

EDITORIALS



Compounding Errors

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Small pharmacies that produce and package (or repack) specific drugs for individual patients are an important part of the medical landscape. These so-called compounding pharmacies formulate therapeutic and diagnostic products for physicians in practice and those engaged in research. They make individualized chemotherapeutic agents, noncommercial formulations (e.g., a liquid rather than a tablet) and doses, preservative-free and dye-free products, flavored products, combination products, products without specific allergens, diagnostic agents, and other customized products. These pharmacies are essential if our health care system is to serve populations with particular needs.

Recently, the valuable role that such pharmacies fill has been eclipsed by the havoc that can be wreaked when the materials they produce are contaminated by infectious microbes. We are in the midst of an epidemic of meningitis and deadly strokes attributable to the mold *Exserohilum rostratum*. This mold was allegedly introduced into patients during epidural injections with contaminated methylprednisolone acetate to treat back pain, a practice for which there are no compelling data.¹⁻⁴ This sort of outbreak is not new: fungal meningitis associated with *Exophiala dermatitidis* was associated a decade ago with epidural injections of methylprednisolone acetate.⁵

We believe that the best way to balance the need for “designer therapeutics” from these pharmacies with the need for product safety is to give the Food and Drug Administration (FDA) broader powers to monitor and control the agents produced by such pharmacies and any adverse events that are associated with them. The current system, in which regulation is almost entirely

state-based, is clearly inadequate to protect the public health. Although Massachusetts, the home of the implicated New England Compounding Center (NECC), has instituted stronger penalties in the wake of the current fungal meningitis outbreak, and other states have increased their oversight, states lack the resources to supervise what has become a national industry with interstate activity.

FDA regulation of compounding pharmacies is not a new idea.⁶ A compounding law was enacted in 1997 but was then in part overturned by the U.S. Supreme Court in 2002 in *Thompson v. Western States Medical Center*. The Court decision, which was based on arguments protecting commercial free speech, left the unchallenged provisions of the law in limbo. This led the FDA to issue new, and weaker, guidance that was apparently largely ignored by the NECC, the pharmacy most closely linked to the current cases of meningitis.

These events make it clear that we need new legislation that gives the FDA stronger and better control of compounding pharmacies. Representative Ed Markey (D-MA) has introduced such legislation: the Verifying Authority and Legality in Drug (VALID) Compounding Act.⁷ The bill, if passed, would give the FDA broader powers to regulate compounding pharmacies while at the same time giving the agency the latitude to ensure that such pharmacies can continue to produce needed medical products. It would preserve state regulatory authority over traditional compounding pharmacies that make customized drugs for individual patients but would place pharmacies that operate as drug manufacturers under FDA regulation. This bill is a generally ap-

appropriate step forward, and we believe it should receive strong bipartisan support.

Compounding pharmacies are businesses that produce important products for patients. These patients, however, do not have the means to check the clinical indications for the use of the products, to ensure the accuracy of the compounding, and to verify the sterility of the delivered products. The FDA has the technical expertise and drug-evaluation experience to do so and should have this authority, and there needs to be a mechanism to ensure that the funding is in place to exercise it effectively.

Regulators need a strong mandate to protect the public health. Too many patients have suffered and died as a result of compounding errors, which should be made a thing of the past.

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Compelling Evidence for Coronary-Bypass Surgery in Patients with Diabetes

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Seventeen years ago, the National Heart, Lung, and Blood Institute issued a clinical alert¹ that coronary-artery bypass grafting (CABG) had better rates of survival than percutaneous coronary intervention (PCI) in patients with diabetes. The alert was based on the results of the Bypass Angioplasty Revascularization Investigation (BARI) trial,² in which patients with multivessel coronary artery disease were randomly assigned to undergo either CABG or PCI.

This recommendation has been controversial ever since, largely because subsequent trials comparing CABG and PCI have enrolled only small numbers of patients with diabetes. A pooled analysis of 10 randomized trials involving 1233 patients with diabetes confirmed that such patients had a particular survival advantage after CABG, as compared with PCI.³ But this evidence was discounted because drug-eluting stents were not used in PCI procedures in the earlier trials, and more recent trials in which drug-eluting stents were used^{4,5} enrolled relatively few patients with diabetes. Settling this controversy would require a trial with a large number of patients with both diabetes and multivessel coronary ar-

tery disease in whom CABG or PCI would be performed with the use of contemporary methods.

Farkouh et al.⁶ now report in the *Journal* the results of the definitive Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM) trial, in which 1900 patients with diabetes (about as many patients with diabetes as in all previous trials combined) were randomly assigned to undergo either CABG or PCI with drug-eluting stents.

As a cardiologist who does not perform either procedure, I find that the FREEDOM trial provides compelling evidence of the comparative effectiveness of CABG versus PCI in patients with diabetes and multivessel coronary artery disease. After 5 years of follow-up, the 947 patients assigned to undergo CABG had significantly lower mortality (10.9% vs. 16.3%) and fewer myocardial infarctions (6.0% vs. 13.9%) than the 953 patients assigned to undergo PCI. However, patients in the CABG group had significantly more strokes (5.2% vs. 2.4%), mostly because of strokes that occurred within 30 days after revascularization. In the CABG group, the primary

REVIEW ARTICLE

CURRENT CONCEPTS

Fungal Infections Associated with Contaminated Methylprednisolone Injections — Preliminary Report

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WE ARE IN THE MIDST OF AN UNPRECEDENTED OUTBREAK OF FUNGAL infections associated with epidural injection of methylprednisolone that was contaminated with environmental molds. The index case, which prompted clinicians at Vanderbilt to call the Tennessee Department of Health and which brought this event to national attention, is now reported by Pettit et al. in the *Journal*.¹

The persistence and progression of neutrophilic meningitis of unknown cause was the trigger for obtaining the history of a recent epidural injection of methylprednisolone. Then events fell into place. After the alarm was sounded about this association, other physicians throughout the country realized that they too had struggled to find a cause for similar cases in recent weeks. What is intriguing about this case report is that the mold causing meningitis was reported to be *Aspergillus fumigatus*, an organism that has not been detected in any of the subsequent 200-plus cases. The major culprit appears to be *Exserohilum rostratum*, a plant pathogen that rarely causes human disease. This mold has been cultured or identified by means of a polymerase-chain-reaction (PCR) assay from cerebrospinal fluid in at least 25 patients and has been detected in at least one unopened vial from the implicated lot of methylprednisolone.

Shortly after the Tennessee Department of Health was notified on September 18, the implicated lots were quickly identified, all centers that had received the implicated lots were alerted, and patients who had received injections (either epidural or intraarticular) from these lots were notified of the potential for fungal infection. It is estimated that over 14,000 patients received injections from these implicated lots. The compounding pharmacy producing the drug was closed, and all products (not just the implicated lots) were recalled. The Centers for Disease Control and Prevention provided timely information regarding appropriate diagnostic testing and treatment, and the agency is providing daily updates on its website (www.cdc.gov). As the outbreak has evolved, numerous questions have been raised by physicians, patients who received injections from the implicated lots, and the public. We attempt to answer some of those questions here.

WHAT DO WE KNOW ABOUT THE IDENTIFIED MOLD?

E. rostratum is a dematiaceous, or black, mold containing melanin in its cell wall. It is widely found in the environment, on plant debris, in soil, and in water.^{2,3} Human infection is uncommon and is usually restricted to allergic sinusitis, keratitis, and localized soft-tissue infection. In rare cases, invasive infection occurs in immunocompromised patients.

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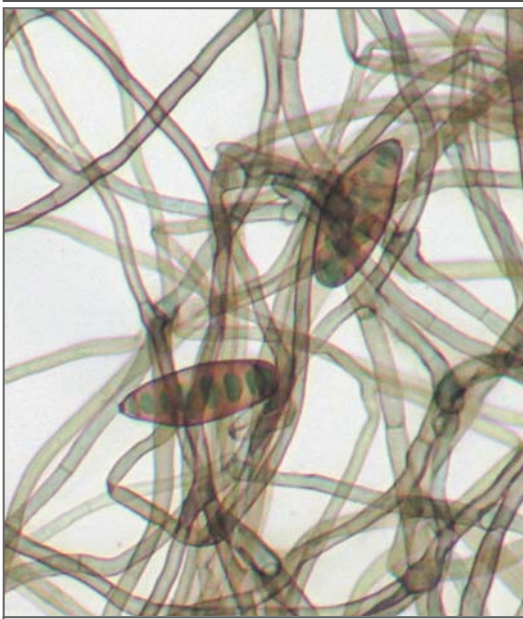


Figure 1. Photomicrograph of *Exserohilum rostratum* Isolate from Cerebrospinal Fluid Grown for 48 Hours on Potato Flakes Agar.

Courtesy of Annette W. Fothergill, Fungus Testing Laboratory, University of Texas Health Science Center at San Antonio.

The conidia of this organism have distinctive morphologic features (Fig. 1) that allow its identification. The organism grows readily on the usual fungal culture mediums, but sporulation to identify the conidia typically requires the use of a plant-based medium, such as potato dextrose agar. Even though the mold grows readily in the laboratory, cultures from cerebrospinal fluid may be negative, as has been true for other mold infections of the central nervous system (CNS). Molecular identification can be used to establish a diagnosis, and PCR assays on cerebrospinal fluid have been useful in the current outbreak. It is important to note that the performance characteristics of this specific PCR assay have not been well characterized.

In tissues, *E. rostratum*, like many other dematiaceous fungi, appears as irregular, beaded hyphae, as compared with the broad, rarely septate, ribbonlike hyphae seen in the order Mucorales and with the narrow, septate, acutely branching hyaline hyphae of aspergillus species. Special stains for cell-wall melanin (e.g., Masson-Fontana stain) are useful to confirm the presence of a dark-walled mold.

Several outbreaks in the past decade have

been associated with contamination with black molds. *Exophiala* species were associated with a disturbingly similar outbreak of infections including meningitis that were traced back to a contaminated lot of glucocorticoid injections from a U.S. compounding pharmacy,⁴ and *Exophiala jeanselmei* was identified in an outbreak associated with contaminated water.^{5,6}

WHAT IS THE SUSCEPTIBILITY TO ANTIFUNGAL AGENTS?

Generally, *exserohilum* species are susceptible to available antifungal agents, but for some strains, the minimal inhibitory concentration (MIC) for the usually recommended agents, including voriconazole, is increased. Thus, susceptibility testing is advised, although there are no clinical data that strongly support that recommendation. Recent series indicate susceptibility to voriconazole for the majority of isolates, with the MIC ranging from 0.06 to 4 μg per milliliter; the MIC for amphotericin B ranges from 0.03 to 1 μg per milliliter.² The MIC is 0.015 to 8 μg per milliliter for posaconazole, 0.015 to 16 μg per milliliter for itraconazole, and 2 to 64 μg per milliliter for fluconazole. Only a limited number of isolates from this outbreak have been tested to date; the MIC for voriconazole has ranged from 0.5 to 2 μg per milliliter.

CLINICAL DIAGNOSTIC ISSUES

HOW HAS THIS OUTBREAK EVOLVED?

Early in the outbreak, patients had symptoms of meningitis for weeks before the diagnosis was made. Neutrophilia in cerebrospinal fluid was extreme in many cases, and complications, including basilar-artery stroke, as in the case reported in the *Journal*,¹ were common. After notifying patients at risk and performing lumbar punctures as soon as even mild headache occurred, clinicians began to see patients who had milder clinical disease. Headache is a prominent symptom and may be accompanied by neck stiffness, photophobia, and weakness. Whether some patients with mild symptoms may have worsening symptoms and complications in spite of antifungal therapy is unknown, but the hope is that early diagnosis and treatment will avert severe complications, such as strokes.

The incubation period for most patients has been 1 to 4 weeks after injection, but at least one patient presented at 6 weeks. It is not clear

whether some of the less common manifestations, such as epidural abscess and osteoarticular infection, fall within this same time period. There have been reports of a few patients with increasing back pain as the only symptom of an epidural abscess, with or without diskitis or vertebral osteomyelitis. We know little about the progression of osteoarticular infection, since only a few cases of septic arthritis have been reported. Pain and swelling are likely to be the major symptoms. It appears that either the risk of development of infection is less or the symptoms are delayed and more subtle in comparison with a CNS infection. Most important, patients who have received epidural or intraarticular injections and their physicians should remain vigilant for symptoms beyond the typical period that has been reported to date.

WHEN SHOULD SPINAL TAP, JOINT ASPIRATION, OR IMAGING STUDIES BE PERFORMED?

Patients should be alerted to tell their physician about any new-onset headache, neck stiffness, photophobia, fever, or strokelike symptoms. Because the symptoms of CNS fungal infection are often more subtle than those usually seen with bacterial meningitis, there should be a very low threshold for performing lumbar puncture if any symptom suggesting possible CNS infection occurs. Even with headache as the only symptom, values for cerebrospinal fluid have been abnormal in some patients. The criterion for initiating therapy should be a white-cell count above that which is considered normal (i.e., >5 cells per cubic millimeter). White-cell counts in patients in this outbreak of fungal meningitis have ranged from 13 cells to 15,000 cells per cubic millimeter almost always with a neutrophil predominance. There are not yet clear data correlating the clinical manifestations with the white-cell count in cerebrospinal fluid. Glucose and protein levels are not suggested as criteria for initiating therapy. Most important, empirical antifungal treatment should be given as soon as pleocytosis is detected in the cerebrospinal fluid, without waiting for results of diagnostic studies.

Increasing back pain or pain that differs in quality from the chronic back pain for which a patient received an epidural injection may be the only symptom of an epidural abscess, diskitis, or vertebral osteomyelitis. Magnetic resonance imaging of the spine should be performed in such patients, since early symptoms of these compli-

cations can be subtle, and localized infection may occur without meningitis. Any collection of epidural fluid should be aspirated, if possible, for culture and PCR studies.

Patients who received an intraarticular injection should be alert for new pain, especially if it differs in quality from their original pain, or if they have erythema or swelling of a joint. In such cases, aspiration of synovial fluid should be performed immediately for diagnostic studies. There is increased variability in what is considered a normal number of white cells in synovial fluid, and no firm guidance has been given for the number of cells required to initiate therapy. Clinical judgment must be used, with the symptoms and signs of joint disease before the injection taken into account. If there is any question of whether infection could be present, arthroscopy to obtain synovial fluid and possibly synovial biopsy for culture and PCR studies should be performed as soon as possible.

Patients who have no symptoms should not undergo lumbar puncture or joint aspiration. However, they should be told to call immediately if symptoms occur.

HOW SHOULD THE INFECTION BE TREATED?

Recommendations for the treatment of this rare infection are based on small case series, individual case reports, and personal experience. A large number of patients in this outbreak are older adults, many of whom have substantial coexisting illnesses that make therapeutic decisions challenging. Treatment recommendations will certainly evolve as clinicians gain more experience with managing these infections. Given the paucity of data pertaining to treatment and the complexity of management, decisions about the treatment of patients with proven or suspected infection should be made with the input of an infectious diseases specialist.

In the current outbreak, initial recommendations for therapy were to use high doses of both liposomal amphotericin B and voriconazole because the causative organism was not known and the index patient had been shown to have infection with *A. fumigatus*. As events moved forward, it quickly became evident that the primary pathogen was a black mold, and clinical experience had shown that an azole was the usual drug of choice for infection with such organisms. In addition, a large number of patients had serious toxic effects from the high doses of amphoteri-

cin B that were recommended. Thus, the therapeutic regimen was modified in favor of monotherapy with voriconazole, except for the sickest patients or those who had substantial side effects while receiving this agent, for whom amphotericin B could play a role.

Voriconazole was selected over posaconazole and itraconazole for several reasons. First and foremost, there is experience in the use of voriconazole for various mold infections. Both intravenous and oral formulations are available, and oral administration produces serum levels equivalent to those achieved by intravenous administration. Levels of the drug in cerebrospinal fluid are approximately 50% of serum levels,⁷ and levels both in cerebrospinal fluid and in serum are above the MIC for many dematiaceous molds. By comparison, neither posaconazole nor itraconazole achieves substantial levels in cerebrospinal fluid, and their oral absorption is erratic.

CURRENT RECOMMENDATIONS

DRUGS AND DOSES

For patients with mild or moderate CNS disease, the current recommendation is to administer voriconazole at a dose of 6 mg per kilogram of body weight twice daily. For patients with severe or refractory CNS disease, therapy with a combination of voriconazole (6 mg per kilogram twice daily) and intravenous liposomal amphotericin B (at a dose of 7.5 mg per kilogram daily) is recommended.

