Fungal Infections Associated with Contaminated Steroid Injections

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ABSTRACT In mid-September 2012, the largest healthcare-associated outbreak in U.S. history began. Before it was over, 751 patients were reported with fungal meningitis, stroke, spinal or paraspinal infection, or peripheral osteoarticular infection, and 64 (8.5%) died. Most patients had undergone epidural injection, and a few osteoarticular injection, of methylprednisolone acetate that had been manufactured at the New England Compounding Center (NECC). The offending pathogen in most cases was Exserohilum rostratum, a brown-black soil organism that previously was a rare cause of human infection. Three lots of methylprednisolone were contaminated with mold at NECC; the mold from unopened bottles of methylprednisolone was identical by whole-genome sequencing to the mold that was isolated from ill patients. Early cases manifested as meningitis, some patients suffered posterior circulation strokes, and later cases were more likely to present with localized infection at the injection site, including epidural abscess or phlegmon, vertebral diskitis or osteomyelitis, and arachnoiditis with intradural involvement of nerve roots. Many patients with spinal or paraspinal infection required surgical intervention. Recommendations for treatment evolved over the first few weeks of the outbreak. Initially, combination therapy with liposomal amphotericin B and voriconazole was recommended for all patients; later, combination therapy was recommended only for those who were most ill, and voriconazole monotherapy was recommended for most patients. Among those patients who continued antifungal therapy for at least 6 months, outcomes for most appeared to be successful, although a few patients remain on therapy.

INTRODUCTION
By late September 2012, several cases of fungal meningitis were reported from different states. Investigation by the Centers for Disease Control and Prevention (CDC) quickly led to the discovery that the causative organism was a rare, usually nonpathogenic brown-black mold, Exserohilum rostratum, and that infection was associated with epidural injection of methylprednisolone acetate that had been contaminated at the compounding center at which it was produced. Although the contaminated lots of methylprednisolone were recalled as soon as the link was discovered, a total of 17,675 vials of potentially contaminated methylprednisolone acetate had been shipped to 76 facilities in 23 states (1). It is estimated that as many as 13,534 patients had been exposed to this product before the recall went into effect.

As the outbreak progressed, it became clear that a disproportionate number of cases were occurring in Michigan. When the CDC issued their last update on this outbreak in October 2013, there were a total of 751 cases, and 264 (35%) were reported from Michigan (2). Most patients were cared for at one hospital, St. Joseph Mercy Hospital (SJMH), in Ann Arbor, MI. We review the epidemiology of the outbreak and discuss our own experiences with the clinical manifestations of E. rostratum infection, which varied from life-threatening stroke to localized epidural abscesses to unremitting arachnoiditis. Treatment with antifungal agents was...
usually, but not always, successful but was accompanied by many adverse effects, some of which had not been reported previously. The legal and political ramifications of this outbreak, which became the largest healthcare-associated outbreak ever reported in the United States, are ongoing.

**EPIDEMIOLOGY**

The Beginning of the Outbreak
The inception of this outbreak occurred on 18 September 2012, when the Tennessee Department of Health was alerted by an astute physician that a patient in Nashville had died of culture-confirmed *Aspergillus fumigatus* meningitis and that this patient had received an epidural steroid injection 46 days earlier (3). By 25 September, 7 additional patients who had received epidural steroid injections at the same clinic were identified as having neutrophilic nonbacterial meningitis, and soon after, a similar case was reported from North Carolina (1). Investigation by the CDC determined that all affected patients had received an injection of preservative-free methylprednisolone acetate compounded at the New England Compounding Center (NECC) in Framingham, MA. The company was immediately notified that their product was implicated (4). Three lots, designated by their date of release as 05212012@68, 06292012@26, and 08102012@51, were contaminated (5). All patients who had received an injection from one of these 3 lots were contacted through state and local health departments, and all clinics that had purchased one of these 3 lots were told to immediately stop giving injections of this material.

By 1 October 2012, the CDC had convened an expert panel to consult on case definitions and treatment regimens for fungal meningitis. Case definitions were established (Table 1). On 4 October 2012, the first health advisory notice was posted regarding this outbreak of fungal meningitis, and the Food and Drug Administration (FDA) reported that fungi were found in unopened vials of methylprednisolone acetate from the implicated lots (6). Both specimens from patients and material from the unopened vials revealed the rarely pathogenic dematiaceous mold *Exserohilum rostratum* (7).

