Early Clinical Observations in Prospectively Followed Patients With Fungal Meningitis Related to Contaminated Epidural Steroid Injections

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Background: Administration of epidural steroid injections (ESIs) with contaminated methylprednisolone resulted in an outbreak of fungal meningitis in many locations in the United States.

Objective: To characterize early clinical findings and initial response to treatment.

Design: Case series with standardized observation studied from 4 October to 31 October 2012.

Setting: An 800-bed hospital in Virginia.

Patients: 172 patients who presented to the hospital with exposure to contaminated ESI.

Intervention: Standardized approach to screening, case definition, treatment, and data collection.

Measurements: Clinical findings, cerebrospinal fluid (CSF) values, magnetic resonance imaging (MRI), serum and CSF voriconazole concentrations, and clinician assessment of response to therapy.

Results: Of 172 patients presenting to the hospital who had had ESI, 131 had lumbar puncture because of symptoms or signs consistent with central nervous system disease. Twenty-five (19%) had neutrophilic meningitis. All were started on voriconazole therapy alone. Three patients developed stroke during treatment. Ten patients had arachnoiditis, another had an epidural abscess, and 9 had urine retention. Fifteen continued to receive voriconazole, and 10 were switched to amphotericin B. Cerebrospinal fluid leukocyte counts began to decrease by day 13 of treatment. Findings on MRI included ventriculitis, leptomeningeal enhancement, infarction, hemorrhage, and arachnoiditis. Serum voriconazole levels varied, and CSF concentrations of voriconazole were approximately 50% of those of serum. Exserohilum rostratum and Cladosporium species have been cultured.

Limitations: This is an observational study of an evolving outbreak. Not all exposed patients presented for evaluation. Follow-up is too short to determine final outcomes.

Conclusion: Meningitis after receipt of contaminated ESI has been diagnosed in many exposed patients presenting to 1 hospital. Most patients have improved on receipt of empirical voriconazole therapy. The full natural history and long-term sequelae of this infection are currently unknown.

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For author affiliations, see end of text.

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On 21 September 2012, the Tennessee Department of Health notified the Centers for Disease Control and Prevention (CDC) of cases of fungal meningitis. On 4 October 2012, the CDC issued the first alert of an outbreak of fungal meningitis linked to contaminated, injectable, preservative-free methylprednisolone acetate used for epidural steroid injections (ESIs) (1).

In Virginia, only 2 facilities within 30 miles of each other used the now-recalled product. An estimated 673 persons received injections of the recalled product within the Roanoke and New River Valley areas, and most have presented to 2 hospitals in the state.

The predominant causative microbe seems to be Exserohilum rostratum, a dematiaceous (black-pigmented) fungus that exists as a mold. Although dematiaceous fungi are ubiquitous, central nervous system (CNS) infection with these organisms is rare (2). Revankar and colleagues (3) reviewed 101 reported cases that occurred worldwide over a 37-year period. Most infectious disease physicians and neurologists have never seen a case.

We report the clinical presentation, treatment, and clinical course in patients diagnosed with meningitis after lumbar puncture (LP) for exposure to contaminated ESI at 1 Virginia hospital.

METHODS

The hospital established a dedicated hotline on 4 October 2012 to direct the public and health care providers because of an inundation of telephone calls about the outbreak. Hotline responders followed a screening algorithm, and the hospital developed a protocol for evaluating patients presenting to the emergency department (ED). Patients with the correct exposure history (defined as receipt of an ESI from either facility that used the contaminated product) and headache, stiff neck, or pain at the injection site had LP, generally after brain imaging.

Appendix Table 1 (available at www.annals.org) lists the studies on the cerebrospinal fluid (CSF) that were done...
on all patients who had LP. All hospitalists and house officers received a digital copy of the protocol outlining which studies to do and when to do them. We defined meningitis as CSF with a leukocyte count greater than 10 cells/mL. Stable patients who did not meet the criteria for meningitis were discharged from the ED and are being followed by infection preventionists and infectious disease clinic nurses on a weekly basis via telephone. These patients were advised on the signs and symptoms for which to be watchful and were told to contact the hotline at any time.