For patients with osteoarticular infection, a loading dose of voriconazole at 6 mg per kilogram for two doses, followed by 4 mg per kilogram twice daily, is recommended. The penetration of voriconazole into the joint space is excellent. The combination of voriconazole and liposomal amphotericin B (at a dose of 5 mg per kilogram daily) should be offered to patients with severe disease. The role of adjunctive surgery should not be underestimated in patients with osteoarticular mold infections.⁸

ADVERSE EFFECTS

Voriconazole is associated with a host of drug–drug interactions. As an example, drugs that induce cytochrome P-450 (e.g., rifampin, long-acting barbiturates, and carbamazepine) substantially decrease voriconazole levels. The coadministration of voriconazole with rifabutin or

phenytoin not only leads to lower voriconazole levels but also may cause toxic serum levels of rifabutin and phenytoin. Voriconazole interferes with the metabolism of several other drugs, including cyclosporine, tacrolimus, sirolimus, and warfarin, leading to toxic levels. The coadministration of voriconazole and other agents, such as statins, benzodiazepines, calcium-channel blockers, sulfa drugs, and proton-pump inhibitors, should be done with care, with attention paid to decreasing the doses of these agents.

There is appropriate concern about the toxicity of voriconazole, particularly at the doses recommended to treat meningitis, which often leads to serum levels of more than 5 μg per milliliter. Visual hallucinations have been especially problematic in patients treated in this outbreak and appear to be related to high serum levels. Decreasing the dose of the drug will obviate this effect. Other adverse effects include visual disturbances (e.g., photopsia), confusion, nausea, hepatic-enzyme elevation, rash, and photosensitivity. The administration of parenteral voriconazole in patients with impaired renal function may lead to the accumulation of the cyclodextrin component of the intravenous solution. There is growing evidence to suggest that accumulation of cyclodextrin in renal failure does not exacerbate underlying renal dysfunction, and if needed, voriconazole can be given intravenously.⁹

OTHER ISSUES RELATED TO TREATMENT

DURATION OF THERAPY

The duration of therapy is not known, but at this time, it is recommended that patients receive at least 3 months of antifungal therapy, and probably more for vertebral osteomyelitis. Therapy should continue until all clinical signs and symptoms have resolved and abnormal laboratory values have normalized.

THERAPEUTIC DRUG MONITORING

Therapeutic drug monitoring is an important aspect of antifungal therapy and is especially important in this outbreak, since there is little experience in treating this condition.¹⁰ The severity of the infection, the possibility of relatively decreased antifungal susceptibility, and the concentration-dependent toxicity of voriconazole make the measurement of serum antifungal drug

levels extremely important. A voriconazole trough level of 2 to 5 μg per milliliter is recommended. Unpublished data from the Fungus Testing Laboratory at the University of Texas Health Science Center at San Antonio show that in 47% of more than 15,000 samples, voriconazole levels were 1 to 5 μg per milliliter, but 14% of samples had undetectable levels, and 15% had levels of more than 5 μg per milliliter. Of 167 measurements of cerebrospinal fluid, the median voriconazole level was 2.77 μg per milliliter, but there was substantial variability.

TREATMENT OF PATIENTS WITH NORMAL CEREBROSPINAL FLUID

Should patients who have symptoms but are found to have fewer than 5 white cells per cubic millimeter in cerebrospinal fluid be treated? Without objective evidence of infection in the cerebrospinal fluid, treatment is not recommended. However, patients who have symptoms should be monitored closely, and if there is even subtle progression of symptoms, a repeat lumbar puncture should be performed immediately. If the number of white cells has increased, then empirical antifungal treatment should be initiated immediately.

PROPHYLAXIS

What should we tell patients who would like to be treated with an antifungal agent to prevent

infection? The agents used for treatment are amphotericin B and voriconazole. It is unlikely that anyone would consider using amphotericin B for prophylaxis. Voriconazole is less toxic, but adverse effects have been encountered frequently in patients treated for CNS infection in this outbreak, and drug–drug interactions are many, as noted above. Another concern is that the prophylactic use of antifungal agents may delay the onset or change the course of the disease so that it appears months later and the organism may have become resistant to the agent used.

SUMMARY

This outbreak of fungal meningitis caused by contaminated methylprednisolone used for epidural injections is evolving rapidly and now involves more than 200 patients. The primary pathogen appears to be *E. rostratum*, but it is possible that other pathogens could emerge, and it remains a mystery as to why the index case is the sole case in which *A. fumigatus* was detected. It is encouraging to note that clinically apparent disease has developed in only a small percentage of exposed patients. Management recommendations will almost assuredly change as more information becomes available regarding the pathogenesis of these infections.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org

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CORRESPONDENCE



Relapse of Fungal Meningitis Associated with Contaminated Methylprednisolone

TO THE EDITOR: Since September 2012, the Centers for Disease Control and Prevention (CDC) and state and local health departments have been investigating an outbreak of fungal infections associated with injections from three lots of contaminated methylprednisolone acetate produced at a single compounding pharmacy.¹ As of May 6, 2013, a total of 741 cases have been reported in 20 states, with 55 deaths. The primary pathogen isolated from patient specimens has been *Exserohilum rostratum*, which has also been recovered from sealed vials of methylprednisolone acetate. Before this outbreak, human infections with *E. rostratum* were rarely reported.^{2,3}

Little is known about the management of *E. rostratum* infections, especially when the disease involves the central nervous system. The current guidance⁴ suggests 3 to 6 months of antifungal therapy for parameningeal infections, with longer therapy in patients with severe disease (e.g., diskitis or osteomyelitis). For patients with meningitis, a minimum of 3 months of treatment is recommended, with up to 1 year of treatment recommended for patients with severe central nervous system involvement (e.g., stroke or arachnoiditis).

An 80-year-old man with no history of an immunosuppressive condition received a lumbar epidural glucocorticoid injection with lot #06292012@26 of methylprednisolone acetate on September 12, 2012. He was taking medications for benign prostatic hypertrophy and elevated blood pressure but was not taking immunosuppressive medication (e.g., prednisone). He presented on October 4 with headache and neck pain. Lumbar puncture showed a white-cell count in the cerebrospinal fluid (CSF) of 119 cells per milliliter, and polymerase-chain-reaction (PCR) as-

say at the CDC was negative for fungi. After 1 day of treatment with liposomal amphotericin B, therapy was switched to voriconazole, with trough levels ranging from 3.0 to 10.7 μg per milliliter (reference range, 1.0 to 5.5). On January 11, 2013, examination of the CSF showed 5 white cells per milliliter. Voriconazole was discontinued on February 19, after 4½ months of therapy. On March 11, 2013, the patient presented to the emergency department with headache and neck pain; CSF analysis showed 2075 white cells per milliliter; PCR assay of the specimen at the CDC was positive for *E. rostratum*. No localized disease was visualized on magnetic resonance imaging of the lumbar spine. The patient was admitted with relapsed fungal meningitis. Voriconazole was restarted, and the patient was discharged home 4 days later. At a home visit conducted by the health department 2 weeks later, the patient reported only fatigue.

This case shows the possibility for relapsed infection among patients after more than 4 months of antifungal therapy, resolution of symptoms, and normalization of the CSF white-cell count. Although the CDC is aware of patients who have not had a relapse of disease after 3 or 4 months of antifungal treatment, the risk of relapse should be considered when deciding whether to discontinue antifungal therapy. Other factors include the severity of infection, the subsequent response to antifungal treatment, and the side effects of long-term therapy. After the discontinuation of antifungal therapy, clinicians should remain vigilant for recrudescence of infection. Close follow-up, including serial lumbar punctures after the completion of antifungal therapy, may be helpful in the early detection of relapse.

Because exserohilum meningitis is a new clinical entity, it is not known whether the current treatment guidance is sufficient. Some patients with central nervous system infection may require prolonged antifungal therapy owing to the chronic nature of fungal diseases and the difficulty in maintaining adequate drug concentrations in the CSF. The frequency of relapse after cessation of antifungal therapy in other fungal infections of the central nervous system, such as coccidioidal meningitis, has led to recommendations of lifetime antifungal treatment.⁵ At this time, the CDC has not revised its treatment guidance as a result of this single report, but the CDC continues to actively review clinical data and reports.

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BRIEF REPORT

The Index Case for the Fungal Meningitis Outbreak in the United States

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SUMMARY

Persistent neutrophilic meningitis presents a diagnostic challenge, because the differential diagnosis is broad and includes atypical infectious causes. We describe a case of persistent neutrophilic meningitis due to *Aspergillus fumigatus* in an immunocompetent man who had no evidence of sinopulmonary or cutaneous disease. An epidural glucocorticoid injection was identified as a potential route of entry for this organism into the central nervous system, and the case was reported to the state health department.

CASE REPORT

A man in his 50s with a history of degenerative lumbar-disk and joint disease presented with headache and neck pain that had become progressively worse over the course of 8 days. The associated symptoms included nausea, malaise, fatigue, chills, and decreased appetite. The patient reported no fevers, rash, photophobia, or vision changes. Four weeks before presentation, he had received the latest in a series of epidural injections of methylprednisolone for low back pain. The patient had no history of immunosuppressing conditions and was not taking any additional immunomodulatory medications.

Assessment of vital signs on presentation revealed a temperature of 36.7°C, pulse of 101 beats per minute, and blood pressure of 144/88 mm Hg. The physical examination was notable only for meningismus. Laboratory testing revealed a peripheral-blood leukocyte count of 7800 cells per cubic millimeter, with 88% polymorphonuclear cells. The remainder of the complete blood count and the comprehensive metabolic panel, including liver-function tests, were within normal limits. Computed tomography (CT) of the head without the administration of contrast material was unremarkable. A lumbar puncture was performed, and 8 ml of clear cerebrospinal fluid was removed. Analysis of the cerebrospinal fluid revealed an elevated protein level (147 mg per deciliter [reference range, 25 to 55]), low glucose concentration (31 mg per deciliter [1.7 mmol per liter], with a reference range of 45 to 75 mg per deciliter [2.5 to 4.2 mmol per liter]), and neutrophilic pleocytosis (2304 white cells per cubic millimeter; 72% polymorphonuclear cells) (Table 1). Gram's staining was negative for organisms. The patient was started on therapy with vancomycin, ceftriaxone, ampicillin, and glucocorticoids and was admitted to the hospital. Routine bacterial cultures of the blood and cerebrospinal fluid were negative, and the glucocorticoids were stopped. The patient's symptoms improved with antimicrobial therapy, as well as analgesia with opiate and nonste-

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Table 1. Results of Laboratory Testing.

Variable	First Admission		Second Admission			
		Day 1	Day 6	Day 11	Day 13	Day 15
Cerebrospinal fluid						
Source of sample	L4–L5	L3–L4	L3–L4	EVD	EVD	EVD
Opening pressure (cm of water)		33	24	>30		
Protein (mg/dl)†	147	319	247	193	93	80
Glucose (mg/dl)‡	31	2	1	63	50	59
White cells (per mm ³)	2304	4422	5863	14	27	341
Polymorphonuclear cells (%)	72	89	92	71	90	97
Lymphocytes (%)	23	4	2	21	4	2
Red cells (per mm ³)	3	34	21	2225	2850	14,700
Gram's staining	No bacteria	No bacteria	No bacteria	No bacteria	No bacteria	No bacteria
Bacterial culture	No growth	No growth	No growth	No growth	No growth	No growth
Fungal culture	Not performed	<i>Aspergillus fumigatus</i> §	No growth to date	No growth to date		No growth to date
Aspergillus antigen index	9.14¶	9.52¶	9.51¶			9.65
Serum						
Glucose (mg/dl)	108	109	107	147	127	139
Aspergillus antigen index			0.23			

* Additional cerebrospinal fluid studies, including tests for herpes simplex viruses 1 and 2 (by means of polymerase-chain-reaction [PCR] assays); varicella-zoster virus (PCR); West Nile virus (IgM antibodies by enzyme-linked immunosorbent assay [ELISA] and PCR); enterovirus (PCR); *Mycobacterium tuberculosis* (PCR); histoplasma antigen and cryptococcus antigen, 14-3-3, and tau protein (ELISA); and acanthamoeba and naegleria (Giemsa staining), as well as India-ink staining, cytologic examination, and acid-fast and viral culturing, were performed and remain negative to date. To convert the values for glucose to millimoles per liter, multiply by 0.05551. EVD denotes external ventriculostomy drain.

† The reference range for protein is 25 to 55 mg per deciliter.

‡ The reference range for glucose is 45 to 75 mg per deciliter.

§ The cerebrospinal fluid culture was positive on hospital day 7.

¶ *Aspergillus* antigen in the cerebrospinal fluid was assessed retrospectively on frozen cerebrospinal fluid samples obtained at the first admission and on hospital days 1 and 6 of the second admission.

|| The serum *aspergillus* antigen index was assessed on hospital day 7. An index of <0.5 is considered to be negative.

roidal antiinflammatory drugs. He was discharged home to complete a course of vancomycin and ceftriaxone for presumed community-acquired meningitis.

The patient presented 1 week after discharge with symptoms of headache and low back pain that had been present and progressively worsening over the previous 2 days. On presentation, his temperature was 36.9°C and he appeared ill, uncomfortable, and agitated, with incomprehensible speech. No erythema or drainage was noted in the lower lumbar area. Neurologic examination was limited by the patient's inability to participate, but there were no gross deficits. Magnetic resonance imaging (MRI) of the brain with gadolinium contrast material revealed pial enhancement and

ventriculitis; spinal imaging revealed thoracic and lumbar pial enhancement and an epidural collection at the L4 to L5 level that was less than 1 cm. A lumbar puncture was performed (Table 1). Findings included a protein level of 319 mg per deciliter, glucose concentration of 2 mg per deciliter (0.1 mmol per liter), and white-cell count of 4422 per cubic millimeter (89% polymorphonuclear cells). Treatment with intravenous vancomycin, meropenem, and levofloxacin was initiated. By hospital day 2, his mental status was markedly improved.

On hospital day 6, increased somnolence, intermittent staring spells, and a transient right facial droop developed. A head CT scan without the administration of contrast material showed

mild hydrocephalus. An electroencephalogram (EEG) did not reveal seizure activity. Lumbar puncture was repeated (Table 1), and empirical treatment with liposomal amphotericin B was initiated. The following day, the microbiology laboratory reported that the cerebrospinal fluid sample from hospital day 1 of the current admission was growing *Aspergillus fumigatus*. Intravenous voriconazole was administered, and liposomal amphotericin B was continued. A CT scan of the chest did not show findings consistent with pulmonary fungal infection. *Aspergillus* antigen (galactomannan) testing from the three available cerebrospinal fluid samples was performed (Table 1). Tests for aspergillus antigen (galactomannan) in the serum were negative. A repeat MRI of the brain revealed new infarcts in the midbrain and cerebellum; examination of the paranasal sinuses was unremarkable.

On hospital day 11, the patient abruptly became unresponsive, with rhythmic shaking of the head that was consistent with seizure activity. He was intubated and mechanical ventilation was initiated. A head CT scan showed intraventricular hemorrhage involving the lateral ventricles, subarachnoid hemorrhage in the perimesencephalic cistern, and worsening hydrocephalus (Fig. 1A and 1B). An external ventriculostomy drain was placed. The results of tests performed on samples of cerebrospinal fluid are shown in Table 1. Cerebral angiographic imaging showed extensive vasospasm and focal dilatation of the right superior cerebellar artery that was suggestive of a mycotic aneurysm (Fig. 1C and 1D) and was not amenable to intervention. The results of EEG monitoring were suggestive of seizure activity, and antiepileptic therapy was initiated. Findings from the repeat analysis of the cerebrospinal fluid are shown in Table 1.

Despite improving findings on cerebrospinal fluid testing and control of seizure activity, there was no meaningful neurologic recovery. On hospital day 15, a repeat brain MRI showed that additional cerebral and cerebellar infarcts had developed (Fig. 1E and 1F). Given the severity of the neurologic injury, the family elected not to pursue aggressive medical intervention, and life support was discontinued. The patient died on hospital day 22, and an autopsy was performed.

