123)^c				
6 mo (n = 107)	1 (1)	73 (68)	20 (19)	13 (12)
12 mo (n = 89)	46 (52)	29 (33)	13 (15)	1 (1)
Osteoarticular infection (n = 12)				
6 mo (n = 11)	0	8 (73)	3 (27)	0
12 mo (n = 8)	3 (37)	5 (63)	0	0

^aNot included are 18 patients who died before the 6-month follow-up.

^bNot included are 7 patients who died before the 6-month follow-up.

^cNot included are 10 patients who died before the 6-month follow-up.

could be initiated (Table 5). Initial treatment was voriconazole alone or combined with amphotericin B in nearly all patients. At 24 months, 5 patients remained on antifungal therapy. Forty patients (40%) had a drainage, washout, or debridement procedure, 6 of whom required a second debridement. Laminectomy was performed in 6 patients.

Ten (8%) patients died, 3 of whom had a stroke; 5 patients died within 3 weeks of diagnosis, and another 5 by 6 months.

At 6 months, of 107 patients for whom data were available, only 1 patient was cured, and 13 (12%) had progression of disease (Table 6). At the 12-month follow-up for 89 patients, 46 (52%) were cured.

Imaging Results for Patients With Spinal/Paraspinal Infection

Magnetic resonance imaging (MRI) results for the 346 patients who had spinal/paraspinal infection allowed classification of the type of involvement (Table 7). Epidural abscess/phlegmon was found in 173 (50%) of patients, ranging from enhancement in the epidural space to phlegmon to well-circumscribed abscesses. Patients who had epidural disease frequently also had paraspinal disease, and many also had arachnoiditis. Arachnoiditis was found in 117 (34%) patients, with findings ranging from discrete intradural abscesses to clumping and enhancement of nerve roots within the spinal canal (Figure 2). Many patients with arachnoiditis had both epidural and intradural infection, as well as involvement of paraspinal structures. Vertebral osteomyelitis/discitis and sacroiliac joint infection were less common and often seen with epidural abscess/phlegmon.

Nonvertebral Osteoarticular Infections

Twelve patients had osteoarticular involvement, including hip (n = 4), shoulder (n = 4), both hip and shoulder (n = 1), and ankle (n = 3). Three of these infections were proven, and 9 were probable. One patient remained in an LTCF for 6 months.

At the initial visit, 4 patients were febrile, and all reported pain in the affected joint. Pain decreased in 7 patients by 3 months, but for 5 patients it continued to interfere with ADLs. The most severely affected patient was unable to walk unaided for 9 months. Six other patients had difficulty ambulating, and 2 required a cane or walker at the 12-month follow-up visit. At 24 months, 1 patient reported persistent pain.

Table 7. Sites of Infection Determined by Clinical Findings and Magnetic Resonance Imaging in 346 Patients who Had Spinal/Paraspinal Involvement With or Without Meningitis/Strokea

Site of Infection	No. (%) ^b
Epidural abscess/phlegmon 173 (50)	
Only	61 (35)
With arachnoiditis	53 (31)
With osteomyelitis/sacroiliac disease	35 (20)
With other spinal/paraspinal disease	50 (29)
Arachnoiditis 117 (34)	
Only	51 (44)
With epidural abscess/phlegmon	53 (45)
With osteomyelitis/sacroiliac disease	10 (8)
With other spinal/paraspinal disease	25 (21)
Other spinal/paraspinal disease 117 (34)	
Only	47 (40)
With arachnoiditis	25 (21)
With epidural abscess/phlegmon	50 (43)
With osteomyelitis/sacroiliac disease	17 (14)
Osteomyelitis/sacroiliac disease 105 (16)	
Only	51 (49)
With arachnoiditis	12 (11)
With epidural abscess/phlegmon	41 (39)
With other spinal/paraspinal disease	23 (22)

^aAs defined in Table 3.

^bPatients had more than 1 site of infection.

