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NEWS AND VIEWS

Compounding drugs contaminated with fungi: a recipe for disaster

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An ongoing outbreak of fungal meningitis in the United States has been traced to injections of contaminated corticosteroids produced by a compounding pharmacy.
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An outbreak in the United States of fungal infections resulting from parenteral injections of contaminated corticosteroids is ongoing.[1] Approximately 14 000 persons in 23 states are thought to have received epidural or joint injections of preservative-free methylprednisolone acetate originating from three potentially contaminated lots supplied by the New England Compounding Center (NECC). As of this writing, over 400 patients have been diagnosed with infection and 31 deaths have been reported. These tolls are expected to grow. While the index case had *Aspergillus fumigatus* meningitis,[2] according to the United States Center for Disease Control and Prevention (CDC), subsequent patients have been infected with *Exserohilum rostratum*.[3] This latter fungus is now thought to be the causative agent of most of the cases. Indeed, *E. rostratum* has been identified in unopened vials from one of the suspect lots. However, the possibility that lots were contaminated with more than one fungal species cannot be discounted. Of additional concern is a heart transplant patient developed an infection with *A. fumigatus* after receiving an NECC-manufactured cardioplegia solution used to paralyze the heart during open-heart surgery.[4] All products manufactured by NECC have been voluntarily recalled.

E. rostratum is a mold that is a frequent component of the fungal flora that inhabits soil and rotting vegetation. While it can be a plant pathogen, prior to this outbreak, *E. rostratum* was a very rare cause of infection in humans.[3] It is a dematiaceous fungus, meaning that it has a brown-black color due to the capacity of its hyphae to produce melanin. While the main role of melanins is likely to facilitate survival under harsh environmental conditions, melanins do impart virulence to dematiaceous fungi in mammalian models of infection.[5] *E. rostratum* grows rapidly on suitable culture media. However, cultures from clinical specimens, particularly cerebrospinal fluid, might be negative due to a paucity of free floating organisms. A PCR based assay has been developed by the CDC to facilitate diagnosis. Based on *in vitro* susceptibility testing and limited clinical experience, voriconazole, is considered the drug of choice for treating serious infections due to *E. rostratum*.[3] This triazole antifungal drug has reasonably good distribution into body compartments, including cerebrospinal and synovial fluids. Nevertheless, voriconazole levels should be monitored as there is considerable patient to patient variability in absorption and metabolism of the drug. In selected individuals, such as those with refractory disease or intolerance to voriconazole, the addition or substitution of amphotericin B should be considered. Prophylaxis of asymptomatic individuals who received potentially tainted injections is not presently advocated. As more experience is obtained, recommendations for diagnosis and treatment may change. The CDC has been providing regular updates.[1]

Although on a smaller scale, a similar situation occurred 10 years ago when 4 patients developed meningitis after receiving epidural injections of methylprednisolone acetate that were contaminated with the dematiaceous fungus, *Exophiala dermatitidis*.[6] One of those patients died and a fifth patient developed sacroiliitis. As in the present outbreak, the adulterated product was supplied preservative-free (preservatives are omitted to avoid potential toxicity to nerves) by a compounding pharmacy which failed to institute adequate controls to ensure sterility. In those cases, it took up to 116 days from the time of injection to the time the patients presented for hospitalization. Thus, if this experience is predictive, more cases of fungal infections associated with the contaminated methylprednisolone preparation will emerge in the coming months. Hopefully, the notification of persons who received potentially tainted lots of methylprednisolone will lead those who develop symptoms to present promptly to health care facilities. Early diagnosis and treatment should lead to improved outcome.

Cases of bacterial infections have also been linked to contaminated products, including corticosteroid injections.[6] However, there are features of fungi that make them ideal candidates to contaminate improperly prepared compounded medications. First, fungal spores are ubiquitous inhabitants of the air and without proper environmental controls can readily colonize facilities where pharmaceuticals are manufactured. Thus, any break in sterile technique could lead to contamination. Second, corticosteroids are immunosuppressive and their administration is a well known risk factor for fungal infections. Moreover, some fungi actually grow better in the presence of pharmacological doses of corticosteroids.[7] Thus, the presence of locally high concentrations of corticosteroids would be expected to enhance the ability of injected fungi to elude host defenses and to grow. Third, fungi

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are able to survive many harsh chemical conditions. Interestingly, and of possible relevance to the case of aspergillosis in the heart transplant patient, cardioplegia solutions contain high concentrations of potassium chloride. Fungal spores have a remarkable ability to survive and even grow in concentrations of potassium chloride as high as 2 M.[8] Fourth, the lungs generally form the first line of defense against airborne fungal spores. In models of mold infections, mice are extremely resistant to pulmonary challenge with spores. However, if the spores are given intravenously, the mice succumb, even when relatively low inocula are administered.[9] Thus, injecting fungi directly into the epidural region or joint space bypasses the normally efficient first-line pulmonary host defenses. Finally, hyphae are able to traverse tissue planes, in part due to their angioinvasive properties. This property enables the fungi to translocate from the epidural space into the central nervous system and also to cause hemorrhagic infarction, a feature of the index case in this outbreak.[2,10]

Before we throw out the baby with the bathwater, we need to appreciate that compounding pharmacies fill an important niche by providing medications in formulations that are not commercially available from traditional pharmaceutical manufacturing companies. In the United States, drugs compounded and sold by compounding pharmacies generally are not strictly regulated by the Food and Drug Administration (FDA). Many of the federal and states laws contain ambiguities and this outbreak is prompting calls for federal legislation to strengthen and clarify the FDA's regulatory oversight, particularly for drugs that are outsourced to many providers. It should also be emphasized that infections have also occurred that were due to fungal contamination of FDA-licensed products. However, as the present outbreak tragically illustrates, meticulous attention to sterility and quality control to ensure the absence of microbial contamination is required for all products that are parenterally administered to humans. Sadly, we keep relearning this lesson.[10]

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