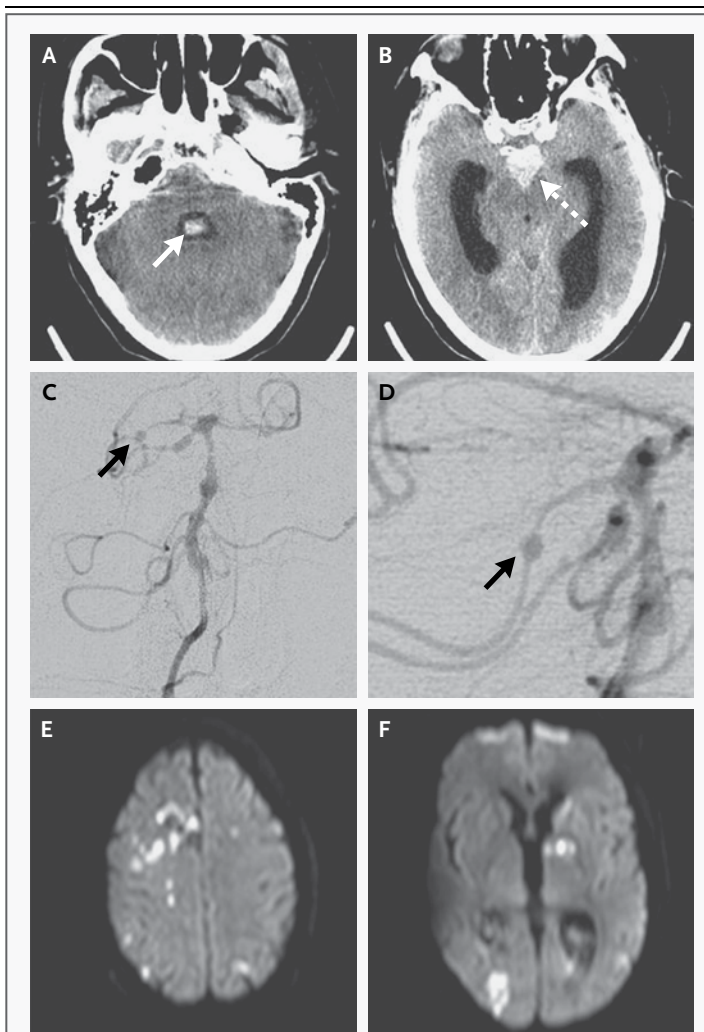


Figure 1. Imaging Studies.

Computed tomographic (CT) images of the head without the administration of contrast material, obtained on hospital day 11, show extensive hemorrhage into the fourth ventricle (Panel A, arrow) and subarachnoid hemorrhage in the perimesencephalic cistern (Panel B, dashed arrow). An angiographic image of the right vertebral artery (Panel C) shows focal segmental narrowing of the basilar artery that is consistent with vasospasm and a focal area of dilatation in the right superior cerebellar artery that is consistent with a mycotic aneurysm (arrow); a close-up view shows the mycotic aneurysm more clearly (Panel D). Diffusion-weighted images (Panels E and F) from magnetic resonance imaging of the brain performed on hospital day 16 show numerous areas of restricted diffusion (white) within cortical and deep structures, which are consistent with cerebral infarcts.

METHODS

CULTURE AND IDENTIFICATION OF FUNGUS

For fungal culturing, cerebrospinal fluid samples and tissue specimens obtained at autopsy were

inoculated directly onto solid agar mediums, including Sabouraud's dextrose agar; brain–heart infusion with 10% sheep's blood, chloramphenicol, and gentamicin; and Mycosel (BBL; Becton Dickinson). Slants were incubated at 30°C. Identification of mold isolates was made by means of macroscopic and microscopic morphologic methods (teasing preparation with lactophenol cotton-blue reagent), with an elevated temperature for growth.

ANTIGEN AND SUSCEPTIBILITY TESTING

Testing for aspergillus antigen (galactomannan) in the serum was performed with the use of an enzyme immunoassay at Associated Regional and University Pathologists (ARUP) laboratories, Salt Lake City. Testing for aspergillus antigen (galactomannan) in the cerebrospinal fluid was performed with the use of an enzyme immunoassay (Platelia, BioRad) at MiraVista Diagnostics, Indianapolis. In vitro susceptibility testing was performed with the use of broth microdilution methods for molds at ARUP laboratories.

AUTOPSY SPECIMENS

Formalin-fixed, paraffin-embedded tissue specimens were obtained from routine sites, as well as from the aneurysm at the right superior cerebellar artery, the spinal cord, and the lumbar spinal leptomeninges. Gomori methenamine silver and Fontana–Masson staining were performed in addition to routine hematoxylin and eosin staining.

RESULTS

FUNGAL CULTURE AND IDENTIFICATION OF MOLD

A mold was observed after 6 days of incubation in the fungal culture of the first cerebrospinal fluid sample obtained during the second hospital admission (Fig. 2A). This isolate was identified as *A. fumigatus*.¹ Extensive microbiologic sampling at autopsy yielded no growth of *A. fumigatus*. A single colony of cladosporium species, of unclear clinical significance, was isolated from an autopsy specimen of the dura overlying the frontal lobes.

ANTIGEN AND SUSCEPTIBILITY TESTING

Tests for aspergillus antigen (galactomannan) in the serum were negative (index, 0.23, with an index of <0.5 considered to be negative). The re-

sults of testing for galactomannan antigen in the cerebrospinal fluid are shown in Table 1. The isolate showed the following minimum inhibitory concentrations: amphotericin B, 1 μg per milliliter; itraconazole, 0.25 μg per milliliter; posaconazole, 0.06 μg per milliliter or less; and voriconazole, 0.5 μg per milliliter. The minimum effective concentration was 0.06 μg per milliliter or less for anidulafungin, caspofungin, and micafungin.

AUTOPSY SPECIMENS

Gross examination of the spine revealed gray discoloration of the left lumbar epidural compartment at the L4 to L5 level. No definitive epidural abscess was identified. A small amount of fluid was present in the L4 to L5 epidural space; a touch preparation and Gram's staining of the epidural fluid revealed septate, branching hyphal elements that were consistent with *A. fumigatus*. Dural puncture sites were not grossly evident for sampling. Incision of the dura revealed brown leptomeningeal discoloration spanning the length of the spinal cord.

Microscopic examination of the spinal cord at the T12 level revealed a focal infarction involving the white matter. Extensive leptomeningeal involvement of the spinal cord by hyphal elements was also identified (Fig. 2D). Results with Fontana–Masson staining were negative.

Gross examination of the brain revealed diffuse cerebral edema with markedly swollen gyri and diffuse, mild opacification of the cerebral meninges. Subarachnoid hemorrhage was present in the pons, midbrain, and superior aspect of the cerebellum. Coronal sections of the cerebral hemispheres revealed hemorrhage within the third and lateral ventricles and an infarct in the right frontal lobe. Two aneurysms of the right superior cerebellar artery were identified: a smaller aneurysm corresponding to that shown in Figure 1C and a second, larger aneurysm with evidence of rupture and an adherent blood clot.

Microscopic examination of the brain revealed multiple cerebral infarctions involving the frontal lobes, right occipital lobe, and left globus pallidus. The aneurysm in the superior cerebellar artery with gross evidence of rupture was examined microscopically and revealed necrotizing inflammation in the adventitia and hemorrhage (Fig. 2B). Rare foreign-body giant cells were identified. Gomori methenamine silver staining re-

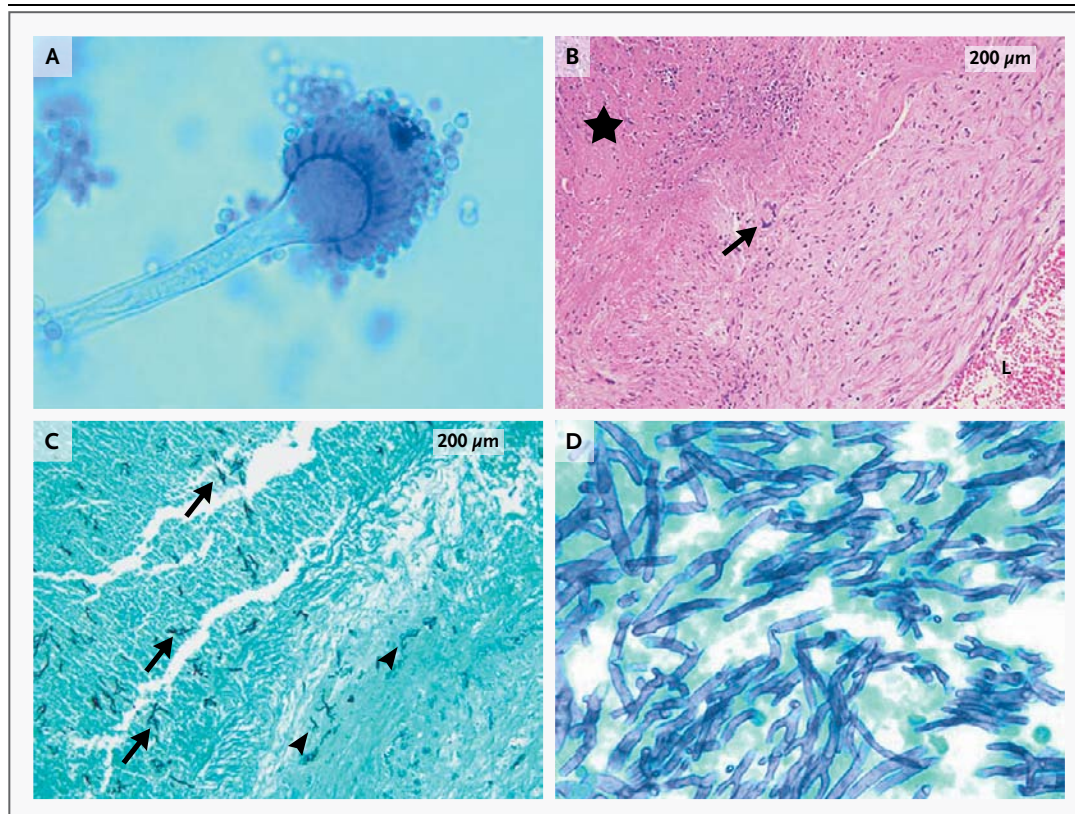


Figure 2. Pathological Studies.

Panel A shows the morphologic characteristics of *Aspergillus fumigatus* in the isolate from the first cerebrospinal fluid sample obtained during the second hospital admission. Panels B and C show sections of the right superior cerebellar artery. In Panel B (hematoxylin and eosin), necrotizing inflammation is evident in the adventitia (star), with foreign-body giant-cell reaction in the region of the aneurysm (arrow). L indicates the vascular lumen. In Panel C (Gomori methenamine silver stain), fungal hyphae can be seen within the wall of the artery (arrowheads), as well as within the area of necrotizing inflammation (arrows). Panel D (Gomori methenamine silver stain) shows a dense fungal hyphal mat in a section of the lumbar spinal leptomeninges.

vealed the presence of hyphae within the wall of the blood vessel as well as within the associated hemorrhage (Fig. 2C), a finding indicative of a mycotic aneurysm. On gross examination, there was no evidence of tissue infarction outside the central nervous system.

DISCUSSION

This case report describes the clinical presentation of neutrophilic meningitis in an immunocompetent man that did not improve despite broad-spectrum antibiotic therapy. Bacteria, particularly *Streptococcus pneumoniae* and *Neisseria meningitidis*, account for the vast majority of cases of acute neutrophilic meningitis.² Persistent neutro-

philic meningitis is a syndrome defined by clinical meningitis, cerebrospinal fluid pleocytosis with more than 50% polymorphonuclear cells, elevated protein levels, and low glucose levels for more than 7 days despite appropriate empirical antimicrobial therapy.³ The differential diagnosis of persistent neutrophilic meningitis is broad and includes both infectious and noninfectious causes. Among the most common infectious causes are atypical bacterial organisms, such as nocardia and actinomyces, and fungal organisms, including candida, aspergillus, and mucorales (formerly zygomycetes).³ In this case, a broad evaluation for potential causes of persistent neutrophilic meningitis was conducted, and ultimately, fungal cultures of the cerebrospinal fluid from

the first day of the second hospital admission grew *A. fumigatus*.

Aspergillus species are ubiquitous in the air, soil, and organic matter.⁴ Invasive disease, most commonly due to *A. fumigatus*, is rare among immunocompetent hosts.^{5,6} The organism typically enters the body through the sinopulmonary tract or through a break in the skin. Invasion of the central nervous system can occur either through direct extension from the paranasal sinuses or by hematogenous dissemination through a pulmonary or cutaneous source.⁷ In this case, the absence of evidence of infection at these sites led to the consideration of alternative portals of entry into the central nervous system. A dural puncture could permit direct transit of an organism from the epidural space into the intradural compartment. In this case, a dural puncture site was not grossly evident. However, the degree of involvement of the lumbar meninges by fungal hyphae is compatible with direct extension. In addition, the absence of infarcts in tissues outside the central nervous system is compatible with direct extension rather than hematogenous spread. Given the identification of a potential exposure through an epidural injection, the state health department was notified.

Aspergillosis in the central nervous system carries a poor prognosis, despite the availability of antifungal agents with good activity against aspergillus species and penetration of the central nervous system.^{8,9} Premortem diagnosis requires a high index of clinical suspicion. Patients typically present with focal neurologic deficits; meningeal signs are rare.¹⁰ Although radiographic imaging may be useful for identifying focal lesions or secondary complications, aspergillus meningitis is usually characterized by an absence of parenchymal lesions.¹⁰ Angioinvasion by this organism is common and results in vascular thrombosis, tissue infarction, and hemorrhage.¹⁰ Chemical testing of the cerebrospinal fluid is nonspecific, often showing pleocytosis with varying proportions of polymorphonuclear and mononuclear cells, elevated protein levels,

and low-to-normal glucose levels.¹⁰ Isolation of aspergillus from the cerebrospinal fluid is difficult and often requires repeated testing of large-volume samples.¹¹ The detection of aspergillus galactomannan in serum samples by means of an enzyme immunoassay has been validated for the diagnosis of invasive aspergillosis. This assay has also shown promise with cerebrospinal fluid specimens for the early diagnosis of central nervous system aspergillosis, although the threshold value for the diagnosis has not been determined.¹²

Early diagnosis and initiation of appropriate treatment can improve the outcomes of central nervous system aspergillosis.¹³ Voriconazole is the primary recommended therapy for this condition. Intrathecal administration of antimicrobial agents is not recommended and may be complicated by chemical arachnoiditis, seizures, headache, and altered mental status.⁷ Surgical resection of focal lesions, if present, should be considered.¹⁴

Diagnostic testing for aspergillus may not be performed routinely in cases of acute neutrophilic meningitis. Additional diagnostic testing for atypical pathogens should be pursued if the symptoms persist despite appropriate empirical therapy. If an atypical pathogen such as *A. fumigatus* is identified, a careful search for potential sources of exposure should be performed. In this case, the identification of potential exposure through epidural injection and the reporting of the case to the state health department led to an epidemiologic investigation that identified a multistate outbreak of fungal meningitis associated with epidural glucocorticoid injections.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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ORIGINAL ARTICLE

Fungal Infections Associated with Contaminated Methylprednisolone Injections — Preliminary Report

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ABSTRACT

BACKGROUND

Fungal infections are rare complications of injections for treatment of chronic pain. In September 2012, we initiated an investigation into fungal infections associated with injections of preservative-free methylprednisolone acetate that was purchased from a single compounding pharmacy.

METHODS

Three lots of methylprednisolone acetate were recalled by the pharmacy; examination of unopened vials later revealed fungus. Notification of all persons potentially exposed to implicated methylprednisolone acetate was conducted by federal, state, and local public health officials and by staff at clinical facilities that administered the drug. We collected clinical data on standardized case-report forms, and we tested for the presence of fungi in isolates and specimens by examining cultures and performing polymerase-chain-reaction assays and histopathological and immunohistochemical testing.

RESULTS

As of October 19, 2012, more than 99% of 13,534 potentially exposed persons had been contacted. As of December 10, there were 590 reported cases of infection in 19 states, with 37 deaths (6%). As of November 26, laboratory evidence of *Exserohilum rostratum* was present in specimens from 100 case patients (17%). Additional data were available for 386 case patients (65%); 300 of these patients (78%) had meningitis. Case patients had received a median of 1 injection (range, 1 to 6) of implicated methylprednisolone acetate. The median age of the patients was 64 years (range, 16 to 92), and the median incubation period was 20 days (range, 0 to 120); 33 patients (9%) had a stroke.

CONCLUSIONS

Analysis of preliminary data from a large multistate outbreak of fungal infections showed substantial morbidity and mortality. The infections were associated with injection of a contaminated glucocorticoid medication from a single compounding pharmacy. Rapid public health actions included prompt recall of the implicated product, notification of exposed persons, and early outreach to clinicians.