As soon as a dematiaceous mold was identified as the likely pathogen, analogy was made to an almost identical outbreak that had occurred a decade before (8). In 2002, four patients, one of whom died, developed meningitis after receiving an epidural injection with methylprednisolone acetate that was contaminated with *Exophiala dermatitidis*. A compounding center in South Carolina had manufactured the product, and unopened vials at that center were found to contain *E. dermatitidis*. What was dramatically different about the NECC outbreak was that the contaminated product had been shipped widely throughout the United States and more than 13,000 patients had been exposed.

The investigation traced back those patients who had received injections soon after the release of the first contaminated lot on 21 May 2012. The first infection that was documented was a spinal or paraspinal infection on 7 July 2012, and the first case of meningitis had symptoms beginning on 16 July 2012 (5) (Fig. 1). Further studies revealed that the lot released on 29 June 2012 (06292012@26) was associated with a higher attack rate than the other two contaminated lots (9).

**Evolution of the Outbreak**
At the outset, most patients were diagnosed with meningitis, and a small number experienced a stroke (10, 11). By mid-October 2012, spinal and paraspinal infections became the predominant types of infection (12, 13). It was not unusual for a patient who was doing well on voriconazole for treatment of meningitis to return to the hospital with increasing back pain at the site of the injection and then to be found by magnetic

![Table 1](https://asmscience.org/MicrobiolSpectrum)

**TABLE 1** CDC case definitions of probable and confirmed fungal infections associated with contaminated methylprednisolone injection

<table>
<thead>
<tr>
<th>Type of infection</th>
<th>Probable infection* in a person who had received an injection after 21 May 2012 from 1 of 3 implicated MPA lots</th>
<th>Confirmed infection* in a person who had received an injection from one of the implicated MPA lots</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meningitis</td>
<td>Signs and symptoms of meningitis (headache, fever, meningismus, or photophobia); unknown etiology; epidural or paraspinal injection; CSF pleocytosis ≥5 WBCs/μl adjusted for RBC</td>
<td>Signs and symptoms of meningitis (headache, fever, meningismus, or photophobia); unknown etiology; epidural or paraspinal injection; CSF pleocytosis ≥5 WBCs/μl adjusted for RBC</td>
</tr>
<tr>
<td>Posterior circulation stroke</td>
<td>Signs and symptoms of stroke; epidural or paraspinal injection; no cardioembolic source; lumbar puncture not performed or CSF pleocytosis if performed</td>
<td>Signs and symptoms of stroke; epidural or paraspinal injection; no cardioembolic source; lumbar puncture not performed or CSF pleocytosis if performed</td>
</tr>
<tr>
<td>Spinal or paraspinal infections</td>
<td>Osteomyelitis, abscess, phlegmon, or soft tissue infection; unknown etiology; epidural or paraspinal injection</td>
<td>Osteomyelitis, abscess, phlegmon, or soft tissue infection; unknown etiology; epidural or paraspinal injection</td>
</tr>
<tr>
<td>Peripheral osteoarticular infections</td>
<td>Osteomyelitis or worsening inflammatory arthritis; unknown etiology; injection of an osteoarticular structure</td>
<td>Osteomyelitis or worsening inflammatory arthritis; unknown etiology; injection of an osteoarticular structure</td>
</tr>
</tbody>
</table>

*MPA, methylprednisolone acetate; CSF, cerebrospinal fluid; WBCs, white blood cells; RBC, red blood cell.

*A confirmed case met the definitions for probable infection and had evidence of fungal infection by culture, histopathology, or molecular assay.

*Three implicated lots produced by the NECC were 05212012@68, 06292012@26, and 08102012@51.
resonance imaging (MRI) study to have localized spinal or paraspinal infection and/or arachnoiditis. Other patients never had meningitis but presented with only spinal or paraspinal infection. Soon the number of cases of spinal or paraspinal infection surpassed the number of meningitis cases, and by October 2013, 476 patients (63%) had either isolated spinal or paraspinal infection or both spinal or paraspinal infection and meningitis (2).

The median incubation period was 47 days (range, 0 to 249 days); this was shorter for patients who experienced a stroke without documented meningitis (median, 24 days, and range, 3 to 157 days) and patients who had meningitis (median, 35 days, and range, 1 to 200 days) and longer for those who had spinal or paraspinal infection or both spinal or paraspinal infection and meningitis (5). One theory for why spinal and paraspinal infections presented late in the outbreak is that the steroid injection may have masked early signs and symptoms of local inflammation and led to delayed clinical presentation. Additionally, the incubation period for a localized Exserohilum infection to become clinically evident may be prolonged, as noted with other central nervous system (CNS) brown-black mold infections (8, 14).