The infectious disease service directed management of all patients with meningitis. Patients initially received intravenous voriconazole at a dosage of 6 mg/kg every 12 hours and were continued on this dose. A switch from voriconazole to amphotericin B was made in the event of worsening clinical signs and symptoms, worsening CSF values, worsening brain magnetic resonance imaging (MRI) results, or intolerable hallucinations. We did not use combination voriconazole plus amphotericin because of theoretical antagonism. Repeated LPs were done on days 4 or 5 of therapy and weekly thereafter on the basis of previously published studies that investigated the treatment of cryptococcal meningitis (4–6).

We did not administer anticoagulation for routine prophylaxis for deep venous thrombosis because of the potential angioinvasive nature of the fungus (7, 8). Patients requiring anticoagulation received a monitored heparin drip; anticoagulation could quickly be reversed, if necessary, by cessation of the drip. Blood patches for post-LP headaches were not done because blood is an excellent culture medium and patients who did not have meningitis would then have altered CSF values, complicating diagnostic interpretation of subsequent CSF results.

Serum was drawn to measure trough voriconazole levels within 60 minutes of the next scheduled 12-hourly dose on day 5 of treatment and then weekly. We measured CSF voriconazole levels with subsequent LPs.

Patients were switched to oral voriconazole after improvement in clinical and CSF values but were not discharged from the hospital until oral voriconazole was available for home therapy. The oral voriconazole dosage was the same as the patient’s most recent dosage of intravenous voriconazole—usually 6 mg/kg every 12 hours, unless previously adjusted for high serum concentrations. At the time of this report, all discharged patients continue to receive oral voriconazole with weekly follow-up in a “fungal meningitis clinic” within the infectious disease outpatient clinic.

Daily listings of patients from the ED, including line listing of CSF test results, drug levels, liver function test results, serum creatinine levels, and information obtained from the medical chart, are entered into a spreadsheet for real-time analysis and decision making. We summarized CSF laboratory values with descriptive statistics and non-parametric testing by using the Wilcoxon signed-rank test and the Wilcoxon rank-sum test in SAS, version 9.1.3 (SAS Institute, Cary, North Carolina).

**Context**

In the autumn of 2012, an outbreak of fungal meningitis caused by contaminated epidural steroid injections occurred in the United States.

**Contribution**

Staff at a hospital in Virginia rapidly set up a telephone screening program for patients presenting with a history of possible exposure to the contaminated product. They developed uniform protocols for diagnosis, treatment, and follow-up in real time, based on evolving information. Here, they report early observations on patients found to have meningitis.

**Caution**

Patients continue to be followed, and long-term outcomes, including optimum treatment duration, are unknown.

**Implication**

A successful response to a 2012 fungal meningitis outbreak was achieved by rapid mobilization at the hospital level.

—The Editors

**RESULTS**

One hundred seventy-two patients presented to the ED, either on their own or at the suggestion of hotline personnel. Eighty-five percent of those presenting to the ED did so between 4 October and 23 October 2012. The incubation period between the first or only ESI to onset of symptoms ranged from 1 to 71 days, with a mean of 23 days and a median of 19 days. The incubation period was counted from the first ESI from a contaminated lot. Nine of 25 (36%) patients with meningitis had more than 1 ESI.

One hundred thirty-one patients had LP; of these, 25 met the meningitis case definition of elevated CSF leukocyte count (>10 cells/mL) and were hospitalized (Figure 1). Meningitis was defined a priori as a CSF leukocyte count greater than 10 cells/mL, but the lowest leukocyte count among our patients was 28 cells/mL.

Two additional patients were not included in this report. One presented moribund with a subarachnoid hemorrhage and did not have LP until the day of death, 6 days into hospitalization. Diagnosis was retrospective. The second patient transferred to our facility from another hospital for ventriculostomy and died on the day of admission.

**Table 1** summarizes the differences in CSF values for patients who were exposed and had an LP and those who
did and did not have meningitis, according to our case definition. Large differences were seen among the CSF leukocyte count and protein and glucose levels ($P < 0.001$). Cerebrospinal fluid erythrocyte count seemed to be more frequently elevated in patients with meningitis, although the comparison did not reach statistical significance.

