Real-Time Treatment Guidelines: Considerations during the *Exserohilum rostratum* Outbreak in the United States

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In this issue of *Antimicrobial Agents and Chemotherapy*, Stevens offers his reflections on the therapeutic approach to the ongoing outbreak of *Exserohilum* infections related to contaminated methylprednisolone injections ([1]). As of 24 January 2012, there have been 678 cases reported from 19 states and 44 associated deaths. Early in the epidemic, other fungi were implicated as possibly related to this outbreak based on the isolation of *Aspergillus fumigatus* from the index case ([2], [3]), but all other proven infections have been related to *Exserohilum rostratum* ([2–5]). For the purposes of this discussion, only *E. rostratum* will be considered as the etiologic agent in question.

In response to the potential public health consequences to almost 14,000 exposed individuals in the United States, the CDC, working with state and local health departments, developed a rapid and coordinated approach to the outbreak. After identifying the contaminated products and exposed patients, the CDC coordinated the effort to contact these persons to assess the need for clinical evaluation. In addition, cases needed to be rapidly identified, and case definitions were developed, as well as a reporting system for states and health care providers. This unprecedented event required the CDC to take a very proactive approach toward developing guidance on the diagnosis and management of potentially infected patients related to this epidemic. Because of the complicated nature of these infections and the lack of extensive experience in the management of this rare condition, the CDC, with input from the Infectious Diseases Society of America, established an advisory group constituted of experts in clinical mycology. Their purpose was to assimilate the available knowledge, to provide input to the CDC and practitioners who are managing these patients, and to develop and continuously review specific recommendations pertaining to the treatment of fungal infections associated with the outbreak. The opinions which have been put forth by these clinical experts are based on the best available knowledge at the time, and these recommendations are fluid and continue to evolve as more data become available ([6], [7]). As such, the recommendations from this expert panel are imprecise but openly discussed and well reasoned and allow for a consistent therapeutic approach. In considering treatment approaches for these patients, the advisory group considered *in vitro* susceptibility of the key pathogen (*E. rostratum*), the pharmacokinetic features of each potential agent, potential toxicity, the collective experience of those who work with animal models, and most importantly, the experience of those managing these infections in humans.

At the onset of the epidemic, fungal meningitis and stroke were the major manifestations of infection ([2–5]). Most of these cases resulted from epidural injections; these patients did not intentionally receive intrathecal injections, as suggested by Stevens. The majority of these cases were presumed to be due to fungal meningitis based on consistent clinical and laboratory findings, plus a history of exposure to a contaminated lot of methylprednisolone, but without firm mycologic evidence of infection. As the epidemic has evolved, signs and symptoms of meningitis and stroke have become less-common presenting complaints, and complications such as epidural abscess, paravertebral phlegmon, sacroilitis, peripheral joint infection, and osteomyelitis have become more common, thus challenging the understanding of "optimal antifungal therapy" as surgery becomes an important therapeutic option in these cases ([4]).

To date, 45 clinical isolates of *E. rostratum* from this outbreak have been tested for *in vitro* susceptibilities to a variety of antifungal agents in the CDC's Fungus Reference Laboratory; these results are currently available on their website (www.cdc.gov/hai/outbreaks/laboratory/lab_testing_results.html). Data are available for amphotericin B (AmB) and the azoles, including fluconazole, voriconazole, posaconazole, itraconazole, and the experimental azole, isavuconazole ([8]). *In vitro* susceptibility data for the echinocandins was not obtained since these agents generally have minor direct antifungal activity against the dematiaceous molds. As shown in Table 1, with the exception of fluconazole, the azoles demonstrate good to excellent activity against this organism. The MIC range for voriconazole is 1 to 4 μg/ml (median, 2 μg/ml); for itraconazole, 0.25 to 2.0 μg/ml (median, 0.5 μg/ml); and for posaconazole, 0.25 to 2.0 μg/ml (median, 0.5 μg/ml). The experimental azole, isavuconazole, has the highest median MIC (4 μg/ml; range, 2 to 4 μg/ml). As expected, AmB demonstrates excellent *in vitro* activity (<0.75 μg/ml) against this organism. Voriconazole achieves excellent cerebrospinal fluid (CSF) penetration (about 50% of serum levels), has reasonably predictable serum levels, has a well-known toxicity profile, and is well tolerated by most patients ([9–11]). Similar to other azoles, there is an extensive list of medications that are contraindicated or should be given with caution when coadministered with voriconazole ([11]). Compared to voriconazole, the potential advantage of posaconazole and itraconazole is based largely on marginally better *in vitro* activity of these two agents ([12], [13]). This potential advantage over voriconazole could be negated by several factors, including much

