

Iatrogenic Fungal Meningitis: Tragedy Repeated

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Recent reports of fungal meningitis cases caused by contaminated corticosteroid injections demand that we remember prior lessons learned, while scrambling to care for currently affected persons even before all the facts are in hand. In 2002, the Centers for Disease Control and Prevention (CDC) detailed 5 cases of *Exophiala (Wangiella) dermatitidis* meningitis or arthritis related to contaminated, injectable, preservative-free methylprednisolone acetate prepared from a compounding pharmacy (1). I was involved in the recognition and management of some of these patients. We learned, or thought we learned, several important lessons from the outbreak: that compounding of preservative-free corticosteroids requires meticulous sterility to ensure lack of fungal contamination; in the absence of that level of sterility and in an environment of highly concentrated steroids, fungi grow aggressively (2) (this has also been occasionally observed in ophthalmology with the accidental treatment of fungal keratitis with topical steroids); and injection of fungus-contaminated corticosteroid solution into the parameninges allows fungus to travel through tissue planes into the subarachnoid space, leading to invasive mycosis. We also learned that the incubation period for appearance of disease from the time of exposure could be up to 6 months, that many persons in several states were exposed but the attack rate for disease was low, and that voriconazole successfully treated these cases of iatrogenic fungal meningitis, except for 1 fatality. However, the cost in patient worry and suffering, medical expenses, and public health surveillance of the 2002 outbreak was high, and the public's trust that medications are safe from microbial contamination was shaken.

The present fungal meningitis outbreak, first recognized in September 2012, seems to be caused by *Exserohilum rostratum* inoculated from contaminated lots of preservative-free methylprednisolone acetate, although it remains possible that other fungi have been involved in some cases. The injections were primarily given as epidural injections to older adults with low back pain and possibly as intra-articular injections. As of mid-October, the number of clinical cases is in the hundreds, with at least 14 000 patients exposed to the contaminated product. The supplier was the New England Compounding Company in Framingham, Massachusetts, which has been shut down. All products received from that pharmacy are to be secured, retained, and not used for any purpose. An aggressive investigation by the CDC, U.S. Food and Drug Administration (FDA), and state health officials is proceeding.

We have a medical culture that appropriately values evidence-based, robust data for diagnosis and management of illness. However, without certainty in diagnosis or treat-

ment and despite the immediate dedicated response of the CDC, assisted by state departments of health and professional societies as well as individual experts, at present decisions will need to be made on a case-by-case basis by treating physicians.

Evidence to date suggests voriconazole as the logical antifungal drug of choice for initial treatment of *Exserohilum* meningitis pending more definitive information. This drug has reported success in *Aspergillus* meningitis (3). It penetrates the central nervous system compartments (4) and was successfully used to treat patients in the 2002 outbreak. However, at this time, exact dosing, correlation of in vitro and in vivo testing for outcome, and monitoring of drug levels can be based only on educated opinion. Individual physicians cannot wait for definitive answers and must act decisively at an early stage of infection.

Patients will need to be followed closely and management refined in real-time. The details of the epidemiology, including the attack rate, remain unclear. The natural history of resultant infections is only now coming into focus, and the manner by which exposed patients should be followed and managed is a work in progress. Unfortunately, the incubation period for these infections, based on prior experience, may extend to months after exposure. Therefore, exposed patients will need to be followed for a long time. The appropriate duration of therapy is similarly unknown, as are such questions as whether to screen with lumbar puncture or joint aspiration and appropriate use of empirical voriconazole. The bottom line is that management will need to be individualized for patients for some time to come.

A full decade after the 2002 fungal meningitis outbreak, we are again painfully reminded of the importance of sterility and the powerful disease-producing interactions between corticosteroids and fungi. Even at this early stage in the epidemic, it is clear that issues surrounding pharmacy compounding and its regulation will need to be revisited at the state and federal levels. Productive discourse among pharmacy societies, the FDA, the pharmaceutical industry, and the legislatures can hopefully balance the demand for individualized, designer products for patient care against the risks for outbreaks that cause suffering and death and erode trust in public health systems. Otherwise, this will surely happen again.

Finally, we must recognize that iatrogenic infections happen daily in our hospitals and other health care settings with much less media attention, and we must continue to invest daily in careful and insightful infection-control policies to prevent, limit, and manage them. For the individual patient, our mandate is clear: to try to restore health.

Therefore, in unfamiliar outbreaks, health care providers may need to accept preliminary—and less than robust—recommendations from experts and health care officials and adapt them to the individual patient at the bedside. Society expects nothing less.

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