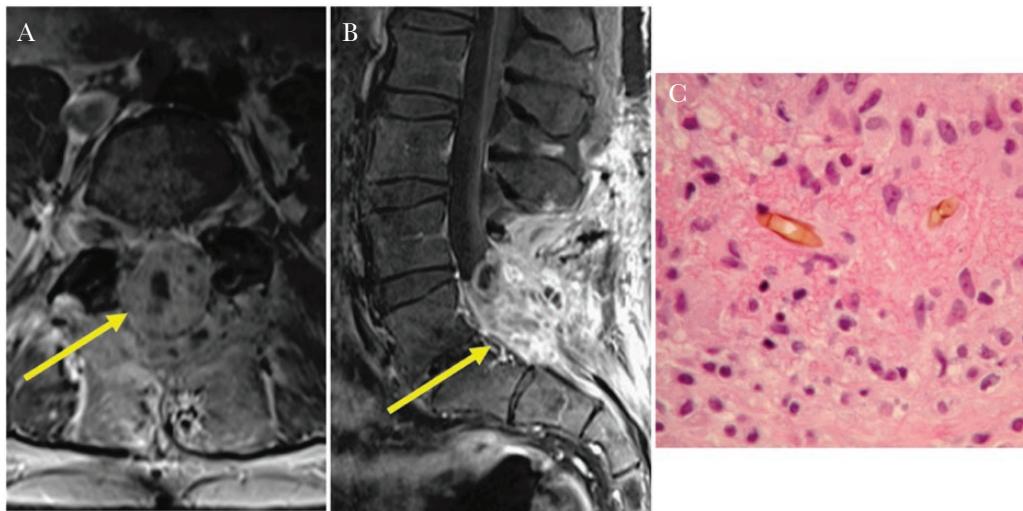


Figure 2. Magnetic resonance images (MRIs) taken 8 months after injection of contaminated methylprednisolone. A, Axial T2-weighted, postcontrast image of the lumbosacral spine showing severe narrowing of the distal thecal sac with thick, multiseptated epidural, dural, and intrathecal enhancement (arrow) consistent with arachnoiditis. B, Sagittal T1 fat-saturated, postcontrast image of the lumbosacral spine showing epidural, dural, and intrathecal enhancement (arrow) consistent with arachnoiditis and epidural phlegmon. C, Tissue obtained at surgery showing pigmented hyphae (hematoxylin and eosin stain). Polymerase chain reaction on cerebrospinal fluid yielded *Exserohilum rostratum*.

Initial treatment of all patients with osteoarticular infections was with voriconazole (Table 5). Debridement or washout procedures were required in 7 patients. All 4 patients with hip infection required revision arthroplasty, and another had resection of the distal clavicle. By 6 months, the infection was improved or stable in all patients. Among 8 patients for whom the status was known at 12 months, 3 (37%) were cured and 5 (63%) were improved (Table 6).

Adverse Effects Associated With Antifungal Agents for All Groups

Adverse events were common among patients receiving amphotericin B and voriconazole. The prominent side effects

of amphotericin B began within the first few weeks of starting therapy and were primarily infusion-related or kidney dysfunction. By the 6-week follow-up visit, 101 patients (61%) had experienced a rising serum creatinine and 104 (62%) had hypokalemia and/or hypomagnesemia.

Voriconazole treatment led to a variety of side effects that were the primary reason for changing from this drug to another azole. By 6 weeks, 292 patients (71%) had experienced a voriconazole-associated adverse event (Figure 3). Changes in liver enzymes had occurred in 191 patients (46%) by 6 weeks, but only rarely did these changes lead to discontinuation of the drug. Photopsia was an early adverse event within the first 6