From the Epidemic Intelligence Service, Scientific Education and Professional Development Program Office (R.M.S., S.G., A.P.), Division of Foodborne, Waterborne, and Environmental Diseases (R.M.S., A.P., A.A.C., K.B., J.R.H., M.E.B., B.J.P.), Division of Healthcare Quality Promotion (M.K.S., M.W., J.J., J.T.W.), and Division of High-Consequence Pathogens and Pathology (D.B.), Centers for Disease Control and Prevention, Atlanta; the Tennessee Department of Health, Nashville (M.A.K., A.D.W.); the Michigan Department of Community Health, Bureau of Epidemiology, Lansing (J. Finks, J. Fielder); the Indiana State Department of Health, Indianapolis (J.D., C.F.); the Virginia Department of Health, Richmond (E.F., L.G.); the Maryland Department of Health and Mental Hygiene, Baltimore (A.C.); the New Jersey Department of Health, Trenton (B.C.); the Florida Department of Health, Tallahassee (A.R.); and the North Carolina Division of Public Health, Raleigh (S.G.). Address reprint requests to Dr. Park at bpark1@cdc.gov.

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THERE HAS BEEN NO SYSTEMATIC SURVEILLANCE in the United States for adverse events that occur after glucocorticoid injections for the treatment of chronic musculoskeletal pain, but infection is a known, although probably rare, risk documented in the medical literature.¹⁻⁶ Infections that develop after a procedure are usually bacterial^{2,7-10}; fungal infections are extremely rare.¹¹⁻¹⁴ We present preliminary data on a multistate outbreak of fungal meningitis and other infections associated with injections of preservative-free methylprednisolone acetate that was purchased from a single compounding pharmacy and describe the initial public health response to the outbreak.

METHODS

INDEX PATIENT AND EARLY EPIDEMIOLOGIC INVESTIGATION

On September 18, 2012, the Tennessee Department of Health received a report of a 56-year-old patient with aspergillus meningitis.¹⁵ The patient had no known risk factors for fungal meningitis but had received an epidural glucocorticoid injection for lower back pain at an ambulatory surgical center 46 days earlier. By September 25, the initial investigation, led by the Tennessee Department of Health in collaboration with the Centers for Disease Control and Prevention (CDC), had identified seven additional patients with meningitis who had been treated at the same ambulatory surgical center. The cerebrospinal fluid cultures from all these patients were initially negative.¹⁶ However, the clinical presentation of these patients was similar to that of the index patient: all had a subacute onset of meningitis and marked cerebrospinal fluid pleocytosis; four had posterior circulation strokes.

All the patients, including the index patient, had received epidural glucocorticoid injections of 80 mg of methylprednisolone acetate per milliliter. All the vials of methylprednisolone acetate used for these injections had been purchased from a single compounding pharmacy, New England Compounding Center (NECC, Framingham, MA); all the injections involved methylprednisolone acetate from lot 05212012@68, 06292012@26, or 08102012@51. Other exposures common to these initial patients included contrast material, povidone-iodine, lidocaine, spinal needles, and epidural tray kits.

On September 25, NECC was informed of the investigation and the exposure of all eight patients in Tennessee to three lots of methylprednisolone acetate from NECC; the company reported orally that it had not previously received any reports of adverse events associated with these lots of methylprednisolone acetate. On September 26, NECC voluntarily recalled these three lots and provided the Food and Drug Administration (FDA) and the CDC with an invoice list for the 76 clinical facilities that had received these lots, dating back to May 21, 2012, the date the first lot was produced. This list was used to initiate case finding in other states. On September 27, the North Carolina Department of Health and Human Services informed the CDC of a single patient in North Carolina who had a negative cerebrospinal fluid culture and a clinical syndrome similar to that of the patients in Tennessee, including subacute meningitis; the patient had a posterior circulation stroke on September 28. This patient had also received an epidural glucocorticoid injection and had been exposed to methylprednisolone acetate from one of the three lots, as well as to the same brands of lidocaine and povidone-iodine as those used for the patients in Tennessee. The report of this additional case suggested the possibility of an exposure that was not limited to the single ambulatory surgical center in Tennessee. Because compounded medications had been the cause of several prior outbreaks,^{14,17,18} methylprednisolone acetate from NECC was considered to be a likely source.

On September 28, state and local health departments, in collaboration with the clinical facilities that had received and administered methylprednisolone acetate from the three lots, initiated the process of identification and notification of exposed patients. Clinical facilities reviewed medical records to compile lists of patients who had received injections from one or more of the three lots of methylprednisolone acetate. The lot number was frequently not recorded in medical records; in those instances, facilities determined the period during which vials from the three lots of methylprednisolone acetate were likely to have been used and included all patients who had received injections of methylprednisolone acetate during that period. Clinical facilities, with help from state and local health departments and the CDC, notified patients by means of telephone calls, home visits, or letters. The objectives of the no-

tification were to refer exposed persons who were symptomatic for immediate medical evaluation and to advise exposed persons who were asymptomatic to seek clinical follow-up in the event of future symptoms. Additional information regarding case finding and outreach efforts is provided in the Supplementary Appendix, available with the full text of this article at NEJM.org.

On October 4, the FDA announced that microscopic evaluation of unopened vials of NECC methylprednisolone acetate from lot 08102012@51 revealed evidence of fungi.^{19,20} The CDC and FDA announced on October 18 that the environmental mold *Exserohilum rostratum*, in addition to the non-pathogenic fungi *Rhodotorula laryngis* and *Rhizopus stolonifer*, had been recovered from unopened vials of methylprednisolone acetate from lot 08102012@51^{20,21}; *E. rostratum* was subsequently identified in vials from lot 06292012@26.²¹

For the purposes of this analysis, a case was defined according to the presence of any of the following conditions at the time of clinical presentation in a person who had been exposed to one of the three lots of methylprednisolone acetate (05212012@68, 06292012@26, or 08102012@51) produced by NECC after May 21, 2012: meningitis of unknown cause that developed after an epidural or paraspinal injection; posterior circulation stroke due to presumed meningitis (without a cardioembolic source and without documentation of a normal cerebrospinal fluid profile) after an epidural or paraspinal injection; clinician-diagnosed osteomyelitis, abscess, or other infection of unknown cause in the spinal or paraspinal structures at or near the site of injection after an epidural or paraspinal injection; or clinician-diagnosed osteomyelitis or worsening inflammatory arthritis of a peripheral joint diagnosed after a peripheral-joint injection, without a known cause. Clinically diagnosed meningitis was defined as signs or symptoms of meningitis and a cerebrospinal fluid profile with pleocytosis (>5 white cells per cubic millimeter), accounting for the presence of red cells (i.e., subtracting 1 white cell for every 500 red cells present).

MICROBIOLOGIC INVESTIGATION

Clinical specimens from case patients, primarily cerebrospinal fluid or joint fluid, were evaluated at the CDC by means of polymerase-chain-reaction (PCR) assays, with the use of broad-range, internal transcribed spacer (ITS) fungal prim-

ers.^{22,23} (PCR for fungal detection is a research test. It has not been cleared or approved by the FDA, and the performance characteristics have not been established. The results of this test should not be used for diagnosis, treatment, or assessment in clinical practice.) Sequencing of amplified fungal DNA and DNA extracted from fungal isolates was performed for the identification of fungal species. Histopathological and immunohistochemical testing of tissue from autopsy or biopsy specimens, as well as PCR testing and DNA sequencing, were also performed at the CDC. In addition, microbiologic testing of specimens from case patients was performed at local, state, and reference laboratories.

INVESTIGATION OVERSIGHT AND DATA COLLECTION

This investigation was part of an emergency public health response; as such, it was not considered to be research that required review by an institutional review board or informed consent from the patients. Clinical data were collected with the use of a standardized case-report form developed for the outbreak.

STATISTICAL ANALYSIS

All analyses were performed with the use of SAS software, version 9.3 (SAS Institute). For case patients who received more than one injection of methylprednisolone acetate, the incubation period was calculated as the number of days from the last injection to the onset of symptoms. National and state-specific attack rates were calculated as the number of case patients divided by the total number of exposed persons. National attack rates were calculated with data from all cases; state-specific attack rates were calculated with data from cases involving injections in nonperipheral joints only. Persons exposed to both types of injections (peripheral-joint and nonperipheral-joint injections) were included in both denominator categories. Lot-specific attack rates were also calculated (for details see the Supplementary Appendix).

RESULTS

EPIDEMIOLOGIC INVESTIGATION

On the basis of records provided by NECC, we determined that the three lots of methylprednisolone acetate comprised 17,675 vials that had been distributed to 76 facilities in 23 states. Active re-

Characteristic	All Cases† (N=386)	Meningitis Only (N=300)	Spinal and Paraspinal Infections Only (N=65)	Peripheral-Joint Infections Only‡ (N=10)
Demographic and clinical data				
Female sex — no. (%)	233 (60)	184 (61)	37 (57)	6 (60)
Age — yr				
Median	64	64	65	51
Range	16–92	16–92	32–87	43–84
Interquartile range	51–74	51–74	53–73	46–59
Immunosuppressed — no. (%)	35 (9)	25 (8)	6 (9)	2 (20)
Incubation period — days§				
Median	20	19	22	21
Range	0–120	0–120	0–92	3–49
Interquartile range	11–29	10–27	13–38	14–29
Incubation period in patients who received only 1 injection — days¶				
Median	22	22	25	21
Range	0–120	0–120	0–70	3–29
Interquartile range	12–32	12–32	11–41	11–27
Initial symptoms — no./total no. (%)				
Headache	292/382 (76)	251/297 (85)	33/64 (52)	3/10 (30)
Back pain	144/382 (38)	94/297 (32)	44/64 (69)	1/10 (10)
Neck pain or stiffness	138/382 (36)	117/297 (39)	16/64 (25)	2/10 (20)
Fever	107/382 (28)	95/297 (32)	7/64 (11)	2/10 (20)
Photophobia	75/382 (20)	66/297 (22)	8/64 (12)	0
Joint pain	33/382 (9)	4/297 (1)	15/64 (23)	10/10 (100)
Exposure data				
Lot exposure known — no./total no. (%)	285/386 (74)	221/300 (74)	51/65 (78)	4/10 (40)
Exposed to lot 05212012@68	41/285 (14)	37/221 (17)	2/51 (4)	0
Exposed to lot 06292012@26	237/285 (83)	177/221 (80)	49/51 (96)	4/4 (100)
Exposed to lot 08102012@51	49/285 (17)	44/221 (20)	3/51 (6)	0
Exposed to only one lot	243/285 (85)	184/221 (83)	48/51 (94)	4/4 (100)
05212012@68	17/243 (7)	16/184 (9)	0	0
06292012@26	201/243 (83)	146/184 (79)	46/48 (96)	4/4 (100)
08102012@51	25/243 (10)	22/184 (12)	2/48 (4)	0
Procedures involving methylprednisolone acetate during the outbreak period — no./patient				
Median	1	1	1	2
Range	1–6	1–4	1–6	1–4
Type of injection known — no./total no. (%)	325/386 (84)	255/300 (85)	50/65 (77)	9/10 (90)
Epidural or paraspinal injection	313/325 (96)	252/255 (99)	50/50 (100)	0
Peripheral-joint or other injection	8/325 (2)	0	0	8/9 (89)
Both	4/325 (1)	3/255 (1)	0	1/9 (11)

Table 1. (Continued.)

Characteristic	All Cases† (N=386)	Meningitis Only (N=300)	Spinal and Paraspinal Infections Only (N=65)	Peripheral-Joint Infections Only‡ (N=10)
Treatment and Outcome				
Antifungal treatment documented — no./total no. (%)	311/386 (81)	236/300 (79)	61/65 (94)	8/10 (80)
Voriconazole monotherapy	180/311 (58)	121/236 (51)	47/61 (77)	8/8 (100)
Amphotericin monotherapy	1/311 (<1)	1/236 (<1)	0	0
Voriconazole and amphotericin	130/311 (42)	114/236 (48)	14/61 (23)	0
Development of stroke — no./total no. (%)	33/386 (9)	28/300 (9)	0	0
Ischemic	23/33 (70)	18/28 (64)	0	0
Hemorrhagic	5/33 (15)	5/28 (18)	0	0
Both	4/33 (12)	4/28 (14)	0	0
Unknown	1/33 (3)	1/28 (4)	0	0
Laboratory data				
Initial lumbar puncture results				
White-cell count — cells/mm ³			NA	NA
Median	165	172		
Range	6–15,400	6–15,400		
Interquartile range	12–1150	12–1190		
Glucose — mg/dl			NA	NA
Median	52	52		
Range	4–244	4–244		
Interquartile range	38–64	38–64		
Protein — mg/dl				
Median	87	87	NA	NA
Range	13–893	13–893		
Interquartile range	50–141	49–141		
Initial joint aspirate results				
White-cell count — cells/mm ³	NA	NA	NA	
Median				721
Range				14–24,000
Interquartile range				516–5374
Evidence of fungus — no.	111	97	8	1
Documented by PCR only	76	67	5	1
Documented by culture only	13	12	1	0
Documented by histopathological assessment only	0	0	0	0
Documented by >1 technique	22	18	2	0
Exserohilum species	100	86	8	1

* Included are data as of November 26, 2012. Cases are classified according to the presenting symptom. To convert the values for glucose to millimoles per liter, multiply by 0.05551. NA denotes not applicable, and PCR polymerase chain reaction.

† Included are cases in patients with meningitis, patients with stroke who did not undergo lumbar puncture, patients with spinal or paraspinal infections, and patients with peripheral-joint infections, as well as patients who met multiple case definitions.

‡ The peripheral joints affected were the ankle (in 3 patients), the hip (in 4 patients), the knee (in 2 patients), and the shoulder (in 1 patient).

§ Data were available for a total of 346 patients, including 275 who had meningitis only, 52 who had spinal or paraspinal infections only, and 9 who had peripheral-joint infections only.

¶ A total of 194 patients had only one injection, including 157 patients who had meningitis only, 27 who had spinal or paraspinal infections only, and 4 who had peripheral-joint infections only.

view of records by clinical facilities and state and local health departments identified 13,534 persons who had potentially been exposed to medication from at least one of the three lots; 12,069 (89%) had been exposed through epidural, spinal, or paraspinal injections, and 1648 (12%) through peripheral-joint or other injections. As of October 19, 2012, state health departments reported that approximately 99% of persons potentially exposed to these lots of methylprednisolone acetate had been contacted at least once.

As of December 10, 2012, a total of 590 cases had been identified in 19 states; 37 case patients (6%) had died. Data from case-report forms were available for 386 case patients (65%) as of No-

vember 26: 300 of these patients (78%) had meningitis, 65 (17%) had spinal or paraspinal infections, 10 (3%) had septic arthritis after a peripheral-joint injection (Table 1), and 5 (1%) met the case definition for stroke due to presumed meningitis. Six case patients (2%) had meningitis in addition to a spinal or paraspinal infection. The median age of the case patients was 64 years (range, 16 to 92); 233 (60%) were women. A total of 35 case patients (9%) had underlying immunosuppression (Table 1). Data on symptoms were available for 382 case patients (99%). The most commonly reported symptoms among case patients with meningitis were headache (in 85%) and neck stiffness (in 39%); among case patients

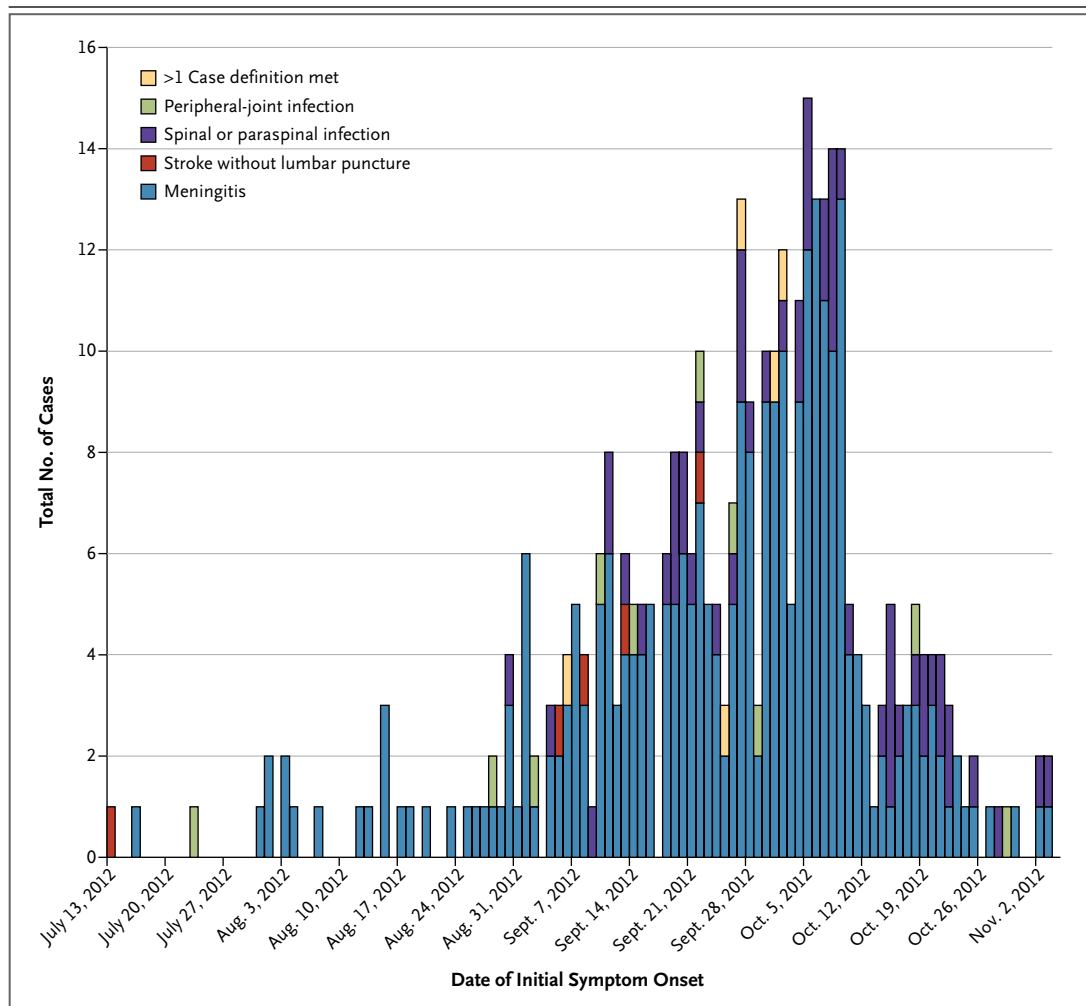


Figure 1. Fungal Infections Associated with Contaminated Lots of Methylprednisolone Acetate, According to Date of Initial Symptom Onset and Presenting Syndrome.