In Michigan, 4 facilities received 2,225 vials of contaminated methylprednisolone acetate, and 1,791 residents of Michigan received a total of 2,537 injections in tissues other than peripheral joints (mostly epidural injections) (12). In a pain facility near Ann Arbor, approximately 544 persons received 1 or more epidural injections of contaminated methylprednisolone acetate—all from the most contaminated lot, 06292012@26. Most patients who developed symptoms were cared for at SJMH. A striking finding was that a disproportionate number of cases of spinal or paraspinal infection were reported from Michigan. Of the 264 cases seen in Michigan, 166 (63%) involved only spinal or paraspinal infections and an additional 46 (17%) included both a spinal or paraspinal infection and meningitis (12, 13, 15).

**MYCOLOGICAL ASPECTS**

*Exserohilum rostratum* is a dematiaceous (brown-black) fungus that is found in soil and on plants throughout the world but most frequently in tropical and subtropical climates. The cell wall contains melanin, and colonies on Sabouraud’s dextrose agar are brown-black. The conidia are large, septate, darkly pigmented structures. The organisms are primarily plant pathogens and rarely infect...
humans; only 3 species, *E. rostratum*, *E. longirostratum*, and *E. mcginnisii*, have been reported to cause disease in humans (16). Those cases that have been reported prior to this outbreak were either localized infections related to traumatic inoculation of the conidia or disseminated infection in immunosuppressed hosts (16–20). A review of the preoutbreak literature, from 1975 through 2012, found 48 cases of infection with *Exserohilum* species, of which only 29 were identified as *E. rostratum* (16). Only one patient had CNS infection as one manifestation of disseminated disease (17). Most reported infections were sinusitis, localized cutaneous lesions, or keratitis.

*In vitro* antifungal susceptibility studies for 34 *Exserohilum* isolates found that the organisms generally were susceptible to amphotericin B, itraconazole, voriconazole, and posaconazole. Echinocandin susceptibility was variable, and the organisms were resistant to fluconazole and flucytosine (21). Subsequent studies on outbreak strains confirmed these findings (22). It should be noted that the MIC90 consistently is slightly higher for voriconazole (0.2 to 2 μg/ml) than for itraconazole (0.03 to 1 μg/ml) and posaconazole (0.03 to 1 μg/ml) (21, 22).

Whole-genome sequencing of strains from patients and from unopened vials of methylprednisolone acetate from 2 of the 3 implicated lots produced at the NECC revealed almost identical genomes, with no more than 2 single nucleotide polymorphisms noted between strains (23). Randomly selected environmental strains differed greatly from the outbreak strains.

**CLINICAL ASPECTS**

By October 2013, there were 751 cases of fungal infection reported in the multistate fungal outbreak, with 64 deaths (8.5%) (2). Among the 751 identified patients who had fungal infections, 325 had spinal or paraspinal infections, 233 had meningitis, 151 had both spinal or paraspinal infections and meningitis, and 7 had strokes without documented meningitis (a lumbar puncture was not performed in these 7 patients). Additionally, there were 33 patients who had a peripheral osteoarticular infection and 2 who had both a spinal or paraspinal infection and a peripheral osteoarticular infection (2). Among 728 patients for whom data were available, the median age was 64 years (range, 15 to 97), and 432 (59%) were women. Underlying immunosuppression was present in only 60 patients (8%) (2).

**Meningitis**

Approximately 90% of patients presenting with meningitis reported a headache, and about half experienced neck pain or stiffness (5). Less common symptoms at presentation were fever, photophobia, and neurological symptoms (15). About one-quarter of patients reported back pain (5).

For the patients with meningitis, the first cerebrospinal fluid (CSF) sample showed a median white blood cell (WBC) count of 83 cells/μl (range, 6 to 15,400 cells/μl); the median glucose concentration was 53 mg/dl (range, 3 to 249 mg/dl), and the median protein level was 84 mg/dl (range, 13 to 2,830 mg/dl) (15).

The occurrence of a stroke was reported for 40 patients (5%). In 33 patients, the stroke occurred in addition to documented meningitis. In the remaining 7 patients, who did not have a lumber puncture performed, stroke was presumed to be associated with fungal infection. The type of stroke was reported for 34 patients: 24 were ischemic, 6 were hemorrhagic, and 4 were both. Almost all strokes (96%) involved the posterior circulation, and over half of the patients who suffered a stroke died (5). The CSF showed a higher WBC count, a lower glucose level, and a higher protein level for those who had a stroke than for patients who had only meningitis (15).