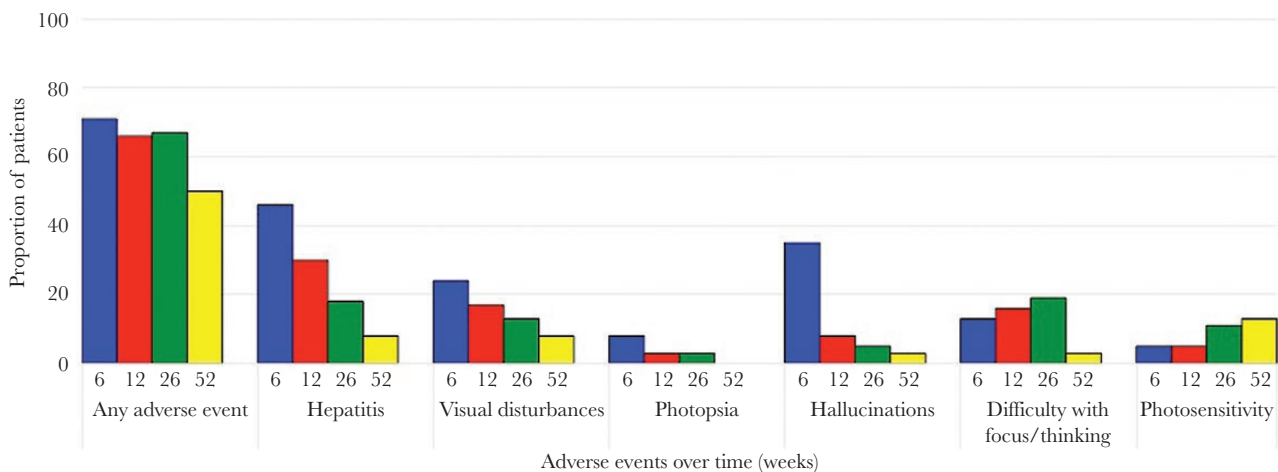


Figure 3. Adverse events experienced by patients taking voriconazole, shown by proportion of patients with specific adverse events in each designated time period.

weeks but was reported infrequently by 12 weeks; however, blurry vision and other visual complaints persisted for as long as 9 months in some patients.

Hallucinations were reported in 144 (35%) patients early in the course of therapy but decreased to <10% at later visits. Trouble focusing on the task at hand and feeling “fuzzy” in the head were still present in almost 20% of patients at 6 months.

Overall Outcomes for All Groups

All-cause mortality was 8% (n = 35) (Figure 4A), with the meningitis/stroke-only group having a nearly 8-fold higher likelihood of death compared with the spinal/paraspinal infection-only group (hazard ratio, 7.62; 95% CI, 3.17–18.37). Although more likely to die, patients with meningitis/stroke had a shorter time to cure compared with patients who had