TABLE 1 Antifungal susceptibilities of outbreak strains of *Exserohilum rostratum*[a]

Antifungal agent (n^b)	Minimum inhibitory concn (µg/ml) at 48–72 h	
	Range (lowest to highest value)	Mode (most frequent value)
Voriconazole (30)	1–4	2
Fluconazole (30)	32–128	64
Itraconazole (30)	0.25–2	0.5
Posaconazole (30)	0.25–1	0.5
Isavuconazole (45)	2–4	4
Amphotericin B (28)	0.008–0.75	0.387

[a] The clinical relevance of MIC testing of this fungal pathogen remains uncertain, and breakpoints with proven relevance have yet to be identified or approved by CLSI or any regulatory agency.

[b] n, no. of isolates tested.

poorer oral absorption, unpredictable pharmacokinetics, and the unavailability of an intravenous formulation. Based on these considerations, voriconazole was a logical choice for an azole among patients with less-severe disease.

For those with severe extraneural disease and among most patients with central nervous system (CNS) or refractory infections, the panel suggested a lipid formulation of AmB. While this is a logical choice for severe infections due to *E. rostratum* based on the *in vitro* activity of AmB, the use of this agent is often limited because of infusion-associated side effects and nephrotoxicity (14, 15). AmB is administered parenterally with intravenous saline given prior to and following infusion to augment intravascular volume and mitigate its nephrotoxic effects. Even with these precautions, the nephrotoxicity of lipid-associated AmB often precludes prolonged administration, and therefore, transition to a less-toxic alternative is essential for patients who require long-term therapy. The expert advisory group supported the use of liposomal AmB specifically over other AmB formulations because of greater experience with this agent in human central nervous system infections (16, 17).

The use of combination therapy with an azole and AmB has been explored in the treatment of selected human infections and to date has not been shown to be harmful or antagonistic. The best clinical examples of combination antifungal therapy with an azole and AmB are from two large studies in which AmB and fluconazole were administered to patients with candidemia and cryptococcal meningitis, (18, 19). Thus, there is no clinical precedent to limit clinicians from using combination AmB and voriconazole in the setting of severe disease.

Direct intrathecal and intraventricular instillation of AmB has been considered by some to be a viable treatment for patients with severe CNS disease. However, the only sizeable and current experience using intrathecal/intraventricular AmB is in conjunction with treatment of patients with refractory *Coccidioides* meningitis (20). Otherwise, direct installation of AmB into the lumbar spinal canal and intracerebral ventricles has largely fallen into disuse due to technical challenges and known direct toxicity of AmB. Consequently, this approach is only rarely used, in dire clinical circumstances, by clinicians who have extensive experience with the administration of AmB intrathecally or via an intraventricular reservoir.

In order to ensure good CSF penetration and achieve adequate

therapeutic levels, high doses of voriconazole (up to 6 mg/kg of body weight twice daily [b.i.d.]) and liposomal AmB (up to 7.5 mg/kg/day) have been recommended. Not surprisingly, several clinicians have reported high rates of adverse events. Visual hallucinations, altered mental status, liver function abnormalities, and rash have been reported frequently and attributed to voriconazole (T. Chiller, personal communication). Similarly, higher than expected rates of nephrotoxicity due to liposomal AmB have been reported, reflecting not only the higher daily dose but also the advanced age of many case patients. Whether using a different azole would lead to fewer adverse events is not certain.

The use of animal models to predict outcomes among humans is an important step in the development of effective antifungal strategies. Limited experience with experimental neuroaspergillosis suggests a high level of penetration of voriconazole into the brain parenchyma (21). However, existing animal models of CNS mycoses have significant limitations in allowing for meaningful comparisons with human disease. The following are limitations of existing experimental murine models of cerebral mold infections: (i) reproducibility is variable unless there is a hyperacute model of direct inoculation of a high load of conidiae (22), especially in a neutropenic background; (ii) with the exception of Wistar rats (23), no immunocompetent models of CNS mold infection exist, since mice are resistant to low-dose infection; (iii) intracerebral administration of a high inoculum of fungi; high mortality and no simulation of both the most common mechanism of CNS seeding (pneumonia) or of direct inoculation that could be low-inoculum disease; (iv) 1 or 2 fungal strains are typically used, with no cross-fungal-species comparisons; (v) different genetic backgrounds in mice used; (vi) different types and degrees of immune suppression used (corticosteroids versus cytotoxic agents, e.g., cyclophosphamide); (vii) geared toward studying pharmacology, not pathogenesis (24); (viii) no systemic efforts to study neuroimaging of experimental infections; (ix) significant pharmacokinetic differences in azole metabolism between humans and murine models; and (x) for direct-inoculation disease, significant differences exist between humans and mice and rats in regards to spinal canal and central nervous system anatomy (25), possibly in microglial physiology and biology.