Included are data as of November 26, 2012. Data on the date of symptom onset were available for 356 cases. A median of 16 days elapsed between the onset of symptoms and the reporting of cases to the Centers for Disease Control and Prevention.

with spinal or paraspinal infections, the most commonly reported symptoms were back pain (in 69%) and headache (in 52%). All case patients with joint infections reported joint pain (Table 1).

A total of 33 case patients (9%) had a stroke. In 5 patients, the stroke was due to presumed meningitis (lumbar puncture was never performed); 28 patients had a stroke in addition to documented meningitis. Of the 32 case patients with available data on the timing and type of stroke, 16 presented with a stroke and 16 had a stroke during the course of their hospitalization. A total of 23 strokes were ischemic, 5 were hemorrhagic, and 4 were both. Of the 25 case patients for whom the location of the stroke was known, 24 (96%) had strokes that involved the posterior circulation.

Data on antifungal treatment were available

for 311 case patients (81%): 180 (58%) received voriconazole alone, 130 (42%) received both voriconazole and amphotericin B, and 1 (<1%) received amphotericin B alone. Among the 356 case patients for whom a symptom-onset date was recorded (Fig. 1), the earliest date of the onset of symptoms was July 13, 2012, in a patient who had a stroke without documented lumbar puncture; the first case patient with documented meningitis had an onset of symptoms on July 15, 2012. Among the 346 case patients with available data on the incubation period (the interval from the date of the last injection to the date of symptom onset), the median incubation period was 20 days (range, 0 to 120) (Fig. 2); among the 194 case patients who received only one known glucocorticoid injection, the median incubation period was 22 days (range, 0 to 120). All case patients with

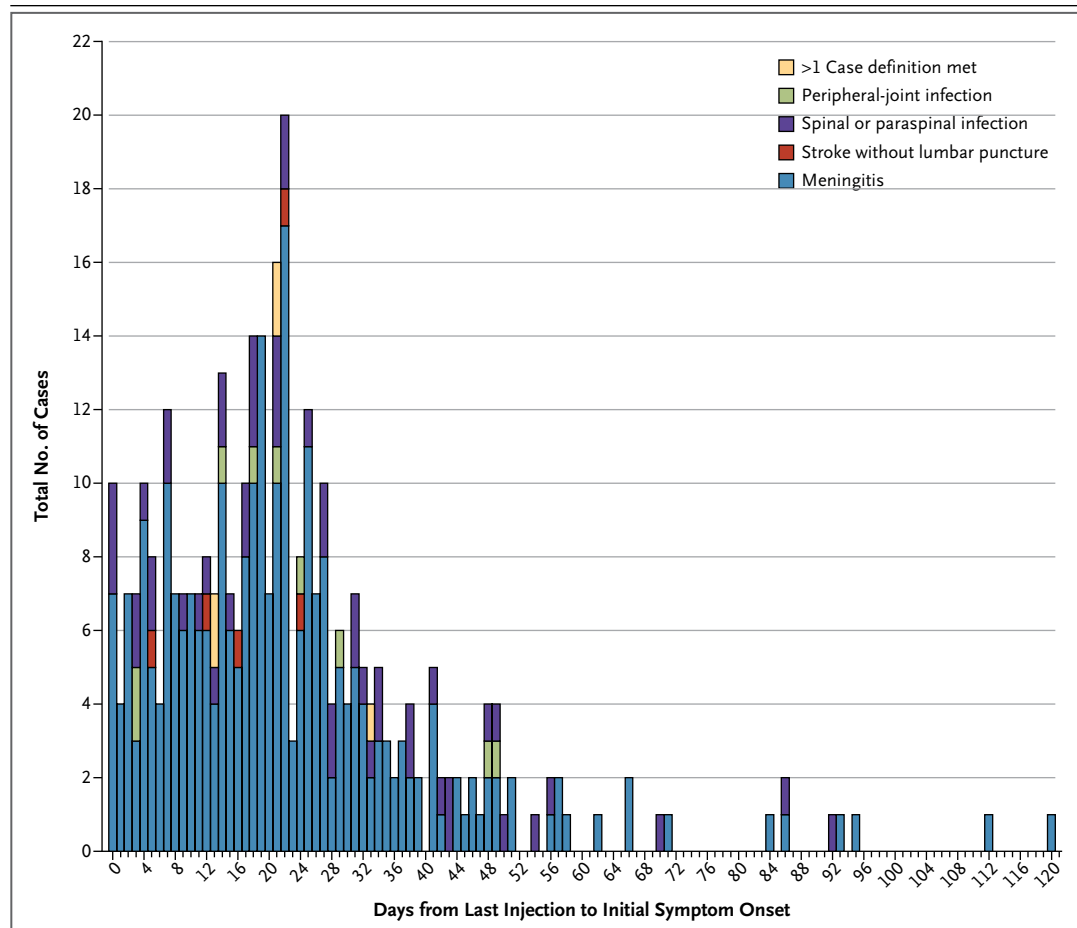


Figure 2. Incubation Period for Cases of Fungal Infections Associated with Contaminated Lots of Methylprednisolone Acetate.

Included are data as of November 26, 2012. Shown are the number of days from a patient's last injection to the date of initial symptom onset, according to the presenting syndrome. Data were available for a total of 346 cases.

meningitis underwent a lumbar puncture; the median white-cell count in the first cerebrospinal fluid sample was 165 cells per cubic millimeter (range, 6 to 15,400), the median glucose concentration was 52 mg per deciliter (range, 4 to 244) (2.9 mmol per liter [range, 0.2 to 13.5]), and the median protein level was 87 mg per deciliter (range, 13 to 893) (Table 1). Among the 8 case patients with peripheral-joint infections and available data on synovial fluid analysis, the median white-cell count was 721 cells per cubic millimeter (range, 14 to 24,000).

Lot-specific exposure data were available for

285 case patients (74%) (Table 1). Using case counts from December 10, 2012, we calculated the overall attack rate (i.e., the rate for any fungal infection meeting the case definition) as 4.4 cases per 100 exposed persons (Table 2). The overall attack rate for nonperipheral-joint infections (meningitis, stroke due to presumed meningitis, and spinal and paraspinal infections) was 4.7 cases per 100 exposed persons, but the rate varied widely by state, ranging from 0 to 11.5 cases per 100 exposed persons (Table 2).

NECC shipped a total of 11,622 ml of the 05212012@68 lot of methylprednisolone acetate,

Table 2. National Attack Rates for All Infections and National and State-Specific Attack Rates for Meningitis and Spinal and Paraspinal Infections, as of December 10, 2012.

Description	No. of Cases	Persons Potentially Exposed*	No. of Cases/100 Persons Potentially Exposed (95% CI)†
National attack rate, all infections	590	13,534	4.4 (4.0–4.7)
National attack rate, meningitis and spinal and paraspinal infections‡	569	12,069	4.7 (4.3–5.1)
State-specific attack rate, meningitis and spinal and paraspinal infections‡§			
Florida	25	1,034	2.4 (1.6–3.5)
Georgia	1	180	0.6 (0.03–2.7)
Idaho	1	47	2.1 (0.1–10.5)
Illinois	2	238	0.8 (0.1–2.8)
Indiana	63	1,362	4.6 (3.6–5.9)
Maryland	25	1,057	2.4 (1.6–3.4)
Michigan	199	1,727	11.5 (10.0–13.2)
Minnesota	12	843	1.4 (0.8–2.4)
New Hampshire	9	601	1.5 (0.7–2.8)
New Jersey	40	639	6.3 (4.5–8.4)
New York	1	405	0.2 (0.01–1.2)
North Carolina	4	100	4.0 (1.3–9.6)
Ohio	19	328	5.8 (3.6–8.9)
Pennsylvania	1	720	0.1 (0.01–0.7)
Rhode Island	3	266	1.1 (0.3–3.1)
South Carolina	1	231	0.4 (0.02–2.1)
Tennessee	110	1,010	10.9 (9.0–13.1)
Texas	2	58	3.5 (0.6–11.4)
Virginia	51	645	7.9 (6.0–10.3)

* For the attack rate of all infections, this category includes all persons who received any type of glucocorticoid injection (peripheral-joint or nonperipheral-joint injection). For the attack rate of meningitis and spinal and paraspinal infections, this category includes persons who received an epidural or spinal or paraspinal injection.

† The number of cases per 100 persons potentially exposed is the attack rate. CI denotes confidence interval.

‡ Included are persons who had meningitis, stroke due to presumed meningitis, and spinal or paraspinal infections.

§ Cases were attributed to the state in which the patient received the injection, not the state of residence. Persons potentially exposed to implicated methylprednisolone acetate were reported in California, Connecticut, and West Virginia, but there were no cases in those states. Implicated methylprednisolone was shipped to Nevada, but no persons in that state were reported to have been exposed, and there were no cases.

10,774 ml of the 06292012@26 lot, and 7092 ml of the 08102012@51 lot. On the basis of data from case-report forms received as of November 26, the lot-specific attack rates were estimated to be 4 cases per 1000 ml of methylprednisolone acetate used from lot 05212012@68, 22 cases per 1000 ml from lot 06292012@26, and 11 cases per 1000 ml from lot 08102012@51 (Table 3).

MICROBIOLOGIC INVESTIGATION

As of November 26, the CDC had received specimens from 372 case patients; for 111 of the case patients from whom specimens were obtained (30%), there was laboratory evidence supportive of a fungal infection: direct detection of fungal DNA in 76 fluid or tissue specimens (68%), a fungal isolate with identification confirmed by DNA sequencing in 13 (12%), and evidence from the use of multiple techniques in 22 (20%). A total of 100 case patients had evidence of *E. rostratum*, 1 had histopathological evidence of invasive disease due to *Aspergillus fumigatus*, and 10 had evidence of other fungi of unknown clinical significance (further details are available in the Supplementary Appendix). For 3 case patients, laboratory evidence of fungal infection was available only from testing at outside laboratories: preliminary fungal growth was reported for 1 patient, and histopathological evidence was reported for the other 2; identification of the species of fungus is pending for these 3.

DISCUSSION

We describe preliminary epidemiologic and laboratory data from a multistate outbreak of fungal infections associated with injection of contaminated methylprednisolone acetate from a single compounding pharmacy. Although the clinical presentations in this outbreak varied, most of the patients had clinically diagnosed meningitis, making this one of the largest outbreaks of health care-associated fungal meningitis reported to date in the United States. This investigation was a collaboration among federal, state, and local public health officials, as well as staff at clinical facilities, all of whom worked rapidly to contact patients and to collect, aggregate, and disseminate clinical and laboratory data, which helped guide interim diagnostic and treatment decisions.

At the outset of this investigation, when patients had been identified only at a single ambulatory surgical center in Tennessee, our hypotheses

Table 3. Lot-Specific Attack Rate for All Infections, as of November 26, 2012.

Lot Number	No. of Cases*	Total Amount of Methylprednisolone Acetate Used <i>ml</i>	No. of Cases/1000 ml of Methylprednisolone Acetate (95% CI)†‡
Primary analysis			
05212012@68	41	11,622	4 (2.4–4.5)
06292012@26	237	10,665	22 (19–24)
08102012@51	49	4,304	11 (8.1–14)
Sensitivity analysis‡			
05212012@68	142	11,622	12 (10–14)
06292012@26	338	10,665	32 (28–35)
08102012@51	150	4,304	35 (30–41)

* Included are cases in persons exposed to the indicated lot; some persons had exposure to more than one lot.

† The number of cases per 1000 ml of methylprednisolone acetate is the attack rate.

‡ In the sensitivity analysis, all cases for which the lot exposure could not be determined were assigned to each lot, in order to assess the maximum possible attack rate for each lot.

about the source of the outbreak included both the possibility of contamination at the center and the chance that this could be part of a broader event involving product contamination at the point of production. Facility-specific contamination had resulted in a previous outbreak of aspergillus meningitis in Sri Lanka, which was traced back to contaminated spinal needles stored in damp closets.¹¹ Although fungal meningitis is extremely rare in immunocompetent hosts, sporadic cases have been reported after epidural injection, probably owing to breaks in aseptic technique during the procedure.¹² The subsequent report of a case in North Carolina suggested that this was not a facility-specific problem and that widespread contamination might have occurred. The FDA announcement on October 4 of visible fungal contamination in unopened vials of methylprednisolone acetate compounded at NECC confirmed the leading hypothesis that contaminated methylprednisolone acetate from NECC was causing serious fungal illness in patients who had received an injection with this medication.

One critical component of the public health response was the rapid, active outreach targeting both patients and clinicians. Anecdotal data collected during the first week of the outbreak indicated that many of the initial patients had mild-to-moderate symptoms that ordinarily would not have prompted urgent medical evaluation.¹⁶

There was added concern that many clinicians would be unable to make a diagnosis of meningitis caused by molds because of the low yield of traditional diagnostic methods, such as culturing.²⁴⁻²⁶ Therefore, there was a considerable potential for missed diagnoses in exposed patients if direct intervention to alert patients and clinicians did not occur. In addition, because the initial nine patients had poor outcomes, including death and posterior circulation stroke, rapid notification could allow for early diagnosis and treatment, reducing the risk of poor outcomes.

The extent of the contamination of the three lots of methylprednisolone acetate is not known. We identified at least two organisms in patients, *E. rostratum* and *A. fumigatus*, that caused infection. Additional fungi, most of which are common environmental molds but rarely cause human disease,²⁷⁻³³ were identified in specimens from case patients, as well as in the product,²¹ but are of unclear clinical significance. Some of these organisms, when injected into a sterile site, might have contributed to the disease by causing inflammatory reactions without true infection. Further evaluation of both the clinical specimens and the product is ongoing.