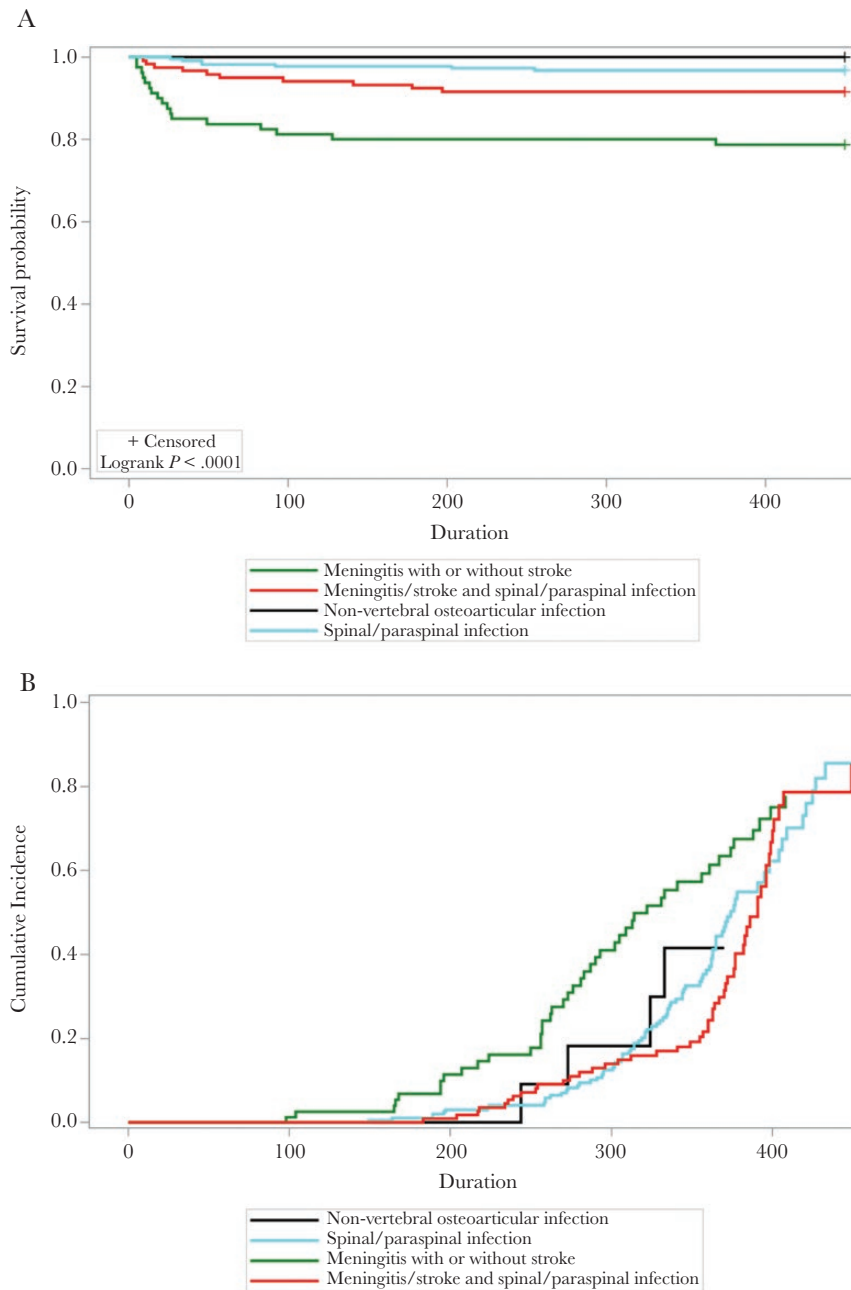


Figure 4. A, Kaplan-Meier survival curve for 4 patient disease categories when the event of interest is all-cause-mortality. B, Cumulative incidence curve for 4 patient disease categories accounting for competing risk of all-cause mortality when the event of interest is cure. With respect to cure, censoring (primarily loss to follow-up) occurred in 60% of patients in the spinal/paraspinal infection category, 50% in the meningitis/stroke and spinal/paraspinal infection category, 23% in the meningitis with or without stroke category, and 67% in the nonvertebral osteoarticular infection category.

spinal/paraspinal infection. Accounting for competing risk of death, the hazard ratio, indicating faster time to cure, was 3.68 (95% CI, 2.64–5.13) (Figure 4B).

Seven patients suffered a relapse of infection: 4 with meningitis and spinal/paraspinal infection, 2 with only spinal/paraspinal infection, and 1 with meningitis alone. Four of the 7 had arachnoiditis. The initial course of antifungal therapy was with voriconazole, but therapy in 1 patient was changed to itraconazole after only 1 week. The median length of therapy (range) was 4 (2–9) months; patients ended therapy a median (range) of 3 (1–14) months before relapse occurred. Two of the 4 patients with arachnoiditis had received antifungal therapy for as long as 9 months, but the other 2 had been treated for only 2.5–4 months. One patient who had meningitis, without initial clinical or radiological signs of spine involvement, relapsed with lumbar vertebral osteomyelitis. All patients responded to a second course of prolonged antifungal therapy.