Importantly, no animal models for black molds, and specifically *E. rostratum*, exist. Moreover, there is no animal model which replicates the current situation in humans, specifically, the introduction of mold directly into the parameningeal/epidural space in the setting of prior and concomitant exposure to a concentrated corticosteroid. Extrapolating from the experimental evidence of CNS infections from an encapsulated yeast (*Cryptococcus neoformans*) or a dimorphic geographically restricted mold (*Coccidioides immitis*) may not be relevant. Thus, without a reproducible and relevant animal model with validated endpoints of measurement of outcome (e.g., PCR, antigen, and/or histopathology) to offer us important insights into the appropriate pathogenesis and management of these infections, we are left to make decisions relating to the dose, duration, toxicity, and efficacy of specific antifungal agents for unusual infections based on imperfect data. Moreover, even good animal models do not necessarily predict treatment responses (and toxicity) in humans. In the current situation, we believe that existing animal models are minimally helpful.

Presently, the overall attack rate for exposed persons is approximately 5%, and the likelihood that substantially more patients will present in the near future is very small. In Tennessee, reported

attack rates have been higher for certain patients who received older vials and specific lots, and this raises the issue of targeted prophylaxis in this group of high-risk patients. To further inform decisions regarding management of asymptomatic patients who received epidural or paraspinal injections with contaminated steroid products, the CDC developed a decision analysis model to estimate the potential incremental risks and benefits of administering antifungal agents to asymptomatic persons compared with the closely monitoring patients. The analysis suggested that the period of greatest risk for the development of fungal meningitis is during the first 6 weeks (42 days) after receiving an epidural or paraspinal injection. The model compared the risks and benefits of the following three options for diagnosing and treating "asymptomatic" patients: (i) closely monitor patients, but with a low threshold for performing lumbar puncture; (ii) perform lumbar puncture on asymptomatic patients; and (iii) initiate presumptive antifungal treatment of all exposed patients. In unpublished observations, the second and third options resulted in a comparable reduced risk of stroke and death, and these options were estimated to reduce the maximal risk of stroke or death from approximately 0.4% to 0.3% in comparison to option i. However, initiation of presumptive therapy for all patients (option iii) would presumably result in a much higher rate of drug-related adverse events. The risks of missing cases from option i or ii must be balanced by the risk of medication-induced side effects from treating all patients (the likely probabilities of a patient suffering a side effect from voriconazole or liposomal AmB are 20 and 30%, respectively). Therefore, clinicians must carefully weigh the benefit of treatment of asymptomatic patients with the significant expense associated with drug acquisition, monitoring drug levels and substantial drug-drug interactions. For this reason, the CDC chose to recommend careful clinical evaluation and imaging for high-risk patients, independent of symptoms, with the goal of finding early indications of infection. This strategy is being successfully employed in several of the epicenters of this outbreak and has led to the diagnosis of a greater number of early infections in those with little to no symptom change from the baseline.

Many aspects of this unusual outbreak challenge our thinking and approach to iatrogenic fungal infections: we are dealing with a rare organism for which there are very few clinical data, a large at-risk population of mostly elderly but otherwise nonimmunocompromised people, unusual sites of infection which are difficult to access technically, uncertainly regarding establishment of a firm diagnosis, and significant questions regarding the type and length of therapy. Despite these major challenges, the public health response to this outbreak has been remarkable and has resulted in an approach to diagnosis and management which is remarkably consistent, generally following the initial recommendations put forth by the CDC early in the course of this tragedy. As more information becomes available in this evolving process, the optimal approach to the type and timing of antifungal therapy for patients with proven or presumed infection and the most appropriate use of targeted prophylaxis will become clearer. Unfortunately, the information generated by this outbreak may not be of as much benefit to current patients compared to those affected by future episodes of iatrogenic CNS fungal infection. However, given the tremendous human suffering resulting from this tragedy, it is our collective hope and desire that there never will be a "next time" for a fungal outbreak of such scope and magnitude related to compounded medications.

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