A Brief Review of the Recent Fungal Meningitis Outbreak

December 7, 2012

Meningitis is a serious condition associated with significant morbidity and mortality. Recently, an outbreak in the United States was identified, linked to contaminated injections of methylprednisolone acetate (MPA) solution originating from a compounding pharmacy, the New England Compounding Center (NECC), in Framingham, MA.[1] Of note, a similar outbreak of fungal meningitis associated with contaminated steroid injections occurred in 2002.[2] The identification of the recent outbreak began on September 18, 2012, when the Tennessee Department of Health was notified of a culture-confirmed case of *Aspergillus fumigatus* meningitis. As more cases were identified, the Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration (FDA) became involved in the investigation. As of November 11, 2012, a total of 438 cases of fungal meningitis or stroke secondary to presumed fungal meningitis had been confirmed by the CDC, with 32 deaths.[3] Cases have been reported in 19 states with the bulk occurring in Michigan (128 cases), Tennessee (81 cases), Indiana (52 cases), and Virginia (50 cases). A total of 23 states received injections from the contaminated lots, which were recalled by the NECC on September 26, 2012, followed by a recall of all compounded products from the NECC on October 6. On October 23, the Massachusetts State Board of Pharmacy permanently revoked NECC's license.[4] An investigation by the FDA of NECC found 83/321 vials of an affected lot of MPA contained "greenish black foreign matter," and an additional 17/321 vials of that same lot to contain "white filamentous material."[5] When 50 vials from this lot were tested, 100% showed "viable microbial growth." Though the index case of fungal meningitis was laboratory confirmed to be *Aspergillus fumigatus*, further testing by the CDC revealed the major causative pathogen to be *Exserohilum rostratum* with 75 confirmed cases as of November 2.[3] Exserohilum rostratum, a brown-black mold, has been known to cause human disease. Several case reports and series have been published highlighting *Exserohilum's* ability to infect both healthy and immunocompromised individuals.[6-10]

Since the outbreak, the CDC has issued a definition for probable fungal meningitis.[3] Patients must have received an epidural or paraspinal preservative free MPA injection and subsequently contracted: 1) meningitis of unknown etiology after May 21, 2012; or 2) had a posterior circulation stroke without documentation of a normal cerebrospinal fluid (CSF) profile. Associated signs and symptoms should include at least 1 of the following: fever, headache, stiff neck, or photophobia, in addition to an abnormal CSF profile (>5 white blood cells, regardless of glucose or protein). Other symptoms include weakness or numbness in any part of the body, slurred speech, and increased pain, tenderness or swelling at the injection site. Cases should be confirmed by the presence of a fungal pathogen in a culture of the blood or CSF.

A report of the index case of fungal meningitis was published recently.[11] The patient, a man in his 50s, presented with symptoms including headache, neck pain, nausea, malaise, chills, fatigue, and decreased appetite. The patient received a course of antibiotic therapy and was discharged. The patient presented again with headache and lower back pain, as well as having incomprehensible speech. A lumbar puncture revealed a protein level of 319 mg/dL, glucose concentration of 2 mg/dL, and a white blood cell count of 4,422 cells/mm^3. After antibiotics were reinitiated, the patient demonstrated improvement until hospital day 6, at which point

increased somnolence, staring spells, and a transient right facial droop were observed. Liposomal amphotericin B was then added. Cultures of CSF were reported to contain *Aspergillus fumigatus* the following day, and voriconazole was initiated. On hospital day 11, the patient became unresponsive with seizure activity and was intubated and started on mechanical ventilation. Intraventricular hemorrhage, subarachnoid hemorrhage, and worsening hydrocephalus were detected by computerized tomography, and cerebral angiographic imaging suggested a mycotic aneurysm. On day 15, magnetic resonance imaging exposed additional cerebellar and cerebral infarcts. Life support was removed and the patient expired on hospital day 22. Another case report of a patient who received a contaminated MPA injection details a similar disease course, resulting in death on hospital day 10.[12]