Of the approximately 384 patients with fungal meningitis, 151 (39%) developed concomitant localized spinal or paraspinal infection (epidural abscess, phlegmon, diskitis, vertebral osteomyelitis, or arachnoiditis) (2, 5). Arachnoiditis (characterized by nodular or linear enhancement of the nerve roots of the cauda equina on MRI) was commonly found among patients who had meningitis (Fig. 2). In a review of 63 cases of arachnoiditis from the 6 states (Michigan, Tennessee, Indiana, New Jersey, Florida, and Virginia) with the most reported cases, lumbar puncture was performed in 58 (92%); 52 of the 58 (90%) patients had CSF pleocytosis. The median WBC count in CSF was increased 10-fold among those patients who had arachnoiditis compared with those who had meningitis alone (539 versus 47 cells/μl). Most patients with arachnoiditis (78%) had both headache and back pain (15).

A multivariable logistic-regression model evaluating risk factors for CNS disease (meningitis, stroke, arachnoiditis, and intradural abscess) in comparison with non-CNS disease (spinal or paraspinal infection) in patients in Michigan showed that the presence of hypertension (odds ratio, 4.28; 95% confidence interval, 1.47 to 12.48) and receipt of a translaminar epidural injection (odds ratio, 3.83; 95% confidence interval, 1.60 to 9.20) were independently associated with CNS disease (15). Earlier work from Tennessee showed that patients who received an injection of methylprednisolone by a
translaminar approach had a higher rate of developing infection than those who received an injection by the transforaminal route; most of the patients in that series had meningitis and not spinal or paraspinal infection (9).

Spinal and Paraspinal Infections

As the outbreak evolved, there was a predominance of patients who manifested symptoms and signs of spinal or paraspinal infections at the injection site (Fig. 3). This phenomenon was most evident in Michigan (1, 13, 24). In a review of 153 spinal and paraspinal infections from SJMH, it was found that the median time from the last epidural or paraspinal injection to diagnosis was 52 days (range, 21 to 232 days). Within this group, the median time from the last injection to diagnosis was 56 days (range, 23 to 232 days) for the 112 patients who presented with spinal or paraspinal infection alone, compared with a median time from injection to diagnosis of 44 days (range, 21 to 75 days) for the 41 patients who had both meningitis and spinal or paraspinal infection (13).

The symptoms reported most commonly among patients with spinal or paraspinal infections were back pain (63%) and headache (36%) (5, 12, 13). However, some patients experienced little to no change in chronic back or neck pain yet were found to have spinal or paraspinal infection (24). Given the insidious onset of spinal or paraspinal infection at the injection site and the often subtle clinical findings, contrast-enhanced MRI screening was initiated at SJMH. In a cohort of 172 patients who underwent screening MRI, 36 (21%) were found to have an abnormal MRI, with findings that included epidural or paraspinal abscess or phlegmon, arachnoiditis, spinal osteomyelitis and/or diskitis, and moderate to severe epidural, paraspinal, or intradural enhancement. Thirty-five of the 36 patients with abnormal MRIs were found to have spinal or paraspinal infection, including 13 (37%) patients who had no change in back or neck pain, no lower-extremity weakness, and no evidence of radiculopathy (24). A single MRI was not always sufficient to detect infection. Some patients for whom the initial MRI showed no evidence of infection were later found to have spinal or paraspinal infection when an MRI was repeated (13).

Evolving guidance from the CDC called for clinicians to remain vigilant when following up patients who had received spinal or paraspinal injections of contaminated methylprednisolone and recommended a contrast-enhanced MRI for anyone who had new or worsening symptoms at the injection site. The CDC also added that consideration should be given to obtaining a contrast-enhanced MRI for patients with persistent pain that was similar to their baseline symptoms (25).

Surgical intervention, usually a total laminectomy or hemi-laminectomy, was often required to decompress neural elements, remove infectious material, and obtain tissue for diagnostic purposes. At SJMH, surgical intervention was performed in 116 (76%) of 153 patients with spinal or paraspinal infection. Epidural phlegmon
and abscess were the most common intraoperative findings (13).

It remains unexplained why Michigan had a disproportionate number of spinal or paraspinal infections. Only 13% of potentially contaminated vials were shipped to the state, yet over 50% of spinal and paraspinal infections were reported from Michigan (12). Possible explanations include state-specific variation in injection approach or possibly higher levels of contamination with *Exserohilum* in the vials shipped to Michigan. It is also possible that the use of MRI to screen for localized infection, regardless of symptoms, led to enhanced diagnosis.

