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Outbreak of Fungal Infections Associated with Contaminated Methylprednisolone Acetate: an Update

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Abstract In September 2012, an unprecedented outbreak of fungal infections due to preservative-free, injectable methylprednisolone acetate (MPA) was identified. *Exserohilum rostratum* was quickly identified as the predominant organism involved in disease cases. Prior to this outbreak, little was known about the pathogenesis, treatment, and prognosis of infections due to this unusual brown-black mold. Almost 2 years after the onset of this outbreak, numerous epidemiologic and basic science studies have provided some guidance in understanding the epidemiology, clinical findings, diagnosis, and treatment of patients exposed to the contaminated medication. Additionally, this outbreak has directly led to the passage of legislation supporting increased regulation in the industry of pharmaceutical compounding. Many unanswered questions, particularly surrounding the long-term prognosis and outcomes for affected patients remain. However, it is clear that a strong relationship between clinicians caring for patients and public health as well as a rapid, effective public health response was critical in preventing additional cases of disease.

Keywords Fungal meningitis · Outbreak · Methylprednisolone acetate · *Exserohilum rostratum* · Epidural injection

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Introduction

In August 2012, a previously healthy man developed presumed community-acquired bacterial meningitis. He declined despite appropriate empiric therapy and was ultimately diagnosed with persistent neutrophilic meningitis due to *Aspergillus fumigatus*. Given the diagnosis of this rare disease in a host lacking classic risk factors, a paucity of evidence for natural routes of entry into the central nervous system (CNS) and identification of a potential route of entry via a recent epidural injection the case was reported to the Tennessee Department of Health (TDH). This patient was subsequently identified as the index case for an outbreak of fungal infections related to a contaminated injectable medication [1•]. Here, we review what we have learned from the outbreak investigation including the epidemiology, clinical findings, diagnostic modalities, treatment, and short-term outcomes as well as the regulatory and legal response. Additionally, we will review what is still unknown about this outbreak and future research questions.

Epidemiology

In response to this single report of an unusual case of meningitis, TDH initiated active case surveillance. Within 48 h, additional cases of immunocompetent adults with meningitis of unknown cause in the setting of recent epidural steroid injections were identified and the Centers for Disease Control and Prevention (CDC) was notified. Preservative-free methylprednisolone acetate (MPA) from the New England Compounding Center (NECC, Framingham, MA) was identified among the list of common products utilized for all case patients. A list of facilities which had received MPA from the implicated lots dating back to May 21, 2012, the date the first lot was produced, was obtained. The

following day, the three lots of MPA associated with case exposure were voluntarily recalled (lot no. 05212012@68, lot no. 06292012@26, and lot no. 08102012@51) [2]. Shortly, thereafter, the North Carolina Department of Health reported a case to the CDC with a clinical syndrome similar to the patients reported from Tennessee, suggesting the outbreak was not limited to a single state. State and local health departments began the process of notification of all exposed patients. Case definitions can be found in Table 1 [3••].

This investigation determined that 17,675 vials of contaminated MPA were distributed to 76 facilities in 23 states leading to 13,534 potentially exposed patients. Data were collected on 386 cases as of November 26, 2012; 78 % had meningitis; 17 % had spinal/paraspinal infection; 3 % had septic arthritis; and 1 % had stroke likely due to meningitis. As the outbreak evolved, the distribution of types of cases changed dramatically. As of July 1, 2013, data were collected on 728 cases; 31 % had meningitis; 43 % had spinal or paraspinal infection; 20 % had concurrent meningitis and spinal/paraspinal infection; 4 % had septic arthritis; 1 % had stroke likely due to meningitis; and <1 % had concurrent septic arthritis and spinal/paraspinal infection [3••].