Per the CDC, the greatest risk of contracting fungal meningitis is within the first 6 weeks after injection of the contaminated product.[3] As the recall date for the affected lots was September 26, 2012, this period ended on November 7. However, there is potential for further cases to develop. A negative fungal culture or polymerase chain reaction based on a sample from the central nervous system (CNS) does not exclude infection. Empiric therapy should be initiated after the collection of a CSF sample for both fungal and other normal pathogens, including bacteria and viruses, based on the patient's etiology. It is important to note that the current outbreak of fungal meningitis in not contagious. Prophylactic treatment is not recommended in patients without symptoms who received an epidural or paraspinal injection. Clinicians have an option to conduct a lumbar puncture to check for evidence of meningitis.

In response to the outbreak, the CDC issued interim treatment guidance for CNS infections associated with the injection of tainted MPA.[3] The recommended therapy for fungal meningitis is voriconazole, possibly with the addition of liposomal amphotericin B depending on severity and patient response. This recommendation coincides with the Infectious Diseases Society of America (IDSA) guidelines for the treatment of aspergillosis of the CNS.[13] Itraconazole or posaconazole may be used in patients unable to tolerate or refractory to voriconazole. There are few data supporting echinocandins (caspofungin, micafungin, anidulafungin) as single agents or in combination with voriconazole for aspergillosis infections of the CNS. Voriconazole is preferred because it is active against brown-black molds, *Aspergillus*, and has good penetration across the blood-brain-barrier, with concentrations approximately 50% of those found in plasma. In order to ensure adequate concentrations are reached, voriconazole should be administered at a dosage of 6 mg/kg every 12 hours, preferably by intravenous (IV) route.[3] Because voriconazole is metabolized through the liver, and there is significant interpatient variability, a trough level should be drawn 5 days after initiation of therapy and weekly thereafter, targeting a level of 2-5mcg/mL. Voriconazole is also available in a tablet formulation, and patients may be transitioned to this once they are clinically stable or improving. In patients who exhibit severe cases of fungal meningitis or are deteriorating despite antifungal therapy, providers should consider adding liposomal amphotericin B. The preferred formulation is AmBisome®, given at 5-6 mg/kg IV daily. Doses as high as 7.5 mg/kg daily may be considered in patients who are not improving. Intrathecal amphotericin B should be avoided. Prolonged therapy is likely necessary to fully cure the infection. A minimum of 3 months of therapy is recommended, and possibly longer in patients with underlying immunosuppression, more severe disease, or disease involving the bone.

Adverse effects associated with voriconazole therapy include transient visual disturbances, hepatotoxicity (elevated alkaline phosphatase, serum bilirubin, and aminotransferase enzyme levels), rash, fever, chills, and headache.[13,14] Voriconazole is a potent inhibitor and substrate of cytochrome P450 (CYP) enzymes, including CYP3A4, CYP2C9, and CYP2C19. Dose adjustments or alternatives may be necessary in patients taking drugs that are metabolized by or induce these enzymes. Adverse effects of amphotericin B include infusion-related reactions (fever, chills, nausea, vomiting, arthralgia, myalgia), dose-limiting nephrotoxicity (azotemia, elevated creatinine, potassium wasting, renal tubular acidosis), hypotension, diarrhea, and elevated liver enzymes.[13,15]

Regarding the 2002 outbreak of fungal meningitis, preservative free MPA injections from a compounding pharmacy led to cases of meningitis, resulting in 1 death.[2] The causative pathogen during this outbreak was found to be *Exophiala (Wangiella) dermatitidis*, a brown-black mold related to *E. rostratum*, which responded to treatment with voriconazole.[16] Cases from the outbreak in 2002 continued to appear over 6 months. Based on this precedent, the currently recommended treatment should be effective, though patients who received injections from the affected lots of MPA should continue to be vigilant for symptoms of meningitis.