All 25 patients meeting CSF leukocyte count criteria for meningitis had received 1 or more ESIs from lot 06292012 of the contaminated methylprednisolone, and 2 had also received ESIs from lot 08102012. No one who had received an ESI from lot 05212012 developed meningitis in our group. The 2 additional patients who presented to the hospital with stroke (1 diagnosed before recognition of the outbreak, and 1 transferred from another hospital) are not included in the analysis of those who received ESIs from lot 06292012.

All patients without meningitis had a negative result for Aspergillus on polymerase chain reaction (PCR). One patient without meningitis had a false-positive Aspergillus galactomannan level of 1.48 (a level <0.7 is negative) as determined by a subsequent negative culture and negative PCR result. This patient had normal CSF glucose and protein levels and a leukocyte count of zero. None of the patients with meningitis had a positive PCR result or galactomannan for Aspergillus. Eight of the 27 patients (25 reported here and 2 diagnosed retrospectively) had a positive PCR result for Exserohilum, 13 had a negative result, and 6 results are pending. Exserohilum PCR was done in the Fungus Reference Laboratory of the Mycotic Diseases Branch of the CDC. Two patients had Exserohilum on CSF culture. One had a negative PCR result and the other had a positive result.

Table 1. Comparison of Initial Cerebrospinal Fluid Values in Exposed Patients, With and Without Meningitis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Meningitis ($n=25$)</th>
<th>No Meningitis ($n=106$)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukocyte count, cells/mL</td>
<td>28–9080</td>
<td>1867</td>
<td>780</td>
</tr>
<tr>
<td>Erythrocyte count, cells/mL</td>
<td>0–2070</td>
<td>1262</td>
<td>52</td>
</tr>
<tr>
<td>Protein level, g/L</td>
<td>0.37–5.52</td>
<td>1.57</td>
<td>1.22</td>
</tr>
<tr>
<td>Glucose level, mmol/L</td>
<td>0.61–6.66</td>
<td>2.66</td>
<td>2.50</td>
</tr>
</tbody>
</table>

* Calculated by using the Wilcoxon rank-sum test.
† This patient had leukocyte and erythrocyte counts of zero but a glucose level of 0.67 mmol/L (12 mg/dL) at the first lumbar puncture. The patient was hospitalized overnight and received no therapy. At the repeated lumbar puncture 18 h later, the patient had a glucose level of 4.05 mmol/L (73 mg/dL) and was classified as "no meningitis."
PCR result for the fungus. Two other patients had Cladosporium on CSF culture, and one of them had a positive PCR result for Exserohilum.

**Clinical Presentation and Baseline Laboratory Results of Patients With Meningitis**

The age range of the 25 patients with meningitis was 32 to 92 years (mean, 63.2 years; median, 62 years). There were 12 women and 13 men. All of the women were white; 11 of the men were white, and 2 were black.

Two additional patients presented with stroke, and both died. One of these patients was hospitalized early in the course of the outbreak for obtundation with subarachnoid bleeding. The connection to the outbreak was made only in retrospect. The other was transferred from another facility for ventriculostomy necessitated by the stroke and died on the day of transfer. Information on the presenting signs and symptoms in the remaining 25 patients is presented in Table 2. These patients were alert and oriented on hospitalization and in moderate distress from headache. They described the headaches as the worst they had ever had—patients who had had migraines stated that the meningitis headache was much worse. Two of the 25 patients had symptoms but normal CSF values on initial LP and returned 11 and 12 days later with meningitis. Table 2 lists the symptoms and signs in order of frequency and baseline laboratory values.

The number of signs and symptoms per patient ranged from 2 to 6. Of the 25 patients with meningitis and 2 patients with stroke, 5 (18.5%) had a peripheral leukocyte count greater than 10,000 cells/mL.

**Brain Imaging Studies**

Twenty-three patients had brain MRI (Figure 2), with and without contrast, on hospitalization or shortly thereafter. Fourteen had normal findings, and 9 had abnormal findings. The most common abnormal finding was enhancement of the leptomeninges in 7 patients. Two of these involved the optic chiasm. Two patients had hemorrhagic infarctions, and 4 had evidence of ventriculitis.