Despite the magnitude of potential exposure to contaminated methylprednisolone acetate — which included more than 13,000 persons — disease has developed in a relatively small proportion of exposed persons, to date. In addition, state-specific attack rates have varied widely, from 0 to more than 11 cases per 100 exposed persons; lot-specific attack rates have also varied considerably. Because all states achieved near-complete notification of exposed persons, the wide range of attack rates observed is unlikely to be due to large differences in case-finding methods. Rather, differences in the degree of contamination, the receipt dates and storage times of the lots, and injection practices might have contributed to the varying attack rates observed in different facilities and states. Nevertheless, these attack rates are likely to be underestimates, since some cases of disease have not yet had sufficient time to be manifested clinically. The longest incubation period in a 2002 outbreak of fungal meningitis after injection of contaminated glucocorticoids was 116 days,¹⁴ reflecting the subacute nature of some fungal infections of the central nervous system. As the outbreak evolves, continued vigilance is warranted for new cases and also for additional infec-

tions (e.g., epidural abscesses) among known cases, since some of these complications may be slow to develop.³⁴

There are several limitations of this investigation. First, we lacked lot-specific data on exposure for most patients, which prevented the exact calculation of lot-specific attack rates. This also made it impossible, in many facilities, to enumerate the exact number of patients exposed to the three lots of methylprednisolone acetate; the numbers presented here are estimates that took into account the time during which the implicated lots of methylprednisolone acetate were in use at clinics and the number of patients who underwent procedures during that time. Second, when estimating the rate of use, we assumed that the use of methylprednisolone acetate ceased within 4 days after the recall and that all methylprednisolone acetate used at each clinic came from NECC. These assumptions might not be true for each facility; some facilities might have stopped using methylprednisolone acetate earlier or later than 4 days after the recall or they might have used methylprednisolone acetate from other manufacturers at the same time that they were using methylprednisolone acetate from NECC. Third, some data, particularly data on symptom onset, are subject to recall bias. Fourth, our investigation was also subject to the limitations of existing diagnostic assays to detect fungal infections. Finally, some aspects of these preliminary data may be subject to change, particularly in this setting of an evolving outbreak.

Our findings have two important implications. First, it is imperative that steps are taken to ensure that compounded medications that are labeled as sterile are safe and uncontaminated. The consequences of contamination of a widely distributed, compounded medication used for injection can be devastating, as was shown in the current outbreak. Compounded medications have been the source of several previous outbreaks^{14,17,18}; understanding how to prevent contamination of products is essential for public health and the public confidence in the health care delivery system. Second, the large-scale public health efforts undertaken in this investigation required a strong public health infrastructure and collaboration among clinicians and public health officials at the state, local, and federal levels. These efforts played a critical role not only in alerting the public to an evolving health threat, but also in collecting,

aggregating, and disseminating information in real time, which was used both to understand the scope and source of the outbreak and to drive efforts to reduce further morbidity and mortality.

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Disclosure forms provided by the authors are available with the full text of this article at nejm.org.

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Regulating Compounding Pharmacies after NECC

Kevin Outterson, J.D.

Food and Drug Administration (FDA) rules are often forged in crisis. After the 1937 sulfanilamide disaster that killed more than 100 people, Congress passed the Food, Drug, and Cosmetic Act (FDCA),

requiring drugs to be safe and properly labeled. In 1962, a requirement was introduced for proof of drug efficacy through “adequate and well-controlled investigations,” partly in response to the thalidomide tragedy. Rules protecting human-research subjects owe a debt to Tuskegee and Nuremberg. Sometimes it takes a disaster to spur the adoption of appropriate regulation.

Today, compounding pharmacies are at the center of a controversy after a rare outbreak of fungal meningitis that was traced to several lots of the injectable glucocorticoid methylprednisolone acetate compounded by the New England Compounding Center (NECC). Congress is already discussing new federal regulations.

Since 1938, the FDA has had clear authority to regulate drug manufacturing, but compound-

ing falls into a gray area between state and federal oversight. The FDA’s authority here is generally limited to reacting to problems identified by others. Traditional compounding pharmacies are not registered with the FDA as drug manufacturers, the agency doesn’t approve their prescriptions before marketing, and related adverse events need not be reported to the FDA. State law generally controls recordkeeping, certifications, and licensing for compounding pharmacies (see timeline).

Such a regulatory structure is not unusual: many U.S. health care laws embrace federalism principles, preserving substantial realms for state control. States have primary authority over the practice of both medicine and pharmacy. But over time, compounding has evolved into a busi-

ness far removed from the mortar and pestle. Once it becomes an industrial-scale national business, the arguments for federal regulation become stronger.

For more than two decades, the FDA has struggled to regulate industrial-scale compounding. In 1992, it issued a Compliance Policy Guide, attempting to police the line between traditional compounding and drug manufacturing. This guide attracted enough criticism that Congress created a safe-harbor compounding statute in 1997, amending the FDCA with a new section, 503A.

But 2 days before this law was to take effect, seven compounding pharmacies sued to block it. Section 503A(c) banned the advertising and promotion of compounded drugs; the theory was that since traditional compounding occurred in response to individual prescriptions, advertising was unnecessary. The advertising ban was the law’s Achilles’ heel. In 2002, in a 5-to-4 decision in *Thompson v. Western States Medical Center* (an early example of the

NECC Compliance with Existing FDA Compliance Policy Guide.	
Rule Violation as Listed in the 2002 Compliance Policy Guide	NECC Compliance, per FDA and Massachusetts Interim Reports
Compounding of drugs in anticipation of receiving prescriptions, except in very limited quantities in relation to the amounts of drugs compounded after receiving valid prescriptions	NECC did not have valid prescriptions for all compounded drugs
Compounding drugs that were withdrawn or removed from the market for safety reasons	No evidence thus far
Compounding finished drugs from bulk active ingredients that are not components of FDA-approved drugs without an FDA-sanctioned Investigational New Drug Application	No evidence thus far
Receiving, storing, or using drug substances without first obtaining written assurance from the supplier that each lot of the drug substance has been made in an FDA-registered facility	No evidence thus far
Receiving, storing, or using drug components not guaranteed or otherwise determined to meet official compendia requirements	No evidence thus far
Using commercial-scale manufacturing or testing equipment for compounding drug products	NECC appears to have used commercial-scale manufacturing or testing equipment
Compounding drugs for third parties who resell to individual patients or offering compounded drug products at wholesale to other state-licensed persons or commercial entities for resale	Unclear thus far
Compounding drug products that are commercially available in the marketplace or that are essentially copies of commercially available FDA-approved drug products (In certain circumstances, it may be appropriate for a pharmacist to compound a small quantity of a drug that is only slightly different from an FDA-approved drug that is commercially available. In these circumstances, the FDA will consider whether there is documentation of the medical need for the particular variation of the compound for the particular patient.)	NECC produced a preservative-free version of a commercially available drug, methylprednisolone acetate
Failing to operate in conformance with applicable state law regulating the practice of pharmacy	NECC appears to have violated Massachusetts law

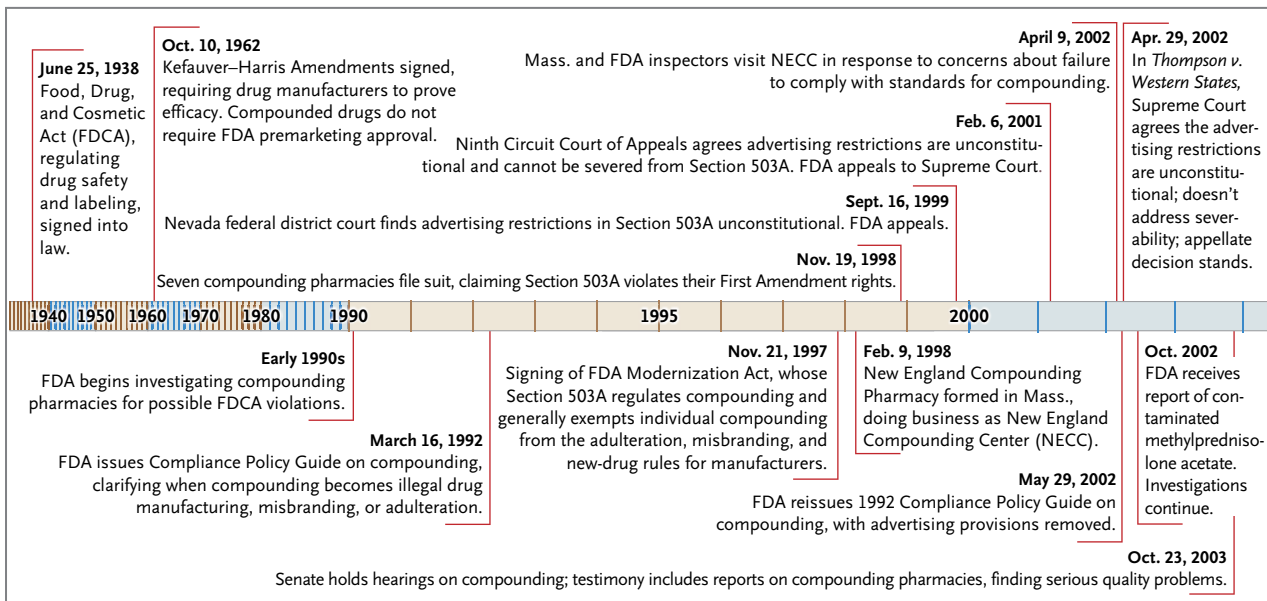
use of free speech against public health regulation),¹ the Supreme Court ruled that compounders have a constitutional right to advertise their drugs.

The FDA salvaged the Compliance Policy Guide by reissuing it without the advertising and interstate-shipment provisions, re-emphasizing the agency's author-

ity under the FDCA. The 2002 Guide articulated nine factors that the FDA would consider as relevant, including many drawn from the nonadvertising provisions of Section 503A. Several of these factors appear to have been violated by NECC (see table).

Some observers have chastised the FDA for not acting sooner

against NECC, given the agency's authority to block illegal drug manufacturing. But this critique ignores the complex regulatory history. FDA authority over compounding has never been straight-forward, and though the agency can react once a problem is obvious, it's unclear how it should proactively gather information on



History of FDA Regulation Relevant to Compounding at NECC.

potential violations before a crisis erupts. The thousands of U.S. compounding pharmacies are not registered with the FDA; they are not subject to federal recordkeeping and reporting rules for drug manufacturers; and, through litigation, the FDA can be blocked for many months from visiting them. Without information about the actual conditions in compounding pharmacies, regulators cannot act to address violations.

It's possible that if the Supreme Court hadn't struck down Section 503A, the tragedy at NECC could have been averted. Several features of that law are relevant.

First, traditional compounding was limited to a pharmacist or a physician serving a specific patient. Section 503A also permitted compounding of drugs "in limited quantities before the receipt of a valid prescription order . . . based on a history of . . . receiving valid prescription orders." According to the preliminary report from the Commonwealth of Massachusetts, NECC far exceeded these limits in preparing and shipping vials of methylprednisolone acetate.² Once

disconnected from individual patients, compounding increasingly resembles drug manufacturing.

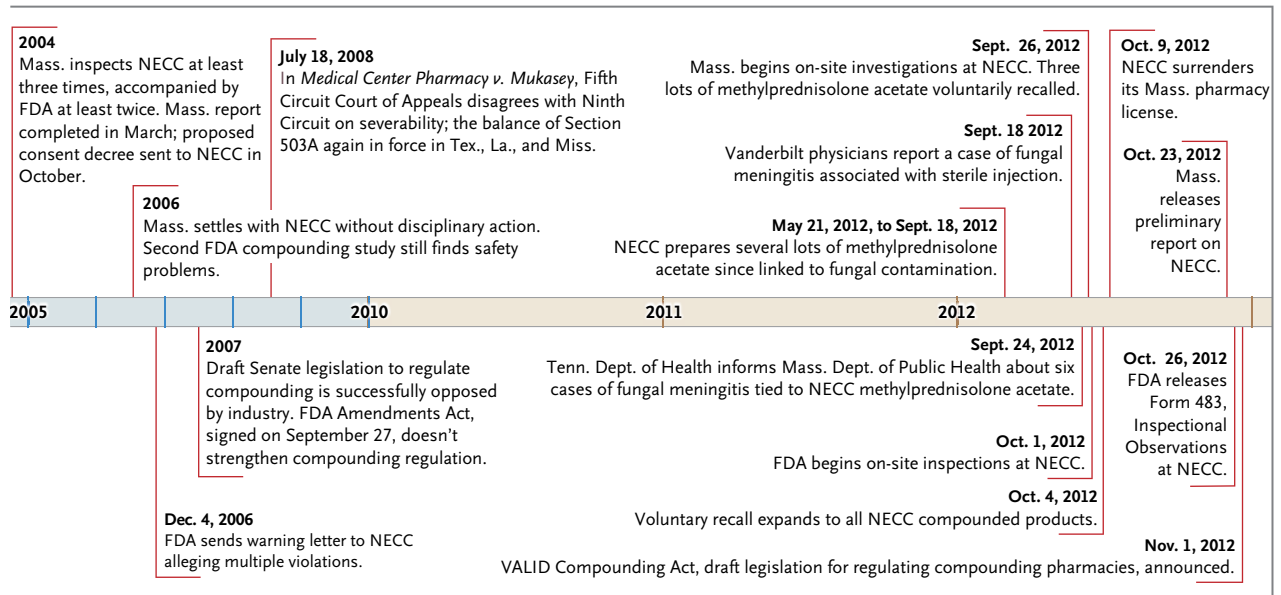
Second, compounding is not needed if a drug is commercially available from an FDA-regulated facility. Section 503A prohibited compounding "regularly or in inordinate amounts" any drugs that were "essentially copies of a commercially available drug product." FDA-approved methylprednisolone acetate is sold by Pfizer and two generics companies, but since NECC's version did not contain preservatives, it could sidestep this regulatory process — with tragic results.

Third, Congress recognized that states could effectively regulate traditional compounding pharmacies, but national-scale businesses required federal coordination. Section 503A provided a test for distinguishing between the two: it limited interstate shipments to no more than 5% of the compounder's business, unless the home state had entered into a "memorandum of understanding" with the FDA, bolstering state and federal cooperation.

NECC shipped substantial quantities of drugs to many states. If Section 503A had not been struck down, both the FDA and Massachusetts would have been more directly involved in regulating NECC for more than a decade.

Yet contamination is only one of five categories of risk associated with compounding pharmacies; the others are subpotency, superpotency, overmedication, and medication replacement.³ Other policy levers that may be needed include enhanced transparency for state-level regulation, mandatory disclosures to physicians and patients, mandatory reporting of adverse events, user fees to support oversight, clear FDA authority to register and inspect nontraditional compounding pharmacies, enhanced incentives for internal whistleblowers, and modification of reimbursement rules to blunt the economic incentives driving industrial-scale compounding.

Fungal contamination at NECC has sickened more than 400 patients and killed at least 29. But it's important to note that many patients received these sterile in-



jections for back and joint pain, a procedure that lacks high-quality evidence of efficacy.^{4,5} These problems cannot be laid entirely at the feet of compounders when clinicians persist in clinical practices despite weak evidence of efficacy.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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Drug Policy for an Aging Population — The European Medicines Agency's Geriatric Medicines Strategy

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In almost every country, the proportion of people over 60 years of age is growing faster than any other age group, as a result of longer life expectancy and declining fertility rates. In Europe, the median age is already the highest in the world, and in 2050 there are projected to be 88.5 million Americans 65 years old or older — more than double the 40.3 million in the 2010 census.

Although population aging is a mark of the success of public health policies, it also challenges the established way of implementing such policies. In the case of the European Medicines Agency (EMA), it has prompted an analysis of whether the regulatory system is adapted to taking the needs of older people into account in the development, approval, and use of medications.

The process started in 2006, when the EMA provided an opinion on the adequacy of guidance on the elderly regarding medicinal products. In 2011, the agency's Committee for Human Medicinal Products adopted the EMA geriatric medicines strategy,¹ marking its commitment to improving our understanding of how best to evaluate the benefit-risk

ratio for a medication in older patients.

First, the strategy recognizes that older people are the main users of medications — not a minority or special population (a fundamental difference between the geriatric and pediatric populations). Therefore, legislative and regulatory frameworks must be designed to ensure that the use of newly approved medicines in the intended population is supported by relevant data on the benefit-risk balance. The strategy's second aim is to improve the availability of information to patients and prescribers, to support safer use of medications.

Analysis of the data submitted in support of recent applications for marketing authorization shows that the current regulatory environment has ensured reasonable representation of “younger old” patients, but drug-usage patterns reveal a high prevalence of use in “older old” patients (see graph). Patients who are 75 years old or older often present a complex picture involving coexisting conditions and frailty: they are the fastest-growing demographic group but are largely underrepresented in clinical trials given

their disproportionately high actual use of drugs. This imbalance will make it increasingly difficult and potentially inappropriate to extrapolate data to these patients.² Though trials are less likely to set unjustified age limits than they were a few decades ago, this improvement must be considered in the context of a rapidly aging population and the continued widespread use of exclusion criteria based on coexisting conditions. Corrective efforts must be maintained to ensure that a representative population of patients covering the entire age range is studied in the preauthorization phase, in accordance with international guidelines.³

Chronologic age alone is inadequate for characterizing the population enrolled in a clinical trial. Frailty is a predictor of clinical outcomes,⁴ and the reduction of frailty has benefits for individuals and society. The EMA is exploring the possibility of reaching a consensus on an operational definition of frailty and tools for evaluating it that could be used for clinical research and to guide therapeutic decisions.