The median incubation period was 47 days (range 0–249 days); this was longest for patients with septic arthritis and shortest for patients who had stroke without documented meningitis. The overall attack rate was 5.5 cases per 100 exposed persons although this rate varied widely by state from 0.1 (Pennsylvania) to 14.9 (Tennessee) cases per 100 exposed persons. Given the 99 % notification rate, this variation is probably not due to differential case ascertainment. More likely, it is due to the degree to which vials were contaminated, the age of the vials at the time of use, and the variations in injection practices between states. The lot-specific attack rates were 6 per 1,000 mL for lot no. 05212012@68, 40/1,000 mL for lot no. 06292012@26, and 22/1,000 mL for lot no. 08102012@51. Of 519 cases for whom CDC received specimens, 173 (33 %) had laboratory evidence supportive of fungal infection, 87 (50 %) by fungal DNA detection, 33 (19 %) by sequencing of a fungal isolate, 53 (31 %) by multiple modalities. This highlights the difficulty with diagnosis of fungal infections, particularly non-endemic fungal infections. Evidence for *Exserohilum rostratum* was identified in 100 cases, *A. fumigatus* in 1 case, and other fungi of unclear significance in 10 cases. Most likely, this outbreak was due to a polymicrobial contamination of the affected lots, but it is unclear why *E. rostratum* was primarily identified [3••].

As the outbreak evolved, the proportion of cases of disease due to meningitis decreased and localized spinal/paraspinal infections increased. This trend was most noticeable in cases from Michigan; 167 of 320 (52 %) were localized compared to 320 of 741 (43 %) nationally [4, 5•]. The Michigan Department of Community Health and CDC conducted a study to determine if there were any epidemiologic of clinical factors which contributed to this finding, though none were found [4]. It is unclear what led to a different distribution of case types in Michigan although it is possible that the primary lot involved or the preferred injection technique (reportedly transforaminal) played a role. Additionally, it is possible that an MRI screening protocol, which will be described later in this review, may have led to an increased ascertainment of spinal/paraspinal disease in Michigan.

As of October 23, 2013, the CDC in conjunction with state and local health departments had identified 751 cases and 64 deaths in 20 states. Michigan had the highest number of cases with 264, followed by Tennessee with 153, and Indiana with 93. There were 233 persons with meningitis only, 151 persons with meningitis and spinal/paraspinal infection, 7 persons with stoke and no spinal fluid sampling, 325 persons with spinal/paraspinal infection only, 33 with peripheral joint infection only, and 2 with spinal/paraspinal infection and peripheral joint infection.

Table 1 Case definitions

Case definition[a]	
Meningitis	Clinical meningitis of unknown etiology following epidural or paraspinal infection[b] with at least one of the following: headache, meningismus, or photophobia with the presence of CSF pleocytocsis (>5 WBCs adjusted for RBCs)
Stroke	Posterior circulation stroke without a cardioembolic source and without documentation of normal CSF analysis following epidural or paraspinal injection[b]
Localized spinal or paraspinal infections	Osteomyelitis, abscess, or soft tissue infection near the site of infection following an epidural or paraspinal injection[b]
Joint infections	Osteomyelitis or worsening inflammatory arthritis of unknown etiology following joint injection

CSF cerebrospinal fluid, *WBC* white blood cell count, *RBC* red blood cell count

[a] A probable case was defined as a person who had received preservative-free methylprednisolone acetate injection after May 21, 2012, that definitely or likely came from one of the three implicated lots produced by NECC and subsequently developed disease. A confirmed case was defined as a probable case with evidence for fungal infection by culture, histopathology, or molecular assays

[b] Paraspinal injections could include spinal facet joint injection, sacroiliac joint injection, or spinal or paraspinal nerve root/ganglion block

Clinical Findings

A study utilizing nationwide data including cases reported to CDC before November 19, 2012, from the six states with the highest number of cases (Florida, Indiana, Michigan, New Jersey, Tennessee, and Virginia) reported on clinical findings from the outbreak. Of 328 cases, 265 (81 %) had CNS infection including 250 (94 %) cases of meningitis, 63 (24 %) cases of arachnoiditis, 35 cases of stroke (13 %), and 3 cases of intradural abscess (1 %). Of 30 patients with stroke and localized findings on imaging, 23 (77 %) involved the cerebellum or brainstem, 16 (53 %) basal ganglia, and 1 (3 %) cerebral cortex. There were 26 (8 %) deaths; 22 (85 %) had stroke. Most deaths occurred early during the outbreak and nine (3 %) died prior to receiving antifungal therapy. Among patients with meningitis, older age, presence of fever, altered mental status, and an elevated CSF WBC were associated with death or stroke. There were 63 (19 %) cases of non-CNS infection only; factors associated with CNS disease compared to non-CNS disease included an injection in a state other than Michigan, a cumulative dose of MPA of at least 80 mg, a translaminar injection, and diabetes. Factors associated with non-CNS disease included receipt of an injection from lot 06292012@26, a nonepidural injection, and a transforaminal approach [6•].