Three patients with initially normal MRI findings had evidence of infarction in the pons, basal ganglia, or cerebellum that appeared after treatment. These changes in MRI findings were discovered when a new, subtle, unilateral facial droop was discovered on daily physical examination template.

Eighteen patients with severe back pain had MRIs of the spine (Appendix Figure 1, available at www.annals.org) that included the ESI site. Ten patients had arachnoiditis, and 1 had myelitis. The number of days of therapy before the development of back pain and the MRI ranged from 1 to 14. Another patient with meningitis had a soft-tissue abscess at the lumbar ESI site, which was surgically drained. Stains did not reveal hyphae, and cultures are pending. This patient had had normal findings on MRI of the spine. The abscess was discovered 25 days into treatment while the patient was still hospitalized.

**Treatment Regimens**

All patients with meningitis were started on intravenous voriconazole at a dosage of 6 mg/kg every 12 hours. We did not use combination intravenous voriconazole and amphotericin B because of theoretical antagonism. The 6-mg/kg dose was maintained until adverse effects, serum levels, or elevated liver enzyme levels necessitated a change. We used total body weight to dose voriconazole in non-obese patients and adjusted body weight for obese patients (body weight >100 kg). Voriconazole steady-state serum levels, which were measured via high-performance liquid chromatography (Quest Diagnostics, Madison, New Jersey), were available in 19 of the 25 patients (Figure 3) on day 5 of intravenous voriconazole dosing, with an average serum trough level of 5.7 μg/mL (range, <0.1 to 10.3 μg/mL). We made dosage changes on the basis of trough levels and serum drawn again on day 5 of the new dosing regimen. Serum levels of voriconazole in CSF were measured at random on repeated LP to ensure CNS penetration. Results were available in 5 of the 25 patients; the

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients, n (%)</th>
<th>Mean (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Symptom</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>25 (100)</td>
<td>–</td>
</tr>
<tr>
<td>Word-finding difficulty</td>
<td>18 (72)</td>
<td>–</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>17 (68)</td>
<td>–</td>
</tr>
<tr>
<td>Fever</td>
<td>16 (64)</td>
<td>–</td>
</tr>
<tr>
<td>Neck stiffness</td>
<td>15 (60)</td>
<td>–</td>
</tr>
<tr>
<td>Fatigue/malaise</td>
<td>14 (56)</td>
<td>–</td>
</tr>
<tr>
<td>Photophobia</td>
<td>10 (40)</td>
<td>–</td>
</tr>
<tr>
<td>Loss of appetite</td>
<td>10 (40)</td>
<td>–</td>
</tr>
<tr>
<td>Pain at injection site</td>
<td>8 (32)</td>
<td>–</td>
</tr>
<tr>
<td>Urine retention</td>
<td>8 (32)</td>
<td>–</td>
</tr>
<tr>
<td>Focal weakness</td>
<td>7 (28)</td>
<td>–</td>
</tr>
<tr>
<td>Gait disturbance</td>
<td>6 (24)</td>
<td>–</td>
</tr>
<tr>
<td>Sensory changes</td>
<td>5 (20)</td>
<td>–</td>
</tr>
<tr>
<td>Dizziness</td>
<td>3 (12)</td>
<td>–</td>
</tr>
</tbody>
</table>

| **Baseline laboratory values**  |                 |              |
| Leukocyte count, 1000 cells     | –               | 9.6 (5.1–28.3)|
| Sodium, mmol/L                  | –               | 138 (134–144)|
| Creatinine, μmol/L              | –               | 74.3 (36.2–187.4)|
| mg/dL                           | –               | 0.84 (0.41–2.12)|
| Albumin, g/L                    | –               | 40 (31–49)|
| Aspartate aminotransferase, U/L  | –               | 23 (11–104)|
| Alanine aminotransferase, U/L    | –               | 24 (6–72)|
| Alkaline phosphatase, μkat/L     | –               | 1.18 (0.43–4.39)|
| Total bilirubin, μmol/L          | –               | 6.3 (1.7–18.8)|
| mg/dL                           | –               | 0.37 (0.1–1.1)|
The average concentration was 3.7 μg/mL, and all samples had detectable voriconazole levels.