Medications commonly prescribed to treat other conditions

ORIGINAL ARTICLE

Fungal Infections Associated with Contaminated Methylprednisolone in Tennessee

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ABSTRACT

BACKGROUND

From the Tennessee Department of Health, Nashville (M.A.K., D.R.R., A.D.W., J.W., M.L.K., J.B., B.E.B., J.R.D., E.P.M., J.Y.M., J.D., T.F.J.); and the Division of Healthcare Quality Promotion (D.B.N., M.E.W., M.K.S.), Epidemic Intelligence Service, Scientific Education and Professional Development Program Office (D.B.N., J.B., R.M.S.), and the Division of Foodborne, Waterborne, and Environmental Diseases (B.J.P., R.M.S.), Centers for Disease Control and Prevention, Atlanta. Address reprint requests to Dr. Kainer at the Division of Communicable and Environmental Diseases and Emergency Preparedness, Tennessee Department of Health, 1st Fl., Cordell Hull Bldg., 425 5th Ave. N., Nashville, TN 37243, or at marion.kainer@tn.gov.

We investigated an outbreak of fungal infections of the central nervous system that occurred among patients who received epidural or paraspinal glucocorticoid injections of preservative-free methylprednisolone acetate prepared by a single compounding pharmacy.

METHODS

Case patients were defined as patients with fungal meningitis, posterior circulation stroke, spinal osteomyelitis, or epidural abscess that developed after epidural or paraspinal glucocorticoid injections. Clinical and procedure data were abstracted. A cohort analysis was performed.

RESULTS

The median age of the 66 case patients was 69 years (range, 23 to 91). The median time from the last epidural glucocorticoid injection to symptom onset was 18 days (range, 0 to 56). Patients presented with meningitis alone (73%), the cauda equina syndrome or focal infection (15%), or posterior circulation stroke with or without meningitis (12%). Symptoms and signs included headache (in 73% of the patients), new or worsening back pain (in 50%), neurologic symptoms (in 48%), nausea (in 39%), and stiff neck (in 29%). The median cerebrospinal fluid white-cell count on the first lumbar puncture among patients who presented with meningitis, with or without stroke or focal infection, was 648 per cubic millimeter (range, 6 to 10,140), with 78% granulocytes (range, 0 to 97); the protein level was 114 mg per deciliter (range, 29 to 440); and the glucose concentration was 44 mg per deciliter (range, 12 to 121) (2.5 mmol per liter [range, 0.7 to 6.7]). A total of 22 patients had laboratory confirmation of *Exserohilum rostratum* infection (21 patients) or *Aspergillus fumigatus* infection (1 patient). The risk of infection increased with exposure to lot 06292012@26, older vials, higher doses, multiple procedures, and translaminal approach to epidural glucocorticoid injection. Voriconazole was used to treat 61 patients (92%); 35 patients (53%) were also treated with liposomal amphotericin B. Eight patients (12%) died, seven of whom had stroke.

CONCLUSIONS

We describe an outbreak of fungal meningitis after epidural or paraspinal glucocorticoid injection with methylprednisolone from a single compounding pharmacy. Rapid recognition of illness and prompt initiation of therapy are important to prevent complications. (Funded by the Tennessee Department of Health and the Centers for Disease Control and Prevention.)

*The members of the Tennessee Fungal Meningitis Investigation Team are listed in the Supplementary Appendix, available at NEJM.org.

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MORE THAN 500,000 EPIDURAL GLUCOCorticoid injections are administered in the United States each year in the Medicare population alone.¹ Complications after epidural glucocorticoid injections are rare; when complications do occur, the most common are epidural abscesses and meningitis due to bacterial pathogens, with the complications frequently occurring in immunosuppressed persons.²⁻⁶ Infectious disease outbreaks associated with epidural glucocorticoid injections have rarely been reported.^{3,5,7}

Fungal infections of the central nervous system are also uncommon and typically occur in immunosuppressed persons. Outbreaks of fungal meningitis after epidural or spinal injection are extremely rare; an outbreak of *Exophiala dermatitidis* meningitis in 2002 associated with contaminated methylprednisolone acetate prepared at a compounding pharmacy affected five patients.³ An outbreak of *Aspergillus fumigatus* meningitis associated with contaminated needles used for epidural anesthesia after the Indian Ocean tsunami affected five patients.^{8,9} *Exserohilum* species are environmental fungi common in grass and soil but have rarely been identified as human pathogens.¹⁰⁻¹³

We report preliminary results from Tennessee of an ongoing multistate investigation of fungal infections associated with preservative-free methylprednisolone acetate produced at a single compounding pharmacy.

METHODS

SURVEILLANCE

The Tennessee Department of Health (TDH) conducts ongoing surveillance for health care–associated infections, including outbreaks. In response to a report of a single patient in whom aspergillus meningitis developed after a recent epidural injection, active surveillance for additional case patients was performed. Hospitals, laboratories, and medical providers performing such procedures were asked to report to the TDH all possible cases of sterile-site fungal infections after epidural injections. Pharmacy records with information on the manufacture and distribution of the implicated product were obtained, and all patients reported by medical facilities as having received potentially contaminated product were actively contacted.

CASE PATIENTS

Case patients were defined as persons who had fungal meningitis or nonbacterial and nonviral meningitis of subacute onset, posterior circulation stroke when no cerebrospinal fluid was obtained (with no other obvious cause of stroke such as dissection of vertebral artery or cardioembolic source), or spinal or paraspinal osteomyelitis or epidural abscess at the site of injection, after an epidural or paraspinal glucocorticoid injection that was administered after May 21, 2012, in Tennessee.¹⁴ Cerebrospinal fluid, isolates, and tissue obtained from clinical specimens were sent to the Centers for Disease Control and Prevention (CDC) for identification of the pathogen with the use of polymerase chain reaction (PCR) amplification of fungal DNA and genomic sequencing.¹⁵ (PCR for fungal detection is a research test. The test has not been cleared or approved by the Food and Drug Administration [FDA]. The performance characteristics have not been established. The results of this test should not be used for the diagnosis, treatment, or assessment of patient health or management.)

For patients meeting the case definition, detailed information was obtained from medical chart reviews and interviews with the patients, their families, and physicians. Data were abstracted with the use of a standardized form that included information on demographic characteristics, symptoms, results of laboratory tests, treatment, and outcomes. For all patients who had received an epidural or paraspinal glucocorticoid injection at one of the three clinics that had received methylprednisolone from the same compounding pharmacy, information on patient characteristics, the type and date of the procedure, the personnel involved, the supplies and equipment used, and the medications administered was also collected. Since medication lot numbers were not recorded in patient clinic records, clinic protocols and invoices were evaluated to determine the probable lot used for each procedure. We determined the lots for each procedure by working back from the remaining vials in the clinic and using data collected on the volume used during each procedure. Lot assignment had to be estimated for our calculations and therefore was not considered authoritative.

STATISTICAL ANALYSIS

A cohort analysis was performed of all patients who had undergone epidural or paraspinal glucocorticoid injection procedures at a single clinic (Clinic A) since July 1, 2012, to assess for risk factors for infection. We performed analyses on both the patient and procedure level, since many patients had undergone multiple procedures. We excluded patients whose case status was under investigation. We stratified exposures according to the assigned medication lot and the vial age (defined as the number of days from lot production to injection). Patient age was analyzed as a dichotomous variable on the basis of the median age of 61 years. We evaluated the risk of infection by developing a logistic-regression model that included the age and sex of the patient, the cumulative dose of methylprednisolone according to the vial age (in 15-day increments) and lot, the procedure approach (translaminar vs. other), and the use or nonuse of contrast material. This model excluded procedures that were performed on days on which two different lots could have been used.

The data were analyzed with the use of SAS software, version 9.3. Fisher's exact test or the Mantel-Haenszel chi-square statistic was used for categorical variables, and Student's t-test or Wilcoxon rank-sum test was used for continuous variables. All data were analyzed as of October 19, 2012. This investigation was considered to be a public health response and was not considered to be research that was subject to approval by an institutional review board or that required written informed consent from patients.

RESULTS

INITIAL INVESTIGATION

On September 18, 2012, an astute clinician reported to the TDH a case of *A. fumigatus* meningitis in an immunocompetent adult after an epidural glucocorticoid injection at Clinic A; this report prompted an epidemiologic investigation.¹⁶ Two days later, active surveillance identified two additional cases of meningitis of unknown cause in hospitalized immunocompetent adults who had also recently received an epidural glucocorticoid injection at Clinic A; the CDC was notified of the TDH investigation. On-site review of Clinic A, which had closed voluntarily, revealed no obvious source of environmental contamination, such as recent construction or water damage, or relevant

lapses in sterile technique. By September 25, a total of eight potential case patients (including the index patient) at Clinic A were identified; the patients had undergone epidural glucocorticoid injections on separate days and different times of the day.

Multiple common products had been used for all the patients. These included a commercially available epidural procedure tray, povidone-iodine, lidocaine, and single-dose vials containing 80 mg per milliliter of preservative-free methylprednisolone acetate from the New England Compounding Center (NECC, Framingham, MA). As specified in the package instructions, all products were stored at room temperature. The TDH contacted the Massachusetts Department of Health on September 24 to express concern and to obtain a distribution list of facilities that had received methylprednisolone from NECC in order to assist with enhanced case finding. On September 25, the TDH, in collaboration with the Massachusetts Department of Public Health, the Massachusetts Board of Registration in Pharmacy, and the CDC, contacted the compounding pharmacy, requested a list of facilities that had received methylprednisolone, and determined that the pharmacy had not received any reports of adverse events. The FDA was also notified about the ongoing public health investigation.

On September 26, 2012, NECC, in consultation with the Massachusetts Board of Registration in Pharmacy, issued a voluntary recall of the three lots of methylprednisolone that had been associated with case-patient exposure (05212012@68, 06292012@26, and 08102012@51); vials from these lots had been distributed to 76 facilities in 23 states. An analysis of Clinic A data identified no important clinic-related risk factors for infection (e.g., with respect to the day and time of the procedure, the room in which the procedure was performed, or the provider) but did indicate a relationship between increased exposure to methylprednisolone from this pharmacy and the likelihood of becoming a case patient. Active surveillance was conducted in the two additional clinics in Tennessee that had received medication from at least one of these three lots. The TDH activated emergency operations with the use of a statewide incident command structure and initiated a large-scale investigation, including personal contact and tracking of exposed patients. On October 4, 2012, the FDA announced that on microscopic examination,

the agency had detected fungal contamination of unopened vials of methylprednisolone (lot 08102012@51) that had been collected from NECC.¹⁷

DESCRIPTION OF CASE PATIENTS

In the three clinics in Tennessee that had received methylprednisolone from NECC, 1009 patients had received epidural or paraspinal glucocorticoid injections with methylprednisolone from one or more of the three recalled lots. A total of 66 of these patients (7%) met the case definition through October 19, 2012. In the index patient, culturing of the cerebrospinal fluid yielded *A. fumigatus*; in

21 patients *Exserohilum rostratum* was identified from cultures of cerebrospinal fluid, tissue, or abscess fluid (6 patients) or was detected by means of PCR in cerebrospinal fluid (14 patients) or tissue (1 patient). Although all the patients had received epidural or paraspinal glucocorticoid injections at one of three clinics in Tennessee, case patients presented in one of seven states, and 2 case patients were outside the United States, when symptoms developed.

The median age of the patients was 69 years (range 23 to 91), and 71% were women (Table 1). A total of 124 procedures were performed in the 66 case patients between July 3, 2012, and Sep-

Table 1. Demographic Characteristics of the Patients and Signs and Symptoms at First Admission.

Variable	Case Patients with Stroke (N=13)	Case Patients without Stroke (N=53)	P Value*	All Case Patients (N=66)
Demographic characteristics				
Age — yr			0.08	
Median	72	67		69
Range	56–91	23–90		23–91
Female sex — no. (%)	11 (85)	36 (68)	0.32	47 (71)
White race — no. (%)†	11 (85)	42 (79)	1.00	53 (80)
Signs and symptoms at first admission — no. (%)				
Fever‡	3 (23)	20 (38)	0.52	23 (35)
Headache	9 (69)	39 (74)	0.74	48 (73)
Nausea	7 (54)	19 (36)	0.34	26 (39)
Vomiting	4 (31)	12 (23)	0.72	16 (24)
Slurred speech	2 (15)	0	0.04	2 (3)
Confusion	2 (15)	1 (2)	0.10	3 (5)
Stiff neck	5 (38)	14 (26)	0.50	19 (29)
New or worsening neck pain	2 (15)	10 (19)	1.00	12 (18)
New or worsening back pain	4 (31)	29 (55)	0.21	33 (50)
Numbness in lower extremities	0	6 (11)	0.58	6 (9)
Vertigo	5 (38)	6 (11)	0.03	11 (17)
New fall or increased falling	6 (46)	3 (6)	0.002	9 (14)
Self-reported hand or leg weakness	2 (15)	3 (6)	0.25	5 (8)
Sensitivity to light	0	6 (11)	0.59	6 (9)
Meningeal signs	2 (15)	8 (15)	1.00	10 (15)
Altered mental status	3 (23)	2 (4)	0.05	5 (8)
Limb weakness on examination	6 (46)	3 (6)	0.002	9 (14)
Facial droop	2 (15)	1 (2)	0.10	3 (5)

* The P values are for the comparison between patients with stroke and those who did not present with stroke or in whom stroke did not develop.

† Race was determined from information in the medical record.

‡ The presence of fever was self-reported.

Table 2. Cerebrospinal Fluid Findings from the First Lumbar Puncture among Patients with Meningitis.*

Finding	Patients in Whom Meningitis Developed by October 19, 2012 (N=59)	Patients Who Presented with Meningitis with or without Stroke or Focal Infection (N=57)
	<i>median (range)</i>	
White-cell count (cells/mm ³)	534 (4–10,140)	648 (6–10,140)
Granulocytes (%)	76 (0–97)	78 (0–97)
Protein (mg/dl)	114 (29–440)	114 (29–440)
Glucose (mg/dl)	45 (12–121)	44 (12–121)

* Meningitis developed in some patients later, and the original findings of cerebrospinal fluid testing were within normal limits. A cerebrospinal fluid white-cell count of greater than 5 per cubic millimeter was considered to be indicative of pleocytosis and together with headache, fever, or neck stiffness was considered to indicate meningitis. To convert the values for glucose to millimoles per liter, multiply by 0.05551.

tember 26, 2012: 110 were lumbar epidural injections, 12 were cervical epidural injections, 1 was a sacroiliac-joint injection, and 1 was recorded as “other.” The median time from the last injection to symptom onset was 18 days (range 0 to 56). All the patients presented with one of three primary syndromes: 47 (71%) had meningitis alone, 11 (17%) had the cauda equina syndrome or focal infection near the injection site (4 of whom had documented epidural abscess), with or without meningitis, and 8 (12%) had posterior circulation stroke (with or without meningitis). Symptoms on admission included headache in 48 patients (73%), with 20 of these (43%) reporting severe headache. Other symptoms included new or worsening back pain in 33 patients (50%), nausea in 26 (39%), and stiff neck in 19 (29%).

Other neurologic symptoms were seen in 32 patients (48%) and included vertigo in 11 patients (17%) and new or increasing falls in 9 (14%). Ten patients (15%) had symptoms suggestive of the cauda equina syndrome: new urinary incontinence or urinary retention in 6 (9%), gluteal or radiating leg pain in 3 (5%), and saddle anesthesia in 3 (5%). Signs on admission included fever (temperature >38°C) in 4 patients (6%), nuchal rigidity in 10 (15%), and altered mental status in 5 (8%). Results of a detailed neurologic examination were not recorded for many patients.

Lumbar puncture was performed within 24 hours after hospital admission in 50 patients (76%). The median time from the last epidural glucocorticoid injection to the lumbar puncture was 25 days (range, 18 to 36). The median cere-

brospinal fluid white-cell count on the first lumbar puncture among patients who presented with meningitis, with or without stroke or focal infection, was 648 per cubic millimeter (range, 6 to 10,140), with 78% granulocytes (range, 0 to 97); the protein level was 114 mg per deciliter (range, 29 to 440); and the glucose concentration was 44 mg per deciliter (range, 12 to 121) (2.5 mmol per liter [range, 0.7 to 6.7]) (Table 2). The results from the first lumbar puncture among patients in whom meningitis developed at any time (until October 19) are shown in Table 2. Initial imaging results identified abnormalities possibly related to fungal infection in 8 of 27 patients (30%) who underwent magnetic resonance imaging (MRI) of the head and in 16 of 35 (46%) who underwent MRI of the spine. Abnormalities included findings consistent with arachnoiditis, neuritis, epidural abscess, psoas or paraspinal muscle abscess, ventriculitis, enhancement of the meninges, and subarachnoid hemorrhage or infarcts involving the thalamus, pons, midbrain, or cerebellum.