**Peripheral Osteoarticular Infections**

Of the 13,534 patients that been potentially exposed to methylprednisolone acetate from one of the three lots, 12,068 (89%) had been exposed by epidural, spinal, or paraspinal injections and 1,648 (12%) had been exposed by injections into peripheral joints or adjacent structures. The attack rate was higher for meningitis and spinal or paraspinal infections than for peripheral osteoarticular infections (5). Patients with peripheral osteoarticular infections were exposed to contaminated methylprednisolone through injection into shoulder, hip, knee, ankle, and tendon insertion sites as well as various bursae (Fig. 3). Joint aspiration yielded a median WBC count of 515 cells/μl (range, 6 to 24,000 cells/μl) (5). The most common symptom among these patients was joint pain (84%). Surgical intervention, including incision and drainage, washout, bursectomy, or total arthroplasty, was often required to treat these infections.

**Long-Term Outcomes**

Recent data from a long-term follow-up study being conducted by the Mycoses Study Group Education and Research Consortium reveal that most patients with fungal infections associated with contaminated methylprednisolone acetate have done well following treatment (26). Of the approximately 450 patients in the long-term follow-up study, most patients received antifungal treatment for approximately 6 months; a small subset continues to require antifungal treatment. Only 8 (1%) of 751 patients have experienced a relapse (27). Among the six relapsed cases with known time from initial completion of antifungal therapy to relapse, the median time to relapse was 90 days (range, 20 to 662 days). Two additional cases have been recently identified, for a total of 753 cases to date (27).

**DIAGNOSIS**

A patient who met the case definition was confirmed as having a proven case if a fungal infection was established by culture, histopathology, or molecular assay (Table 1).
Culture
Growth of *E. rostratum* in culture was an insensitive diagnostic tool in this outbreak. An interim analysis of 268 patients who had samples sent to the CDC showed that only 96 had definite evidence of *E. rostratum*. Of the 96, only 30 had *E. rostratum* isolated in culture; 15 of these 30 also had a positive PCR. An additional 66 patients had only a positive PCR assay for *E. rostratum* (15). Very quickly, PCR became the preferred tool to establish the diagnosis of *E. rostratum* infection (22). There are no data on the overall rate of culture positivity among patients in the outbreak. The difficulty of growing fungi from the CSF in this outbreak is unexplained but is well known for several other fungal infections, such as coccidioidomycosis and histoplasmosis (28).

Polymerase Chain Reaction
Early in the outbreak investigation, the CDC developed a novel real-time PCR detection test with broad-range fungal primers, including an *Exserohilum*-specific primer (29). Among 139 patients who had both real-time PCR and culture results obtained for the same specimen, PCR was found to be more sensitive than culture for detecting fungus, 47% versus 14%.

A total of 751 clinical specimens (547 CSF samples, 120 fresh-frozen tissue samples, 27 formalin-fixed paraffin-embedded tissue samples, and 38 other body fluid samples, including synovial and epidural fluid) from probable and proven cases of fungal infection were tested at the CDC (22). *E. rostratum* DNA was detected in 90 CSF samples from 82 patients (23% of all patients from whom CSF was submitted). CSF samples from which *E. rostratum* was identified by culture or PCR had significantly more WBCs (970/μl versus 25/μl [P < 0.001]) than samples from which fungi could not be detected or isolated. All CSF samples from 136 patients initially suspected to have fungal meningitis but shown to have no WBCs in their CSF were negative by PCR testing (22).

Histopathology
Histopathology was described for 40 patients whose samples were sent to the CDC (30). The histopathological features of fatal *Exserohilum* cases included necro-suppurative to granulomatous meningitis and vasculitis with thrombi and abundant angioinvasive fungi and extensive involvement of the basilar arterial circulation of the brain. A hypothesis for pathogenesis of *E. rostratum* migration to the brain was suggested to involve fungal penetration into the CSF at the injection site, with transport through CSF to the basal cisterns and subsequent invasion of the basilar arteries, rather than migration through the vasculature.

Identifications of hyphae were similar for the Gomori methenamine silver stain and polyfungal immunohistochemistry. However, immunohistochemistry proved to be more sensitive because it labeled remnants of degraded fungi in areas of inflammation that lacked intact hyphae. Immunohistochemistry also was more sensitive than PCR for detecting *Exserohilum* in formalin-fixed paraffin-embedded tissues. The lower sensitivity of PCR may be due to few intact fungi in tissues and difficulty with breaking down fungal cell walls during the DNA extraction process (30).