Of the 25 patients treated with voriconazole, 16 (64%) developed elevated aminotransferase levels, defined as an aspartate aminotransferase or alanine aminotransferase level greater than the upper limit of normal (per local laboratory standards) compared with baseline (Table 3). The mean time from the start of voriconazole treatment to abnormal aminotransferase levels was 9 days (range, 1 to 13 days). Elevated aminotransferase levels were not a cause for discontinuation of voriconazole therapy in any patient. To date, 5 of the 7 patients with elevated aminotransferase levels who were switched to amphotericin therapy (all for reasons other than hepatic toxicity) have had decreasing levels. Half of the patients treated with voriconazole also had hallucinations.

Fifteen of the 25 patients continue to receive voriconazole; in the other 10 patients, it was switched to intravenous amphotericin B desoxycholate because of worsening clinical symptoms or signs combined with worsening CSF values or new stroke (Appendix Table 2, available at www.annals.org). No patients were switched from voriconazole to amphotericin because of laboratory toxicity.

The average time to onset of increase in serum creatinine level was 5.5 days. Six patients were later changed from amphotericin B desoxycholate to liposomal amphotericin B because of concern about renal toxicity. With 2 exceptions, all patients who were switched to amphotericin B had improvement in clinical and CSF variables. One exception was patient 14 (Appendix Table 2), who had metal plates, mesh, and screws in the lumbar spine from previous surgery. The other, patient 22 (Appendix Table 2), had an increase in CSF leukocyte count of 74 cells/mL while receiving amphotericin B.
CSF Changes During Treatment

Twenty-five patients have reached the point of the second LP, and 19 have reached the third LP. A downward trend in total CSF leukocyte count was noted by day 13 of treatment, with a significant decrease by day 19 (Appendix Figure 2, available at www.annals.org). The shift from a predominance of neutrophils to lymphocytes occurred by day 6. There was not a significant difference between mean CSF levels of glucose and protein by day 13 of treatment.

Decision Variables for Discharge

Eight patients have been discharged. The decision to discharge was based on improvement in clinical signs and symptoms, stable neurologic findings, marked improvement in CSF values, home situation, and availability of oral voriconazole.

Follow-up at 1 to 3 Weeks

Patients discharged from the hospital are being seen in a clinic that was established for this purpose within the infectious disease clinic. Physical examinations, voriconazole levels, complete blood counts, and chemistry studies are done weekly. Repeated LPs are planned every 3 to 4 weeks until negative results are obtained. A standardized electronic medical record template has been established to help monitor clinical symptoms and laboratory values.

Patients who were able to remain on voriconazole alone are being discharged more rapidly than those who required switching to amphotericin B. Some of these patients are going to a rehabilitation facility for reconditioning and strengthening before going home.

Of the 8 patients discharged while receiving oral voriconazole, 1 has been rehospitalized and placed on intravenous amphotericin B. The others are stable, with the most common symptom being extreme fatigue.

DISCUSSION

Because of the very rare occurrence of phaeohyphomycotic infections of the CNS, little information is available in case reports and reviews (3, 10) to predict the clinical course of the infection or guide treatment. Many of the reported cases were fatal (11–13). The large number of patients now presenting with these infections provides an opportunity to fill information gaps and inform therapy. Even so, many questions remain unanswered.

After adjustment for lot number, preliminary case counts and exposures in Virginia suggest an attack rate of approximately 11%, but pooling of cases that are widely dispersed geographically will be needed to refine this estimate and to analyze risk factors predictive of meningitis development. Many questions remain about why some individuals develop CNS infections and others do not (14).

Many other exposed individuals continue to present with symptoms but have normal LPs. These patients will need to be followed carefully for an indeterminate duration.

The presenting symptoms and signs are typical of CNS infections. However, the incidence of arachnoiditis with signs and symptoms of the cauda equina syndrome seems to be higher than usual, perhaps due to the anatomical location of the ESI procedure.

Although the most common forms of fungal meningitis due to Cryptococcus neoformans and Coccidioides immitis present with a CSF lymphocytosis, the meningitis reported here has a neutrophilic predominance. This predominance shifts to lymphocytosis early in treatment, but not in all patients. Cerebrospinal fluid glucose and protein concentrations will need to be followed over time because no significant trend in change of these variables has occurred over the first 3 weeks of treatment.