Laboratory Diagnosis

The confirmed case definition was based on evidence for fungal infection by culture, histopathology, or molecular assays. The development of sensitive and rapid assays were critical in response to this outbreak.

Polymerase Chain Reaction Testing

The CDC developed a qualitative polymerase chain reaction (PCR) assay for fungal DNA detection. Among 469 case patients, 799 samples were analyzed (547 CSF samples, 67 fungal isolates, 120 fresh-frozen tissue samples, 27 formalin fixed paraffin embedded (FFPE) tissue samples, and 38 other body fluid samples including synovial fluid and epidural fluid). *E. rostratum* DNA was detected in 191 samples from 150 patients (32 % of all case patients). CSF samples from which *E. rostratum* was identified by culture or PCR had a more significant pleocytosis (970 WBCs vs. 25 WBCs, $p<0.001$). All 136 samples obtained from patients as part of this investigation, but later found not to be affected by the outbreak, were all negative [7•].

The CDC also developed an *E. rostratum*-specific PCR assay. Analysis was performed on 627 samples from 413 patients with disease, 506 CSF samples, 18 synovial fluid samples, 7 abscess aspirates, and 96 tissue samples. Of these, 124 (20 %) samples from 115 (28 %) patients were positive. The *E. rostratum*-specific primers were able to confirm infection among 25 patients with disease and negative pan-fungal PCR results [8].

Although the index case was found to be infected with *A. fumigatus*, the predominant organism in this outbreak was later identified to be. *E. rostratum*. Additional fungi have been detected from clinical samples and unopened vials of MPA; however, these are of unclear clinical significance. It is known that some species of fungi possess receptors for human sterols which lead to accelerated growth and metabolism and in vitro studies have suggested that exposure to methylprednisolone may enhance the virulence of *E. rostratum* [9, 10]. Additional virulence factors by which one species of fungi may outcompete another include thermophilia and the presence of melanin. Alternatively, host factors including polymorphisms in immune response may be playing a role [11].

CSF 1,3 Beta-D-Glucan

A small case series, including specimens from five patients infected during this outbreak suggested the possible utility of this assay in the diagnosis and monitoring of response to therapy [12]. A second, larger study included specimens from 41 confirmed cases of fungal meningitis and 66 controls. This study identified an optimal cutoff of 138 picograms (pg) per milliliter (mL) which provided 100 % sensitivity and 98 % specificity for the diagnosis of iatrogenic fungal meningitis confirmed microbiologically [13]. The largest study of CSF 1,3 beta-D-glucan (BDG) utilizing specimens from this outbreak included 233 patients, 45 with meningitis, 53 with spinal/paraspinal infection, and 135 exposed patients who never developed disease. Using the manufacturer's cutoff (BDG ≥80 pg/mL), the sensitivity and specificity were 96 and 95 % for confirmed meningitis and 84 and 95 % for probable meningitis. The optimal cutoff value for confirmed meningitis of 66 pg/mL had a sensitivity of 100 % and specificity of 94 % [14•]. The findings from these studies show that CSF BDG is highly sensitive and specific for the diagnosis of fungal meningitis associated with contaminated MPA.

Histopathology Analysis

A case series of 40 patients was conducted to evaluate the pathologic findings and correlate these findings with clinical and laboratory data in order to gain an understanding of the pathogenesis of these infections. Among meningitis cases, the leptomeninges covering the base of the brain and the associated large arteries were most frequently involved. This supports the hypothesis that the infection spread to the brain from the lumbar subarachnoid space with pooling in the basal cisterns and invasion of adjacent vascular structures.

