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Treatment of Iatrogenic Fungal Infections: A Black Mold Defines a New Gray Zone in Medicine

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Defining appropriate medical treatment incorporates evidence to balance risk and benefit. Yet, sometimes physicians find themselves in an uncomfortable “gray zone” that necessitates decision making with a paucity of data. This gray zone is where we find ourselves as we struggle to manage an outbreak of central nervous system (CNS) and joint infections that occurred due to injection of methylprednisolone acetate contaminated with filamentous fungi when poor sterility practices were used at a compounding pharmacy in Massachusetts.

The outbreak, now recognized to be predominantly due to a black mold, involves more than 14 000 persons with potential exposure to contaminated medication. As of 10 December 2012, the Centers for Disease Control and Prevention (CDC), which provides frequent updates on the investigation and treatment recommendations, had documented 368 cases of meningitis, 192 cases of paraspinal/spinal infections, and 21 cases of arthritis clustered in 19 states, with 37 deaths (1). We focus here on questions likely to be on the minds of clinicians.

How Should Clinicians Approach Persons Exposed to Potentially Contaminated Methylprednisolone Acetate?

Once symptoms occur and cultures are positive for filamentous fungi, prognosis is typically poor. The recent outbreak of *Exserohilum rostratum* meningitis follows this pattern, with early reports of stroke, neurologic deficits, and death (2, 3).

Given poor outcomes once symptoms manifest, it is hoped that early treatment will reduce morbidity and mortality rates. However, one of the most perplexing questions is about determining the best approach for exposed persons who have no or mild symptoms. Before

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administering preventive therapy, we must consider the potential adverse effects of both diagnostic evaluation and antifungal therapy.

While caring for patients potentially exposed to contaminated medication, we have seen symptomatic complications due to lumbar puncture, including symptoms related to changes in intracranial pressure and cerebrospinal fluid (CSF) leaks. Other risks include introduction of secondary infections and potential transfer of fungus from the epidural to the subarachnoid space (1). Widespread panic after exposure and demand for aggressive diagnostics could lead to more harm than benefit.

When concerned patients present, it is important that clinicians acknowledge these risks and the limited understanding of this infection. Epidemiologists report that most cases occur within the first 6 weeks of the last potentially contaminated injection, leading to the recommendations to consider lumbar puncture for even mildly symptomatic persons during that time frame (2). However, given the rarity of *Exserohilum rostratum* meningitis, we know little about its natural history.

The CDC currently advocates an “empirical” approach to management (2, 4) and recommends contacting potentially exposed patients and their clinicians so that even mild symptoms will prompt action. Kauffman and colleagues (5) reported seeing patients with mild disease after lumbar punctures were performed even for mild headache, but the effectiveness of this approach is unproven. The definition of inflammatory CSF suggested by CDC guidelines (greater than 5 leukocytes, with or without elevated protein) and our understanding of predictive “meningitis symptoms” are somewhat arbitrary and based on infections with other pathogens that invade through different routes (1). Although theoretically attractive, we lack evidence about the net benefit of early antifungal therapy.

At present, the CDC advises against widespread antifungal prophylaxis for all persons exposed to implicated steroid lots. This seems wise. To date, fewer than 2% of potentially exposed patients have developed invasive infection. Although voriconazole is generally well-tolerated, it can cause drug interactions and CNS, liver, and skin toxicities. The risks of exposing large numbers of patients who will likely never develop infection to prophylactic voriconazole probably outweigh the benefits. The calculus of the risk–benefit equation may change after identification of subgroups with particularly high risks for infection and poor outcomes.

Clinical trials that led to approval of available antifungal drugs enrolled persons with different characteristics from those affected by the current situation, so we lack data on drug effectiveness in patients similar to those involved in this outbreak, whose older age and obesity may affect drug dosing and tolerability.

How Should Clinicians Treat Presumed or Documented Fungal Infection?

The CDC suggests high-volume (at least 10 to 15 mL) CSF testing with culture and polymerase chain reaction done at a CDC reference laboratory (1). Current recommendations for treatment of persons with documented CNS infection in this outbreak include administration of high-dose voriconazole (6 mg/kg twice daily), with consideration

of using both liposomal amphotericin B and voriconazole in severe cases. In usual practice, these drugs are rarely used together and the combination carries substantial risk for toxicity.