Three of the 25 patients developed stroke while receiving treatment. Two patients who were not among the 25 reported here presented with stroke and died quickly. This suggests that Exserohilum is angioinvasive. In the patients reported here, no obvious correlation was found between

### Table 3. Adverse Events Associated With Intravenous Voriconazole

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>25</td>
</tr>
<tr>
<td><strong>Aminotransferase level</strong></td>
<td></td>
</tr>
<tr>
<td>No elevation</td>
<td>9 (36)</td>
</tr>
<tr>
<td>&gt;1.5 to &lt;2 times ULN</td>
<td>6 (24)</td>
</tr>
<tr>
<td>&gt;2 to &lt;3 times ULN</td>
<td>2 (8)</td>
</tr>
<tr>
<td>≥3 times ULN</td>
<td>8 (32)</td>
</tr>
<tr>
<td><strong>Hyponatremia</strong></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>13 (52)</td>
</tr>
<tr>
<td>Mild (130–134 mmol/L)</td>
<td>7 (28)</td>
</tr>
<tr>
<td>Moderate (120–129 mmol/L)</td>
<td>5 (20)</td>
</tr>
<tr>
<td>Severe (&lt;120 mmol/L)</td>
<td>0 (0)</td>
</tr>
<tr>
<td><strong>Hallucinations</strong></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>9 (36)</td>
</tr>
<tr>
<td>No</td>
<td>16 (64)</td>
</tr>
</tbody>
</table>

ULN = upper limit of normal.

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the presence and number of cells in the CSF and an abnormal finding on brain MRI. The high number of patients with word-finding difficulty is of interest, and further analysis of neurologic histories, examinations, and brain imaging will be done. Questions remain about the risk for long-term neurologic sequelae. Ten patients have arachnoiditis, and 1 patient developed a soft-tissue abscess well into treatment.

Two deaths occurred in this outbreak in Virginia (not included in this series). Both had autopsies, and brain findings are still pending. Autopsy findings will be critical in further defining the pathogenesis of the disease.

The index case of this outbreak reported from Tennessee was due to Aspergillus (15), but most microbiologically documented infections to date have involved Exserohilum, as was documented by culture in 2 of our cases (16, 17).

All of our patients initiated treatment with intravenous voriconazole as monotherapy. Most continue to receive voriconazole and are improving, albeit slowly. Adverse effects (an increase in liver aminotransferase levels or hyponatremia) of voriconazole did not necessitate a change in antifungal therapy in any patient. One patient did have intolerable hallucinations, leading to a switch from voriconazole to amphotericin. Trough levels of serum voriconazole should be followed, because many were greater than the accepted concentrations to avoid toxicity. Voriconazole undergoes significant saturable hepatic metabolism. Its pharmacokinetics are therefore nonlinear and dependent on the administered dose. Serum concentrations can vary substantially from one patient to the next and are affected by age, underlying liver function, genetic polymorphisms of CYP2C19, and drug–drug interactions (18, 19).

Other options for treatment need to be explored. In a study by da Cunha and colleagues (20), amphotericin B and the azoles itraconazole, posaconazole, and voriconazole had the best in vitro activity against Exserohilum. The echinocandins had widely variable results and do not achieve good CNS concentrations. In 2009, Li and de Hoog (21) described the difficulties encountered in treating patients with cerebral phaeohyphomycosis.

Ten patients were switched from intravenous voriconazole to amphotericin B, most because of the combination of increasing CSF leukocyte count and worsening symptoms or change in brain MRI findings. All but 1 of these patients had a substantial decrease in CSF pleocytosis at the next LP after the switch, along with alleviation of symptoms. All of these patients had an increase in serum creatinine level, but not to threatening concentrations; no patients have required dialysis. At the discretion of the infectious disease clinician, 6 of these patients were switched to liposomal amphotericin B after 1 week of amphotericin B desoxycholate to avoid nephrotoxicity. More data on in vitro antifungal minimum inhibitory concentrations of various antifungal agents and possible synergistic combination therapies are needed.