Moreover, fungi were more often detected in the outer walls of vessels compared to the lumen suggesting an invasion from outside the vessels. Tissue samples from patients with localized infection only (compared to tissue samples from patients with meningitis) more commonly had a lymphocytic versus necrosuppurative infiltrate, lower fungal burden, and longer time from injection to tissue collection. It is unclear if this reflects different host immune responses or differences in fungal burden between the two groups. For seven patients with fatal meningitis, tissues outside the CNS were evaluated and none revealed evidence for inflammation, vasculitis, or fungal infection which supports the lack of disseminated infection in this outbreak.

Of interest, conidia were detected in some tissue samples suggesting that this organism may undergo sporulation in vivo. An alternative hypothesis is that the conidia were present in the contaminated MPA and were injected directly into the tissue. This distinction is important because the presence of conidia in the tissue which may later sporulate may lead to recurrence of infection and have implications for treatment duration.

Polyfungal immunohistochemical staining (IHC) was detected in all 40 cases. Fungi were detected in 17 (43 %) with hematoxylin and eosin (H&E) and 38 (95 %) with Grocott's methenamine silver (GMS) staining. In general, IHC staining was more widespread and detected in tissue samples which lacked intact fungal hyphae, potentially detecting degraded fungal organisms. Fungal PCR was performed on 32 of 40 cases; fungal DNA was detected in 16 (50 %); and all 16 were also positive by polyfungal IHC. It is possible that IHC was positive more often than PCR due to difficulty with DNA extraction. In three cases PCR was performed on both fresh and paraffin-embedded tissues; all three fresh tissue specimens were negative, but only one paraffin-embedded tissue was negative. This suggests that fresh-samples may have been improperly handled during collection and shipment [15].

Radiographic Diagnosis

Magnetic resonance imaging (MRI) with contrast has been recommended among patients with localized symptoms at the injection site as well as those diagnosed with meningitis. Radiographic findings from a large review of 153 cases with spinal or paraspinal infection showed a variety of MRI findings including epidural enhancement (61.2 %), paraspinal enchancement (61.2 %), epidural phlegmon (34.2 %), arachnoiditis (26.3 %), intraspinal enhancement (25.7 %), paraspinal phlegmon (24.3 %), epidural abscess (Fig. 1) (16.4 %), and paraspinal abscess (9.9 %) [5•].

Additionally, it has been recommended to consider imaging for patients with persistent baseline symptoms based on an observation that many patients subsequently developed infection. Malani et al. developed an MRI screening protocol for asymptomatic patients evaluated at St. Joseph Mercy Hospital (Ann Arbor, MI). Of 218, 172 had a screening MRI performed; 34 (20 %) were abnormal; 30 (17 %) were equivocal; and 108 (63 %) were normal. Of those with an equivocal result, 25 underwent repeat imaging; 2 were abnormal; 13 remained equivocal; and 10 were normal. Of the 36 patients with abnormal MRI results, 13 (36 %) did not have lower extremity weakness, radiculopathy, or any change in back or neck pain. The results of this study supported evaluation of patients with persistent baseline symptoms using MRI, particularly patients who received an injection from the "hot" lot 06292012@26 [16•].

Treatment

Medical Treatment

Treatment guidelines were developed rapidly in response to the outbreak by the CDC in collaboration with national experts in mycology as well as clinicians caring for patients affected by the outbreak. The lack of an animal model of CNS mold infection and measurable, validated outcomes made the development of these guidelines difficult. There were many factors considered, including the predominant pathogen identified, site of infection, published literature on the treatment of fungal infection, pharmacokinetics of antifungal therapy, and the clinical course/complications of the disease.

Fifty-three isolates of *E. rostratum* have been tested by the CDC for their in vitro susceptibility to antifungal agents (Table 2). Susceptibility to amphotericin B was determined using the Epsilometer (Etest) according to manufacturer's instructions and to several azole agents by broth microdilution according to Clinical and Laboratory Standards Institute (CLSI)-defined methods. Echinocandins were not evaluated as these agents are known not to have activity against molds. Breakpoints for susceptibility have not been identified by the CLSI [6•].

Voriconazole was chosen over the other azoles given the vast experience in treating mold infections with this agent, increased CNS penetration, availability in oral and intravenous formulations, excellent bioavailability, predictable drug levels, and toxicity profile in addition to the in vitro susceptibility data.