The predominance of *E. rostratum* in the outbreak influences these recommendations. Although this organism has been identified in most culture-positive cases, there are caveats. The diagnostics are insensitive (culture), not yet validated (polymerase chain reaction), and applied in a context in which several microbial causes are possible. Although not validated on CSF, tests to detect microbial antigens, such as the galactomannan enzyme immunoassay, may be helpful to enhance sensitivity to detect additional cases of *Aspergillus* infection (6). The utility of (1-3)-*β*-D-glucan testing is also unclear, although this detects more fungi. Although the CDC does not recommend routine use of either antigen assay, we believe that clinicians should consider them when available to provide information about the full breadth of fungal organisms involved in the outbreak. They should not be done in lieu of either culture or polymerase chain reaction.

Maintaining a heightened suspicion for several potential microbial causes, including potential nonfungal contamination, is important, given egregious sterility breaches at the implicated pharmacy (7). Other organisms, including *Rhizopus stolonifer* and *Rhodotorula laryngis*, have been recovered from vials (1). Although these organisms are less likely to cause invasive disease due to poor growth at body temperature, this observation emphasizes the “nonclonal” nature of this product contamination. We may still learn of additional implicated environmental organisms.

The recommended dose and route of voriconazole administration are additional areas of uncertainty. Although the CDC recommends administration of higher doses of voriconazole (6 mg/kg twice daily) to ensure CNS coverage, accompanied by monitoring of serum levels to maintain “therapeutic” levels, we will need to observe outcomes carefully. A voriconazole trough serum level of 2 to 5 mcg/mL is recommended based on data in other (immunocompromised) populations. Trough serum levels of voriconazole greater than 5 mcg/mL were associated with high risks for hepatotoxicity in phase 1 evaluation of healthy volunteers and with a reported high incidence of neurotoxicity in patients with hematologic cancer (8, 9). It has been our anecdotal experience that older adults poorly tolerate voriconazole. This may prove problematic, given that the median age of patients with documented disease to date in this outbreak is approximately 68 years (2).

A simulation study using voriconazole levels obtained from a recently completed trial that evaluated patients with aspergillosis estimated that at the standard dose of 6 mg/kg every 12 hours followed by 4 mg/kg every 12 hours, at steady state, approximately 83% of patients will have trough concentrations greater than 2 mcg/mL and only 24% would have levels greater than 5 mcg/mL (10). At the CDC-recommended dose of 6 mg/kg every 12 hours for both a loading and maintenance dose, the proportion of patients with trough concentrations greater than 2 mcg/mL increases to 91%. However, 60% of persons are projected to have levels greater than 5 mcg/mL. Elderly patients make up only 20% of persons in this simulation; in an exclusively elderly population, the levels would probably be higher (9). Thus, clinicians should anticipate toxicities at this higher dose and ideally monitor

voriconazole serum levels. However, level monitoring is not routinely done in most hospitals.

The route of administration is important to timely achievement of adequate levels and avoiding hepatotoxicities. Current recommendations state that oral therapy may suffice in persons with mild disease. Clinicians should be aware, however, that 1 day of IV "induction" therapy shortens the time to achieve adequate levels, justifying its routine use in previous studies of severe infections (11). Also, first-pass hepatic metabolism may lead to increased toxicities associated with high doses of oral drug.

How Do We Move Forward With So Many Unknowns?

The lack of a clear understanding of the scope, treatment, and anticipated outcomes of this outbreak illustrate the need to maintain vigilance and anticipate evolving recommendations as we practice in the gray zone. Although the experts convened by the CDC and other authorities have done a formidable job of assembling available evidence to guide recommendations, key questions remain. Clinicians should alert patients to this uncertainty and involve them, when possible, in choosing an approach based on individual risks and preferences.

To facilitate information transfer, the CDC has established a volunteer Clinicians Consultation Network, comprising experts in treatment of fungal diseases. These clinicians are available for consultation and are facilitating capture of treatment and outcome data. The service can be accessed by calling 1-800-CDC-INFO (1-800-232-4636).

Finally, clinicians should be aware of the potential of other complications, even during receipt of adequate antifungal therapy. Persons with presumed and documented meningitis have also developed strokes, arachnoiditis, and infections at the injection site, presenting with such findings as epidural abscess and discitis. Management may require a surgical approach.

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