The 13 patients who had a stroke did not differ significantly from those who did not have a stroke with respect to the site of injection (lumbar, cervical, sacroiliac-joint, or other), the time from symptom onset to lumbar puncture (7 days [range, 0 to 43] and 8 days [range, 0 to 39], respectively; $P=0.76$), or the time from symptom onset to initiation of intravenous antifungal therapy (12 days [range, 0 to 44] and 10.5 days [range, 0 to 39], respectively; $P=0.65$). Eight of these 13 patients initially presented with posterior circulation stroke; of these, 4 had onset of symptoms less than 48 hours before admission. The remaining 5 patients had a posterior circulation stroke during hospitalization; none of these 5 patients had received antifungal therapy on admission. These 5 patients presented with meningitis early during the outbreak before a fungal cause was clearly established. We compared these 5 patients with the 46 patients who did not have a stroke at admission and who received antifungal therapy. There was no significant difference with respect to the median time from onset of symptoms to the initiation of intravenous antifungal therapy (12 days [range, 10 to 26] and 10.5 days [range, 0 to 39], respectively; $P=0.33$); however there was a significant difference in the median time from admission to initiation of intravenous antifungal therapy (6 days [range, 3 to 23] as compared with 1 day [range, 0 to 31];

P=0.006). Three patients presented with posterior circulation strokes early in the outbreak and did not undergo a lumbar puncture before death to confirm meningitis. No alternate explanation for stroke in this vascular territory was found (e.g., no cardioembolic source or evidence of dissection of vertebral artery).

A total of eight patients (12%) died. Seven of the eight deaths (88%) occurred in patients who had a stroke. The other patient who died initially presented after 2 weeks of having nonspecific symptoms that developed into radicular pain in a saddle distribution, headache, and fever. Imaging revealed extradural and intradural abscesses; the results of a lumbar puncture showed meningitis. He was given liposomal amphotericin B and voriconazole, with resulting improvement in cerebrospinal fluid variables but paroxysmal atrial fibrillation developed, and he had a fatal arrest.

Voriconazole was initially administered in 61 of the patients (92%); 35 of those patients (57%) were also treated with liposomal amphotericin B. The median time from symptom onset to initiation of voriconazole therapy was 10 days (range, 0 to 44), and the median time from symptom onset to initiation of amphotericin B therapy was 14 days (range, 0 to 44). Serum drug levels were tested in 29 of the patients who received voriconazole (48%). The median time from initiation of voriconazole therapy to the first test for serum voriconazole level was 8 days (range, 3 to 21). Initial levels were greater than 2 μg per milliliter in 24 patients (83%); of these, 7 (29%) had levels higher than 6 μg per milliliter. Treatment with liposomal amphotericin B was discontinued in 34 patients (97%) after a median of 4 days (range, 1 to 25), primarily because of renal toxic effects. In these patients, the glomerular filtration rate decreased from baseline by a median of 31% (with the change ranging from 28% to -88%).

ASSESSMENT OF RISK FACTORS FOR INFECTION

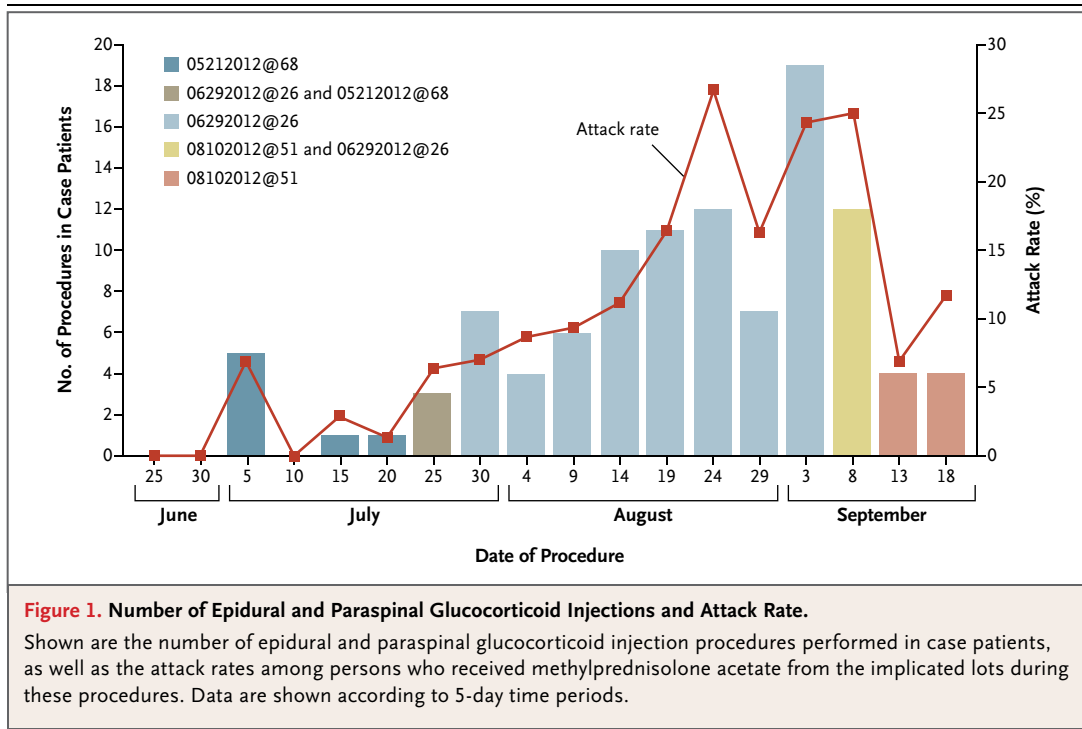
Clinic A used 1663 vials of methylprednisolone from the three recalled lots during the outbreak period (83% of the vials they had received). Clinic B used 189 vials (86%), and Clinic C used 211 vials (70%). For the cohort analysis, we abstracted data on 817 patients who underwent a total of 1335 procedures at Clinic A between July 1, 2012, and September 20, 2012. The procedures included 779 translaminar epidural glucocorticoid in-

jections (23 thoracic, 146 cervical, and 610 lumbar), 368 transforaminal epidural glucocorticoid injections, 132 caudal injections, 31 facet-joint injections, 17 sacroiliac-joint injections, and 8 other injections. A patient-level cohort analysis revealed that all the patients had received methylprednisolone; no cases of fungal infection occurred among 124 persons who underwent procedures without methylprednisolone.

In a univariate analysis of patients in this cohort with known case status (including those who did not receive methylprednisolone) (Table 3), patients who had multiple procedures had an increased risk of a fungal infection (11.5% [41 of 355 patients] vs. 4.0% [17 of 425 patients]; relative risk, 2.9; 95% confidence interval [CI], 1.7 to 5.0). The attack rates were 5.0%, 8.4%, 13.7%, and 14.3% among those who had undergone one, two, three, and four procedures, respectively. Patients who had received at least one epidural glucocorticoid injection with the use of a translaminar approach were more likely to become case patients than were those who had never been treated with a translaminar approach (9.6% [47 of 488 patients] vs. 3.8% [11 of 291 patients]; relative risk, 2.5; 95% CI, 1.3 to 4.8). Women were nearly twice as likely to become case patients as were men (9.5% [41 of 431 patients] vs. 4.9% [17 of 346 patients]; relative risk, 1.9; 95% CI, 1.1 to 3.4). Patients older than 60 years of age were four times as likely to become case patients as were those 60 years of age or younger (11.8% [47 of 400 patients] vs. 2.9% [11 of 380 patients]; relative risk, 4.1; 95% CI, 2.1 to 7.7). There were no significant associations between infection and factors related to physicians, technicians, operating room, operating room time, time spent with physician or techni-

Table 3. Univariate Patient-Level Analysis of Risk Factors among Clinic A Patients with Known Case Status.

Risk Factor	Cases	Non-Cases	Relative Risk
			(95% CI)
	no. of patients/total no.		
Female sex	41/431	17/346	1.9 (1.1–3.4)
Age >60 yr	47/400	11/380	4.1 (2.1–7.7)
Translaminar epidural glucocorticoid injection	47/488	11/291	2.5 (1.3–4.8)
Multiple procedures	41/355	17/425	2.9 (1.7–5.0)
Methylprednisolone, lot 06292012@26, vial >50 days old	29/149	6/190	6.2 (2.6–14.5)



cian, time of day, day of the week, or cervical versus lumbar sites.

Among 656 persons who received methylprednisolone at Clinic A, infections developed in 58 (9%). The risk of disease among patients who had any exposure to the 06292012@26 lot was significantly greater than the risk among those who had exposure to the 05212012@68 lot or the 08102012@51 lot alone: infections developed in 51 of 424 patients (12%) who received methylprednisolone from the 06292012@26 lot as compared with 7 of 231 (3%) who had received injections from one of the other lots (relative risk, 4.0; 95% CI, 1.8 to 8.6). Figure 1 shows the attack rate on a procedure level, according to lot number, over time. Among patients receiving methylprednisolone from the 06292012@26 lot, exposure to only older vials (vial age >50 days) was associated with higher attack rates than was exposure to only newer vials, with infections developing in 29 of 149 patients exposed to methylprednisolone from older vials (19%) as compared with infections in 6 of 190 (3%) exposed to methylprednisolone from newer vials (relative risk, 6.2; 95% CI, 2.6 to 14.5). Among recipients of medication from the older vials from lot 06292012@26, the attack rates after injection of 40 to 80 mg, 120 to 160 mg, and more than 160 mg were 15% (11 of 73 patients),

19% (26 of 138), and 35% (8 of 23), respectively.

We performed a multivariate analysis confined to patients who received methylprednisolone with a known case status and excluded time periods of potential lot overlap. This analysis confirmed the following risk factors: age older than 60 years (adjusted odds ratio, 4.01; 95% CI, 1.95 to 8.24); female sex (adjusted odds ratio, 2.56; 95% CI, 1.29 to 5.12); and cumulative dose of 06292012@26 lot injected 45 to 60 days and more than 60 days after production, in 40-mg increments (adjusted odds ratio, 1.29; 95% CI, 1.02 to 1.63 and adjusted odds ratio 1.65; 95% CI, 1.29 to 2.11, respectively). Two factors improved the fit of the model, but were not significant: a translaminar approach (adjusted odds ratio, 2.01; 95% CI, 0.96 to 4.23) and the use of contrast material (adjusted odds ratio, 0.23; 95% CI, 0.05 to 1.14).

DISCUSSION

The case cluster described here is part of the ongoing multistate outbreak of fungal infections associated with epidural, paraspinal, and peripheral-joint glucocorticoid injections. On October 18, the CDC and FDA announced that *E. rostratum* had been identified in unopened vials of methyl-

prednisolone from the 08102012@51 lot; exserohilum was also subsequently identified in the 06292012@26 lot.¹⁶ The outbreak is ongoing and involves multiple states¹⁴; morbidity and mortality have been high. Rapid recognition and evaluation of infections after a patient's exposure to implicated methylprednisolone are critical, and appropriate therapy should be initiated promptly.

We found a strong association between the age of the methylprednisolone vials and the rate of infection in one clinic. One possible explanation for this observation is that the level of contamination in the vials may have increased over time, with subsequent higher fungal burdens present in older vials. Injectable, preservative-free glucocorticoid preparations have been shown to be suitable media to support or increase the growth of pathogenic fungi, including *A. fumigatus*.^{3,18} We also describe the increased risk of infection associated with increasing amounts of methylprednisolone administered. This may reflect exposure to an increasing amount of contaminant with increased volume of methylprednisolone administered. In addition, because the medication came in 80-mg vials, multiple injections or single injections with a dose of more than 80 mg increased the likelihood of exposure to at least one contaminated vial.

Among the most striking features of this outbreak are the high prevalence and anatomical location of strokes. Epidural glucocorticoid injections can lead to localized infection, and fungal pathogens can invade the dura, leading to meningitis and, in some patients, invasion of the posterior circulation vasculature leading to stroke, hemorrhage, or both.¹⁶ Stroke was seen more commonly early in the outbreak, with four patients presenting with stroke less than 48 hours after the onset of any symptoms. The incidence of stroke declined as diagnostic testing became more prevalent and aggressive and patients were identified earlier in their clinical course; stroke did not develop in any patients in this report in whom therapeutic doses of antifungal medications were instituted within 48 hours after the initial presentation.

In this series, the mortality associated with untreated *A. fumigatus* and *E. rostratum* meningitis was very high; all eight deaths in our series occurred in persons who received delayed, minimal, or no treatment. We found that the initial presenting symptoms were frequently mild and non-specific and often difficult to distinguish from

the chronic symptoms for which the epidural or paraspinal glucocorticoid injection was originally administered. Lumbar puncture performed promptly at the first suspicion of clinical illness allowed early identification of infection and prompt initiation of therapy.

Exserohilum species are environmental fungi that are common in grass and soil but have rarely been identified as human pathogens.¹⁰⁻¹³ Although uncertainty exists about the appropriate treatment of exserohilum infections,^{12,19} treatment recommendations have been developed by the CDC in response to this outbreak. These recommendations include treatment with voriconazole (at an initial dose of 6 mg per kilogram of body weight every 12 hours). The addition of liposomal amphotericin B can be considered in patients who present with severe disease or whose conditions deteriorate or do not improve with voriconazole alone.^{14,20} Voriconazole can cause substantial side effects, including hepatotoxic effects, rash, central nervous system toxic effects including visual disturbances and hallucinations, prolongation of the corrected QT interval, and drug interactions.²¹⁻²⁴ Serum voriconazole levels can be assessed as soon as the fifth day of treatment, with a suggested therapeutic range of 2 to 5 μg per milliliter.¹⁴ The use of liposomal amphotericin B was associated with decreasing renal function and early cessation of therapy in all but one of the patients in this series. Additional studies are needed to assess the best possible treatment.

There are several limitations of this investigation. First, the pathogen was laboratory-confirmed in only 22 patients at the time of the analysis. PCR assay was helpful in identifying the pathogen in several patients; however, the sensitivity of a fungal PCR assay is unknown. Second, there was a potential for misclassification of exposure to specific lots of medication. Third, because case patients continue to be identified, the overall estimates of risk and risk by lot may change over time. Fourth, we do not have long-term outcome data for many of the patients in this series, data that will be important in developing more definitive treatment recommendations. Fifth, our attack rates represent cumulative risk at the time of last injection; as the time from injection increases, the current risk of an infection decreases dramatically. Sixth, our analysis was conducted on data available as of October 19, 2012, and the clinical status of

patients, including complications, continues to evolve. Finally, the results of the investigation in Tennessee may not be generalizable to other states because of differences in lot exposure and procedure types.

Pharmaceutical compounding refers to the combining, mixing, or altering of ingredients of a drug by a licensed pharmacist to produce a drug that is tailored to an individual patient's medical needs, on the basis of a valid prescription from a licensed medical practitioner. There are few reliable data on the prevalence of compounding, but it has been estimated that 0.25% to more than 2% of dispensed prescriptions in the United States are compounded drugs.¹⁴ Under certain conditions, compounding may serve an important public health benefit by providing access to medications tailored to the needs of individual patients when a commercially available product is unavailable; however, compounded drugs are not approved by the FDA and should not be confused with generic drugs. Unlike brand name and generic drugs, all of which must be approved by FDA before marketing, compounded drugs are not reviewed and approved by the FDA; therefore, their safety, efficacy, quality, and conformance with federal manufacturing standards have not been established. The current outbreak is only the most recent example of deaths and serious adverse events associated with drugs made by a compounding pharmacy.^{3,5,25-28} The regulatory authority of the FDA over compounding pharmacies is different and more limited

than is its authority over pharmaceutical manufacturers; states license pharmacies and have primary responsibility for the oversight of the day-to-day operations of compounding pharmacies.

An aggressive public health response to a single report of an unusual infection resulted in the identification of a multistate outbreak of fungal infections and the rapid recall of the implicated product involved. The investigation of this outbreak in Tennessee required a close and collaborative approach between the public health system and the medical community. Maintaining a strong public health infrastructure is critical to ensuring that there is capacity to investigate such outbreaks quickly and effectively.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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