Voriconazole 6 mg/kg every 12 h was recommended to obtain adequate drug levels in the CNS; lower doses of 4 mg/kg were used for infections not involving the CNS or spine, such as peripheral joint infections. This dose was adjusted based on serum steady-state levels with goal trough levels of 2–5 mcg/mL. Trough levels were monitored weekly for the first 4–6 weeks of therapy. In a small study including 25 patients with meningitis from Virginia, serum steady-state

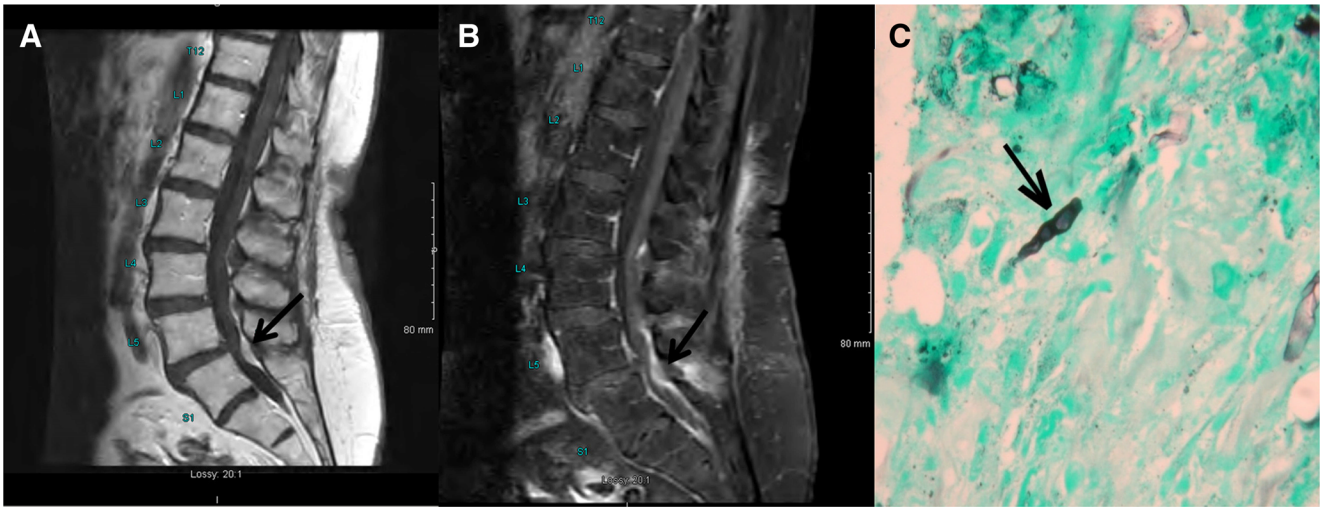

Fig. 1 Sagittal T1 post contrast (**a**) and sagittal T1 fat-saturated post contrast (**b**) images of the lumbar spine show slender epidural enhancing tissue (*arrows*) at the L5-S1 level consistent with an epidural abscess. Tissue obtained during surgery showed fungal hyphae using Grocott's methenamine silver (GMS) staining and culture was positive for *Exserohilum* species (**c**)

voriconazole trough levels (Quest Diagnostics, Madison NJ) measured on day 5 of intravenous therapy revealed an average of 5.7 μg/mL (range <0.1 to 10.3 μg/mL). Random CSF voriconazole levels were measured in five patients with an average of 3.7 μg/mL [17•]. Overall, patients achieved goal serum levels at recommended doses, but some patients required dose adjustments to reach the goal—highlighting the importance of therapeutic drug monitoring.

Liposomal amphotericin B (5–6 mg/kg) was considered as adjunctive therapy among patients with severe disease, patients who did not improve as expected, or patients who declined while on voriconazole monotherapy. Additionally, it was considered as alternative therapy among patients intolerant to voriconazole. AmBisome was preferred over other formulations due to improved penetration into the CNS.

If patients were intolerant to both voriconazole and liposomal amphotericin B, treatment with posaconazole or itraconazole was most often initiated. However, these agents lack data on efficacy in mold infection and have less favorable bioavailability and CNS penetration.