DISCUSSION

In this retrospective review, we report the outcomes of 440 patients with infection caused by injection of methylprednisolone acetate contaminated with *E. rostratum*. The epidemiology, clinical manifestations, diagnosis, and treatment aspects of this large outbreak and a similar, but much smaller, outbreak have been reported previously [2, 3, 5–9, 11–18]; we report the long-term morbidity and mortality associated with this outbreak.

Outcomes differed based on patient category. Morbidity was especially striking in patients with spinal/paraspinal involvement, and their response to antifungal agents was slow. A year after the injection, many of these patients could not walk without an assistive device. Back pain, which was the primary reason for the injection, became much worse with infection, and persistent pain was noted to interfere with the ability to perform ADLs in 13% of these patients.

We noted an unexpected dichotomy in outcomes experienced by patients who had meningitis/stroke compared with those who had localized spinal/paraspinal infection. Patients who had only meningitis/stroke had a mortality rate of 22% within 6 months of the diagnosis, but by 12 months, the cure rate for survivors was 89%, and only a handful of patients had residual neurological symptoms. The group with only spinal/paraspinal infection had a mortality rate of 2%; however, the 12-month cure rate was only 48%, and 43% remained on antifungal therapy. At 12 months, a third of patients in both groups that had spinal/paraspinal involvement continued to have symptoms and to require treatment with antifungal agents.

Arachnoiditis proved to be exceptionally difficult to treat, which has been noted in prior reports of this condition due to other causes [19]. Several patients with arachnoiditis had prolonged courses of antifungal therapy, as well as operative intervention, but still had persistent pain and bowel and

bladder dysfunction. Four of 7 relapses were in patients who had arachnoiditis.

In comparison with patients who had epidural injections of methylprednisolone, infections associated with osteoarticular injections were less severe, but nevertheless associated with significant morbidity. Three patients had difficulty walking for at least 12 months, and 1 remained in an LTCF for >6 months.

Prolonged antifungal therapy contributed to the morbidity experienced by these patients. Voriconazole was the drug of choice because of its *in vitro* activity against *E. rostratum* and its ability to achieve adequate concentrations in the central nervous system (CNS). Adverse effects were expected based on prior experience and the need to give higher-than-usual doses of voriconazole initially when treating CNS infection. For example, by 6 weeks, one-third of patients had experienced hallucinations, an adverse effect associated with elevated serum trough concentrations of voriconazole [20–22], but with dose reduction and subsequent decreased serum voriconazole concentrations <5.5 µg/mL, the proportion of patients with hallucinations decreased to <10%.

Although not as dramatic as hallucinations, a surprising number of patients complained of feelings of foggy and slowness in carrying out their day-to-day activities. Family members noted that forgetfulness increased over time and that intermittent confusion and difficulties with word finding were common. These symptoms persisted for months and did not appear to be related to voriconazole serum concentrations. Most patients stated that these symptoms resolved when another azole agent was substituted for voriconazole.

The limitations of this study include the fact that only 440 (58%) of the 753 patients from only 8 sites were included. Some important events may have been missed because of this selection bias; for example, at least 2 other patients with a relapse were not included in this cohort [23, 24]. An unexpected limitation was that we could not follow the entire cohort because only 75% of patients were actively followed for 12 months and only a small, nonrepresentative proportion could be followed for 24 months. Given the observational nature of the study, patient visits did not correspond precisely with the stated follow-up time points, and retrospective data collection made it difficult to capture all possible treatment-related adverse events experienced by patients. Nevertheless, the study was able to describe the longest follow-up of patients who were affected by this fungal infection.

In conclusion, we report long-term sequelae associated with a large outbreak of fungal meningitis and spinal/paraspinal infections associated with the injection of contaminated methylprednisolone. Most patients who survived meningitis had total resolution of symptoms with antifungal therapy, whereas many of those who developed localized spinal/paraspinal infection had persistent pain and inability to perform ADLs for at least 12 months.

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