CSF (1,3) beta-d-glucan
The (1,3) beta-d-glucan assay detects this cell wall constituent, which is present in many different fungi. In this outbreak, this assay performed on CSF proved to be both sensitive and specific for fungal meningitis (31–33). The largest study tested CSF specimens from 233 patients from Michigan and Tennessee. Forty-five patients had meningitis (28 proven), 53 had spinal or paraspinal infection (19 proven), and 135 did not develop disease (33). Using the manufacturer’s cutoff (≥80 pg/ml), the sensitivity and specificity were 96% and 95% for proven meningitis and 84% and 95% for probable or proven meningitis. The optimal cutoff for proven meningitis was found to be 66 pg/ml (sensitivity, 100%, and specificity, 94%); for probable or proven meningitis, it also was 66 pg/ml (sensitivity, 91%, and specificity, 92%). A second study included specimens from 41 proven cases of fungal meningitis and 66 controls; the optimal cutoff was found to be 138 pg/ml, which provided 100% sensitivity and 98% specificity for the diagnosis of fungal meningitis that was confirmed microbiologically (32). Testing samples obtained serially from a small number of patients showed that beta-d-glucan levels that decline with therapy may predict therapeutic response.

TREATMENT
Initial Treatment Regimens
Because fungal CNS infections caused by molds are uncommon, the CDC sought advice from a panel of physicians who had expertise in treating fungal infections. The initial treatment regimen that was suggested was liposomal amphotericin B, 7.5 mg/kg intravenously (i.v.) daily, combined with voriconazole, 6 mg/kg i.v. twice daily. This recommendation was based on the presumption that the pathogen was likely *A. fumigatus*,
because the index case had this organism isolated from CSF (3). When it became apparent that further cases were caused not by A. fumigatus but rather by E. rostratum, recommendations for treatment were changed (10). Treatment recommendations also were modified because many patients, especially those who were elderly, did not tolerate high doses of liposomal amphotericin B and voriconazole, and because it became apparent that antifungal therapy would have to be safe enough to be given for months.

The recommended dosage of liposomal amphotericin B was decreased to 5 to 6 mg/kg i.v. daily, and it was recommended that combination therapy with liposomal amphotericin B and voriconazole be reserved for patients who had severe or refractory disease (34). For patients with mild to moderate meningitis and localized spinal or paraspinal infections, the recommendation was to treat with voriconazole alone, starting at a dosage of 6 mg/kg twice daily (34).

The standard practice for administering voriconazole is to modify the daily dose based on the serum concentration, aiming to achieve a level between 1 μg/ml and 5 μg/ml (35, 36). For patients in this outbreak who had CNS mold infections, the aim was to achieve a serum concentration of 2 to 5 μg/ml to better ensure adequate voriconazole concentrations in the CSF (37, 38). In some patients, this led to a dose reduction from that given initially, but in many, a higher daily dose of voriconazole was required to achieve these concentrations.

For patients who had osteoarticular infections, voriconazole monotherapy was recommended using a loading dose of 6 mg/kg for two doses, followed by 4 mg/kg twice daily. These patients were less ill, and the penetration of voriconazole into the joint space is excellent. It was thought that there was no compelling reason to add amphotericin B to treat these infections. Surgical debridement was recommended when feasible (39).

Amphotericin B

The recommendation to use liposomal amphotericin B for patients in this outbreak was based on past experience with treatment of other CNS dematiaceous mold infections (14, 40). Liposomal amphotericin B was recommended because of animal data suggesting that higher CSF and brain concentrations could be achieved with this formulation than with amphotericin B lipid complex or amphotericin B deoxycholate (41). Most patients who were treated with amphotericin B as initial therapy received this agent for several days to weeks. However, some patients who failed to respond to voriconazole monotherapy or who had recalcitrant arachnoiditis were treated with liposomal amphotericin B for months. Excluding the few patients who were treated for months for severe arachnoiditis, the median time liposomal amphotericin B was given to 115 patients who had spinal or paraspinal infections at SJMH was 13 days.

Adverse effects

The adverse effects of amphotericin B are well known and occurred in most patients who were treated with this agent in the outbreak. The extent of electrolyte disturbance, specifically tubular loss of potassium and magnesium, was dramatic in some patients and required aggressive i.v. replacement therapy in the hospital to correct the deficits. Nephrotoxicity, not unexpectedly, was more severe in older adults and those with preexisting chronic kidney disease. Infusion reactions were generally not severe, but routine pretreatment with hydrocortisone, diphenhydramine, and acetaminophen was given to many patients.