At least 3 months of therapy was recommended for patients with meningitis alone. Extension of therapy to at least 6 to 12 months was recommended for patients with underlying immune suppression, those with more severe disease, and those with persistently abnormal CSF findings.

Table 2 Antifungal susceptibility testing for 53 isolates of *Exserohilum rostratum*

Drug	Range (μg/mL)	MIC 50 (μg/mL)
Voriconazole	1–4	1
Fluconazole	16–128	64
Itraconazole	0.25–4	0.5
Posaconazole	0.25–1	0.5
Amphotericin B	0.03–2	0.25

MIC minimum inhibitory concentration

Medical Treatment Toxicity

Voriconazole has well-described toxicities including hepatotoxicity, rash, CNS toxicity including visual disturbances and hallucinations, prolonged QT interval in addition to significant drug-drug interactions. In the study of clinical findings conducted by the CDC, 55 (19 %) patients developed elevated liver function tests, 77 (26 %) developed visual disturbances, and 49 (16 %) developed hallucinations [6•].

As a result of treatment of patients during this outbreak, a previously described rare side effect of voriconazole, alopecia, and a new side effect of nail changes were better characterized. This cross-sectional survey included 152 patients who had received voriconazole for at least 1 month cared for at St. Joseph Mercy Hospital (Ann Arbor, MI). Alopecia was reported by 125 (82 %) patients; sites included the scalp (96 %), extremities (42 %), eyebrows (38 %), and eyelashes (38 %). The mean time to onset of alopecia was 75 days. Of those who had been off voriconazole therapy for at least 3 months prior to the time of the survey, 82 % reported that the hair loss had stopped and 69 % reported regrowth. These findings were similar to those reported among patients who switched from voriconazole to itraconazole or posaconazole suggesting that alopecia is not a class effect of azoles. Prevalence of alopecia was not associated with the mean daily dose of voriconazole or supratherapeutic serum drug levels. Nail changes were reported by 106 (70 %) patients; changes described included brittle nails (20 %), split nails (19 %), thin nails (15 %), and nail loss (9 %). Among patients reporting alopecia, 98 (78 %) also reported nail changes [18•].

Periostitis, related to the tri-fluorinated molecular structure of voriconazole, was seen in over 10 % of patients cared for at St. Joseph Mercy Hospital (Ann Arbor, MI). Twenty-eight patients received a bone scan and plasma fluoride level at the same time or within a month; 21 were found to have periostitis. Periostitis was present throughout the appendicular and axial skeleton with the most common locations being the ulna and ribs. Blood fluoride, serum alkaline phosphatase, daily voriconazole dose, and cumulative voriconazole dose were associated with periostitis. Discontinuation or dose reduction of voriconazole resulted in improvement of pain in 17 of 19 (89 %) patients [19•].

Liposomal amphotericin B is known to produce electrolyte abnormalities, decreased renal function, and infusion-related rigors. In the study on clinical findings conducted by the CDC, acute kidney injury occurred in 46 (26 %) patients on amphotericin B and three of these patients required dialysis. The median time to this toxicity was 5 days (IQR 4–8 days) [6•].

Surgical Treatment

Decisions regarding surgical therapy, including debridement and drainage, for soft tissue infection, abscess, osteomyelitis, and septic arthritis, were made by the patient in consultation with their infectious disease physicians and surgeons.

In a study by Moudgal et al., 116 of 153 (76 %) patients with spinal/paraspinal infection underwent a surgical procedure. A total of 101 (87 %) patients had positive intraoperative findings including epidural phlegmon (60.3 %), epidural abscess (25.9 %), epidural fluid (1.7 %), intradural nerve root clumping and purulence (5.2 %), discitis (2.6 %), and paraspinal purulence (12.9 %). Of those who underwent surgery, 69 (59.5 %) had confirmation of fungal infection; this includes 6 of the 15 patients without significant intraoperative findings. These results suggest that surgical therapy may lead to more cases of confirmed fungal infection. However, it is unclear if surgery leads to improved quality of life, decreased duration of antifungal therapy, or decreased risk for disease recurrence [5•].