Clinical and CSF responses to treatment at 3 weeks are slow and vary widely. Many patients have improved to the point that their major complaint is boredom, as wary clinicians wait for better CSF values. However, others remain symptomatic, primarily with arachnoiditis and urine retention, and 3 have had strokes. Although CSF leukocyte counts improved after 13 days, no case has returned to zero. On the initial LP, only 1 patient with meningitis had a CSF leukocyte count less than 100 cells/mL. On the third LP, 6 of 17 patients (35%) had CSF leukocyte counts less than 100 cells/mL (range, 20 to 1400 cells/mL). The occurrence of stroke and lack of difference in the CSF erythrocyte count between LPs suggest that angiinvasion may be taking place. With only early data, we are not able to predict who will respond and remain well and who will respond more slowly or have a stroke.

At this time, the decision about discharging a patient to continue on oral voriconazole must be individualized. Follow-up data will need to be analyzed to ascertain whether there are common variables that predict safe discharge or a need for rehospitalization.

In summary, early data suggest that the involved organism or organisms may be angiinvasive, some patients are susceptible to strokes, and initial therapy with intravenous voriconazole alone can be confidently recommended. However, patients need to be closely monitored clinically with repeated CSF analysis because of the low threshold for changing to amphotericin B. Given our treatment approach, we cannot comment about any role for combination therapy. Many questions remain unanswered. How long do patients need to be treated? What is the definition of a “cure”? How long do patients need to be followed after completion of treatment? Will there be long-term neurologic sequelae? Only with a continued systematic approach to patient care, combined with common data collection and analysis across the nation, will these and other critical questions be answered.

From Virginia Tech Carilion School of Medicine, Roanoke, Virginia.

Potential Conflicts of Interest: Disclosures can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M12-2734.

Reproducible Research Statement: Study protocol, statistical code, and data set: De-identified data, protocol, and statistical analysis are available on request.

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Relevant references to include:


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Final approval of the article: T.M. Kerkering, M.L. Grifasi, E. Bansal, D.C. Garner, J.A. Smith, D.D. Demicco, V.A. Savaliya.
Provision of study materials or patients: M.L. Grifasi, C.J. Schleupner, V.A. Savaliya.
Statistical expertise: T.M. Kerkering.

Appendix Table 1. Studies Ordered on CSF

<table>
<thead>
<tr>
<th>Study</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cell count (2 tubes)</td>
<td></td>
</tr>
<tr>
<td>Differential (2 tubes)</td>
<td></td>
</tr>
<tr>
<td>Protein</td>
<td></td>
</tr>
<tr>
<td>Glucose</td>
<td></td>
</tr>
<tr>
<td>Gram stain</td>
<td></td>
</tr>
<tr>
<td>Routine bacterial culture</td>
<td></td>
</tr>
<tr>
<td>Fungal culture and smear</td>
<td></td>
</tr>
<tr>
<td>AFB culture and smear</td>
<td></td>
</tr>
<tr>
<td><em>Aspergillus</em> galactomannan</td>
<td></td>
</tr>
<tr>
<td><em>Aspergillus</em> PCR</td>
<td></td>
</tr>
<tr>
<td>Aliquot to CDC</td>
<td></td>
</tr>
</tbody>
</table>

AFB = acid-fast bacilli; CDC = Centers for Disease Control and Prevention; CSF = cerebrospinal fluid; PCR = polymerase chain reaction.
Appendix Figure 1. Representative magnetic resonance images of the spine.

A. Sagittal T1 postgadolinium: dural/leptomeningeal enhancement at L5/S1. B. Sagittal postgadolinium: dural and leptomeningeal contrast enhancement. C and D. Axial postgadolinium T1 images that correlate with A and B, respectively, and show dural and nerve root enhancement (postcontrast).
## Appendix Table 2. Summary of 10 Patients Switched From Intravenous Voriconazole to Intravenous Amphotericin B Product