Voriconazole

Voriconazole was selected over posaconazole and itraconazole for several reasons. First and foremost, there was experience in the use of voriconazole for various invasive mold infections (42, 43). Second, there were some data, later confirmed for the isolates from this outbreak, that showed in vitro activity of voriconazole against Exserohilum species (21, 22). Third, both i.v. and oral formulations were available, and oral administration on an empty stomach produced serum levels similar to those achieved by i.v. administration. Fourth, concentrations of voriconazole in CSF are approximately 50% of serum levels, and levels in both CSF and serum are above the MIC for many dematiaceous molds (21, 38). By comparison, posaconazole and itraconazole, although slightly more active in vitro against dematiaceous molds, at the time were not available in an i.v. formulation, neither achieved substantial levels in CSF, and absorption of the oral formulations was often erratic.

Adverse effects

Adverse effects associated with the use of voriconazole are well described. Most commonly these include hepatotoxicity, transient photopsia (seeing bright spots and flashing lights), visual hallucinations, and rash (44). Because this agent was used at relatively high doses for prolonged periods in patients who did not have a hematological malignancy, had not received a transplant, and had not been given immunosuppressive
drugs, adverse effects came to the fore that had been documented only rarely or had been masked by these serious underlying illnesses.

The most obvious was alopecia, which was dramatic in these patients who had no other reason to lose their hair. At SJMH, a cross-sectional survey of 152 patients who were treated with voriconazole for at least a month found that 82% had developed alopecia, mostly involving the scalp but also involving the extremities, eyebrows, and eyelashes (45). The loss of scalp hair was profound enough in 19 patients that they wore a wig or a head covering to hide the loss. The mean time to onset of alopecia was 75 days after beginning voriconazole. Alopecia was reversible, with 69% of patients reporting regrowth of hair within 3 months of stopping voriconazole. Alopecia was associated with brittle or split nails, and a few patients lost nails. Alopecia and nail changes did not appear to be related to the daily dose of voriconazole or serum concentrations of voriconazole.

Although CNS effects due to voriconazole are well known, the extent of dysfunction while on voriconazole was striking. Patients routinely complained of feeling “foggy” and being unable to concentrate on day-to-day tasks. Family members noted that patients were increasingly forgetful and at times were confused. These adverse CNS effects were not associated with high serum concentrations of voriconazole. They disappeared when voriconazole was stopped or when another azole was substituted for voriconazole. In contrast, hallucinations definitely were dose related and were seen predominantly when patients received high doses of voriconazole i.v. and had serum voriconazole levels of >5 μg/ml, as noted previously (35). Decreasing the dose or changing the route of administration of voriconazole often led to resolution of hallucinations.

Periostitis is a rarely described side effect of voriconazole (46–48). Periostitis was seen in this outbreak, most likely because voriconazole was given at high doses for a prolonged period (49). The prominent manifestation of this uncommon side effect is bone pain, and the bones most commonly involved are the ribs and wrist bones (49). Radiographic diagnosis can be made by finding abnormal uptake on a whole-body bone scan (Fig. 4).

The pathogenesis of voriconazole-associated periostitis is related to fluoride toxicity, which has been documented by elevated serum fluoride concentrations 4- to 7-fold above normal in all patients with this adverse effect (46, 48, 49). The excess fluoride molecules replace calcium molecules in bone and cause bone pain and osteomalacia. The structure of voriconazole contains 3 fluorine molecules, more than in any otherazole antifungal agent. The development of periostitis has been correlated with the daily and the cumulative dosage of voriconazole; thus, the amount of fluoride consumed, and not serum voriconazole concentrations, predicts the development of periostitis. All symptoms resolve when the dose of voriconazole is decreased or the drug is discontinued.

Voriconazole, as well as other azoles, has been known to cause rashes, chapped lips, and dry skin. However, voriconazole is unique in its propensity to cause photosensitivity rashes. The photosensitivity is severe in some patients, and with continued administration of voriconazole, actinic changes and ultimately multicentric squamous cell skin cancers can arise in sun-damaged areas (50, 51). Melanomas also have been reported for patients on long-term therapy with voriconazole (52).

Voriconazole has many drug-drug interactions because it is metabolized by 3 different cytochrome P-450 enzyme systems (44). Drugs, such as rifampin and carbamazepine, that induce cytochrome P-450 activity greatly decrease voriconazole levels. Voriconazole interferes with the metabolism of many drugs, and interactions with cyclosporine, tacrolimus, sirolimus, and
warfarin can result in toxic levels of these drugs. The coadministration of voriconazole and other agents, such as statins, benzodiazepines, and calcium channel blockers, should be avoided or done with careful attention paid to decreasing the doses of these agents. Because of its propensity to prolong the QTc interval, voriconazole must be used with caution with drugs, such as amiodarone, quetiapine, citalopram, and fluoroquinolones, that also prolong the QTc. Frequent monitoring of electrocardiograms is required when voriconazole is used concomitantly with medications that prolong the QTc interval.