Prognosis and Long-Term Outcomes

At this point, little is known about the prognosis and long-term outcomes for these patients. One reported relapse involved an 80-year-old man with fungal meningitis treated with voriconazole with resolution of symptoms and CSF pleocytosis. After 4.5 months of therapy, voriconazole was discontinued; however, his symptoms recurred 3 weeks later. CSF revealed recurrent pleocytosis and PCR was newly positive for *E. rostratum*. MRI was negative for localized disease [20].

On the other hand, a report has been published describing resolution of fungal meningitis and an associated mycotic aneurysm. In total, the patient received 32 weeks of antifungal treatment, 18 weeks of combination therapy, 8 weeks of voriconazole monotherapy, and 6 weeks of liposomal amphotericin B monotherapy. Imaging at the end of therapy revealed resolution of the aneurysm, and there was no recurrence on imaging 3 months after discontinuation of therapy [21]. Furthermore, of 153 patients described in the recent review of spinal and paraspinal infections from St. Joseph Mercy Hospital (Ann Arbor, MI), only 20 remained on antifungal therapy as of January 31, 2014, and no cases of relapse of fungal infection were reported [5•].

A large study by the Mycoses Study Group (MSG) including 359 eligible patients has recently reported 6-month outcomes for 242 patients. A cure or partial response to antifungal therapy was achieved among 76.1 %; this proportion differed by disease site with 83.3 % of patients with only fungal meningitis, 74.6 % of patients with only epidural abscess, and 65.2 % with both sites of disease achieving a cure or partial response [22••].

The appropriate duration of therapy as well as the incidence of and risk factors for recurrent disease are currently unknown. It is suggested that the severity of disease, treatment response, and side effects of therapy should be taken into account in deciding when to discontinue therapy. Additionally, patients should be followed closely after therapy discontinuation and health care providers must remain vigilant for signs and symptoms of relapse.

Legal and Regulatory Implications

Compounded medications are medications that are prepared in response to an individual patient's prescription in a dosage or formulation not commercially available. Compounding pharmacies are not regulated by The Food and Drug Administration (FDA) and instead by State boards of pharmacy.

In November, 2012, the US Senate Committee on Health, Education, Labor, and Pensions held a hearing to investigate the role of pharmacy compounding in this outbreak. The NECC was invited, but declined to participate. In May, 2013, another hearing on proposed legislation for pharmacy compounding was held. In September, 2013, HR 3204-The Drug Quality and Security Act was introduced to the House of Representatives and was signed into law in November 2013. This legislation created a new class of large compounding pharmacy, termed an "outsourcing facility," which would be allowed to provide compounded medications in bulk to hospitals and would be regulated by the FDA. This legislation also created a national set of standards that would allow medications to be tracked through distribution. In response to this outbreak, many hospital pharmacies have re-evaluated their in-house and outsourced policies for compounding of medications.

Conclusions

This is the largest outbreak of fungal infections associated with compounded medications in history. It has highlighted the critical importance of a strong relationship between public health and health care providers in the community as well as a well-organized and effective public health response.

While this outbreak has provided an opportunity to study these rare fungal infections, we still have much to learn. Why didn't all exposed persons develop disease? Why did those who develop disease have varying manifestations and symptoms? What is the effect of future steroid injections on the risk of fungal infection among those who did not initially develop disease or on the risk of recurrence among those previously treated? What is the most effective and safest treatment regimen, dosage, or duration? Will patients treated surgically have more rapid cure, decreased risk of recurrence, or improved long-term outcomes?

Finally and perhaps most importantly, it is unclear if patients with disease will have long-term functional sequelae. How long after treatment should patients be followed and at what interval should they be evaluated? Several studies, including the study by the Mycoses Study Group [22••], which may help solve these unanswered questions are currently underway. Although the full duration of the risk period is not known, it is reassuring that no new cases of disease have been reported since October 23, 2013. Recent legislation regarding drug compounding is hopefully the first step in eliminating the risk of recurrent outbreaks associated with compounded medications in the future.

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Compliance with Ethics Guidelines

Conflict of Interest April Pettit has no conflicts of interest. Anurag Malani received a grant from the University of Alabama, speakers' payment from Cubist pharmaceuticals in 2012, and has stock in Pfizer pharmaceuticals.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the author.

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