The current outbreak of fungal meningitis associated with contaminated MPA injections from the NECC indicates the importance of maintain sterility when compounding injectable medications.[17] Patients who received injections from the 3 identified lots should continue to be vigilant for symptoms. It is imperative that providers begin antifungal treatment empirically in patients with probable fungal meningitis, and can optionally perform a lumbar puncture in patients without symptoms. Voriconazole is the treatment of choice, and liposomal amphotericin B may be added if needed. Though the compounded products have been recalled, cases may continue to appear through March of 2013.

References:

1. Multistate outbreak of fungal infection associated with injection of methylprednisolone acetate solution from a single compounding pharmacy - United States, 2012. *MMWR. Morbidity and mortality weekly report*. Oct 19 2012;61:839-842.
2. Perfect JR. Iatrogenic Fungal Meningitis: Tragedy Repeated. *Annals of Internal Medicine*. 2012.
3. Multistate Fungal Meningitis Outbreak Investigation. *Centers for Disease Control and Prevention* 2012; http://www.cdc.gov/hai/outbreaks/meningitis.html. Accessed November 11, 2012.
4. Remarks of Governor Deval L. Patrick. *Executive Office of Health and Human Services* 2012; http://www.mass.gov/eohhs/docs/dph/quality/boards/necc/remark-governor-p.... Accessed November 11, 2012.
5. Multistate outbreak of fungal meningitis and other infections. *Food and Drug Administration* 2012; http://www.fda.gov/Drugs/DrugSafety/FungalMeningitis/default.htm. Accessed November 11, 2012.
6. Adam RD, Paquin ML, Petersen EA, et al. Phaeohyphomycosis caused by the fungal genera Bipolaris and Exserohilum. A report of 9 cases and review of the literature. *Medicine*. Jul 1986;65(4):203-217.
7. Anandi V, George JA, Thomas R, Brahmadathan KN, John TJ. Phaeohyphomycosis of the eye caused by Exserohilum rostratum in India. *Mycoses*. Nov-Dec 1991;34(11-12):489-491.

8. Aquino VM, Norvell JM, Krisher K, Mustafa MM. Fatal disseminated infection due to Exserohilum rostratum in a patient with aplastic anemia: case report and review. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. Jan 1995;20(1):176-178.
9. Bhigjee AI, Parmanand V, Hoosen AA, Roux L, Bill PL. Disseminated Exserohilum infection. *The Journal of infection*. May 1993;26(3):336-337.
10. Burges GE, Walls CT, Maize JC. Subcutaneous phaeohyphomycosis caused by Exserohilum rostratum in an immunocompetent host. *Archives of dermatology*. Oct 1987;123(10):1346-1350.
11. Pettit AC, Kropski JA, Castilho JL, et al. The Index Case for the Fungal Meningitis Outbreak in the United States. *The New England Journal of Medicine*. Oct 19 2012.
12. Lyons JL, Gireesh ED, Trivedi JB, et al. Fatal Exserohilum Meningitis and Central Nervous System Vasculitis after Cervical Epidural Methylprednisolone Injection. *Annals of Internal Medicine*. 2012.
13. Walsh TJ, Anaissie EJ, Denning DW, et al. Treatment of aspergillosis: clinical practice guidelines of the Infectious Diseases Society of America. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. Feb 1 2008;46(3):327-360.
14. Voriconazole (Vfend) prescribing information. Pfizer Inc. New York, NY. 2011; http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021266s035,0212.... Accessed November 13, 2012.
15. Amphotericin B liposome (AmBisome) prescribing information. Gilead Sciences, Inc. San Dimas, CA. 2012; http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/050740s021lbl.pdf. Accessed November 13, 2012.
16. Richardson MD, Warnock DW. *Fungal infection : diagnosis and management.* 4th ed. Chichester, West Sussex, UK: Wiley-Blackwell; 2012.
17. Alcorn T. Meningitis outbreak reveals gaps in US drug regulation. *Lancet*. Nov 3 2012;380(9853):1543-1544.