<table>
<thead>
<tr>
<th>Patient*</th>
<th>Initial CSF Leukocyte Count, cells/mL</th>
<th>CSF Leukocyte Count While Receiving Voriconazole, cells/mL</th>
<th>Time Receiving Voriconazole Before CSF Leukocyte Count and Switch to Amphotericin B, d</th>
<th>CSF Leukocyte Count After 7 d of Amphotericin B, cells/mL</th>
<th>Serum Creatinine Level, μmol/L (mg/dL)</th>
<th>Time Receiving Amphotericin B Therapy, d</th>
<th>Reason for Switch</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>293</td>
<td>1058</td>
<td>6</td>
<td>714</td>
<td>74.3 (0.84)</td>
<td>7</td>
<td>3 Worsening headache and arachnoiditis; increasing CSF leukocyte count</td>
</tr>
<tr>
<td>9</td>
<td>1165</td>
<td>2366</td>
<td>6</td>
<td>993</td>
<td>66.3 (0.75)</td>
<td>8</td>
<td>3 Worsening confusion; increasing CSF leukocyte count; stroke</td>
</tr>
<tr>
<td>10</td>
<td>830</td>
<td>1155</td>
<td>5</td>
<td>724</td>
<td>83.1 (0.94)</td>
<td>5</td>
<td>6 Intolerable hallucinations; increasing CSF leukocyte count</td>
</tr>
<tr>
<td>12</td>
<td>3996</td>
<td>18†</td>
<td>3</td>
<td>43‡</td>
<td>100.8 (1.14)</td>
<td>6</td>
<td>3 Clinical deterioration; worsening MRI findings; stroke</td>
</tr>
<tr>
<td>14</td>
<td>370</td>
<td>762</td>
<td>4</td>
<td>2924</td>
<td>58.3 (0.66)</td>
<td>4</td>
<td>– Unrelenting headache; worsening CSF leukocyte count; hardware</td>
</tr>
<tr>
<td>17</td>
<td>2505</td>
<td>1440</td>
<td>7</td>
<td>Pending</td>
<td>Pending</td>
<td>–</td>
<td>2 Worsening headache, localized to left side</td>
</tr>
<tr>
<td>19</td>
<td>545</td>
<td>1670</td>
<td>11</td>
<td>40</td>
<td>68.1 (0.77)</td>
<td>7</td>
<td>3 Unrelenting headache, back pain, and urine retention</td>
</tr>
<tr>
<td>20</td>
<td>754</td>
<td>1400</td>
<td>14</td>
<td>26</td>
<td>96.4 (1.09)</td>
<td>9</td>
<td>2 Stroke; worsening CSF leukocyte count</td>
</tr>
<tr>
<td>22</td>
<td>1530</td>
<td>940</td>
<td>14</td>
<td>1014</td>
<td>Pending</td>
<td>–</td>
<td>2 Headache; confusion; hyponatremia</td>
</tr>
<tr>
<td>23</td>
<td>9080</td>
<td>1652</td>
<td>18</td>
<td>173</td>
<td>70.7 (0.80)</td>
<td>–</td>
<td>6 Outpatient treatment with oral voriconazole failed</td>
</tr>
</tbody>
</table>

CSF = cerebrospinal fluid; MRI = magnetic resonance imaging.

* Patient numbers correspond with those in Appendix Figure 2.
† Second CSF leukocyte count after 3 d of voriconazole and 5 d of amphotericin B.
‡ After 10 d of amphotericin B.
Appendix Figure 2. Change in CSF leukocyte count over time in individual patients.

Patient numbers correspond with those in Appendix Table 2. CSF = cerebrospinal fluid; LP1 = lumbar puncture at time of hospitalization; LP2 = second lumbar puncture, a mean of 6 d into treatment (range, 4 to 8 d) for 24 patients; LP3 = third lumbar puncture, a mean of 13.5 d into treatment (range, 11 to 17 d).

* Patient 6 declined a second lumbar puncture until day 18, at which time his CSF leukocyte count was 2 cells/mL.
CORRECTION: EARLY CLINICAL OBSERVATIONS IN PROSPECTIVELY FOLLOWED PATIENTS WITH FUNGAL MENINGITIS RELATED TO CONTAMINATED EPIDURAL STEROID INJECTIONS

The label on the x-axis of Figure 3 on page 159 should be “Intravenous Voriconazole Dose, mg” as opposed to “mg/kg”.

This has been corrected in the online version.

Reference