**Other Azoles**

As treatment with voriconazole continued for months among patients who had meningitis and/or localized spinal or paraspinal infections, many of the side effects of voriconazole became limiting. The CNS effects were especially bothersome, and the adverse effects seen after long-term therapy, such as alopecia and periostitis, led clinicians and patients to change therapy to itraconazole or posaconazole. These two agents have activity against *E. rostratum* (21) but were not recommended initially because the levels attained in the CNS were low and absorption of the oral formulations was not reliable (34). However, for patients who had responded to initial antifungal therapy and were doing well and for those who had not meningitis but rather paraspinal or osteoarticular infections, these agents became more attractive as the side effects of voriconazole became more problematic. Most patients at SJMH who required antifungal therapy for more than 6 months had their therapy changed to itraconazole. A few had adverse effects, primarily nausea, vomiting, and abdominal discomfort, with this agent, and they were then treated with posaconazole. For both drugs, measurement of serum drug concentrations was essential for successful management. Currently, long-term follow-up data are not available regarding how many patients were changed to oral itraconazole or posaconazole and how they responded.

**CAN THIS HAPPEN AGAIN?**

This large outbreak served as a dramatic wake-up call regarding the risks of compounded drugs. This was not the first time that medications produced by a compounding center had been found to be contaminated and to cause life-threatening or sight-threatening disease. This outbreak, except for its size and the involvement of a different dematiaceous mold, was almost an exact replica of an outbreak a decade earlier (8). Earlier in 2012, two outbreaks involving one compounding center led to visual loss in 39 of 40 patients (98%). That compounding center, Franck’s Compounding Lab, sold brilliant blue G dye (used during retinal surgery) that was contaminated with *Fusarium* species and triamcinolone acetonide for intraocular injection that was contaminated with the dematiaceous mold *Bipolaris hawaiiensis* (53).

Compounded drugs are prepared for individual patients in formulations and dosages that are not available from pharmaceutical firms; this includes chemotherapeutic agents, preservative-free and dye-free preparations, medications with different flavorings for children, and other products (54). Clearly, there is an important role for compounding pharmacies in providing specific medications for specific patients.

The regulation of compounding pharmacies differs greatly from that of pharmaceutical firms in that they are not regulated by the FDA but instead are under the purview of individual state boards of pharmacy. The FDA was specifically blocked from exerting authority over compounding pharmacies by a series of legal decisions and congressional acts that occurred in the 1990s (55, 56). The FDA does have authority to enter a compounding pharmacy and inspect conditions at that firm if a problem has been identified, but the inspection can be delayed through various legal maneuvers by the company.

The basic tenet of a compounding pharmacy was ignored when the NECC did not produce drugs in response to prescriptions for individual patients but instead shipped large amounts of their product to many different states, resulting in hundreds of patients becoming infected. In this respect, they acted as if they were a pharmaceutical firm but without regulatory oversight by the FDA. When the FDA did inspect the NECC facility after the first cases were reported, multiple vials from one of the contaminated lots were found to contain particulate material, the cleanliness of the environment and the equipment did not meet expected standards, and it was noted that nonsterile products were used to prepare preservative-free drugs, such as methylprednisolone acetate.

As a result of this large outbreak that endangered many lives, Congress passed the Drug Quality and Security Act in November 2013. This law created a new class of compounding pharmacies that are able to produce medications in bulk and distribute them to many states. The law states that these compounding pharmacies will be designated as “outsourcing facilities” and will be regulated by the FDA. However, registering as an
outourcing facility is voluntary. Whether market pressure will force compounding pharmacies to enter this program if they wish to produce medications for more than single-patient use or whether it will be business as usual remains to be seen.

CONCLUSIONS

Injection of methylprednisolone acetate that had been manufactured by the New England Compounding Center and that was discovered to be contaminated with the brown-black mold, 

*Exserohilum rostratum*, caused infection in 751 patients in the fall of 2012. Of the 751 patients, 233 had meningitis, 7 had a stroke, 325 had spinal or paraspinal infection, 151 had both meningitis and spinal or paraspinal infection, and 35 had osteoarticular infection. Sixty-four patients died, mostly from meningitis or stroke. Treatment with a combination of liposomal amphotericin B and voriconazole, with or without liposomal amphotericin B, plus surgical debridement for spinal or paraspinal infection appeared to be successful for many, but not all, patients. Congress enacted legislation increasing the oversight of compounding pharmacies by the Food and Drug Administration after this outbreak in hopes of averting similar devastating events in the future.

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REFERENCES


