The Centers for Disease Control and Prevention (CDC), state and local health departments, and the Food and Drug Administration are continuing their ongoing investigation of an outbreak of serious fungal infections associated with steroid injections. This email provides a situation update from the IDWeek meeting in San Diego. Subsequent important updates on case definitions, treatment, and management of asymptomatic persons are now included.

**Etiologic Agents**

Nearly all the fungal isolates to date have been *Exserohilum rostratum; Aspergillus fumigatus* and *Cladosporium* each have been isolated once. *Exserohilum* is a brown-black environmental fungus, commonly found in soil and on grasses. Hyphae are septate and irregular. It has caused disseminated infection in immunocompromised hosts. In immunocompetent hosts, most infections are from local injury or inhalation, and are manifest as allergic sinusitis, keratitis, or localized cutaneous and subcutaneous lesions [4]. *Exserohilum* has not previously been reported to cause CNS infection, but a black mold, *Exophiala*, caused a similar outbreak a decade ago [5].

**Illness Incubation Period**

The range of time from injection to onset of symptoms has been 1–42 days (median 15 days) [6]. Clinicians need to remain vigilant that longer incubation periods are likely to be seen.

**Case Definitions**

Updated case definitions for meningitis and septic arthritis have been posted [7]. Now included are infections of unknown etiology at the site of previous injection with methylprednisolone definitely or probably made by New England Compounding Center. The scope has also been widened to include injections that used products (other than methylprednisolone) labeled as sterile and made by New England Compounding Center [8].
Clinical Manifestations

The median age for the initial 70 patients was 68 years (range, 23–91); two-thirds were female. Presentations included meningitis (91%), stroke without lumbar puncture (LP; 3%), epidural abscess (3%), and multiple findings (4%) [5]. Many patients had very mild symptoms at presentation. Cerebrospinal fluid (CSF) profiles were as follows: white blood cells, median 1299/μL (range, 13–15 400 μL) with neutrophilic predominance; glucose, median 42 mg/dL (range, 11–121 mg/dL), and protein, median 129 mg/dL (range, 45–588 mg/dL).

A highly instructive case report with imaging and pathologic findings has been published [9]; the latter showed considerable angioinvasion, vasculitis, and infarction in brain and spinal cord. A detailed description of the clinical course of the index case provides a graphic view of the severity of the illness, and the brain pathology, which showed several cerebral aneurysms [10]. A very helpful expert commentary has reviewed the current situation and provided thoughtful points for clinicians to consider in managing cases [11].

Diagnostics

Routine testing (cell counts and chemistries; crystals for joint fluid), bacterial and fungal cultures of CSF, joint fluid, abscess aspirate, and other body fluid or tissue should be sent directly to the clinical laboratory. Instructions for sending remaining aliquots or additional specimens to CDC through the state health department are available [12].

Cultures of CSF have not commonly been positive, similar to what is seen in other fungal CNS infections. Clinicians are encouraged to reserve CSF for polymerase chain reaction (PCR) rather than obtain galactomannan testing if cultures are negative. An important caveat is that fungal infection is not ruled out by negative tests for fungi (cultures or PCR assay) on diagnostic specimens such as CSF, aspirate, joint fluid, bone, or other tissue.

Exserohilum does grow well, but may be slow to produce conidia (which are used for identification) unless plated on plant-based medium such as potato dextrose agar. Referral to a reference laboratory may facilitate identification.

Treatment

Interim guidance on treatment of CNS or paraspinal infection recommends voriconazole at 6 mg/kg every 12 hours. Consideration should be given for the addition of liposomal amphotericin B (Ambisome) at 7.5 mg/kg in patients with severe infection or those with progressive disease [13]. The consideration for the higher doses is based on the somewhat higher minimum inhibitory concentration (MIC) values for Exserohilum and the need to maximize CSF penetration. The liposomal preparation of amphotericin B has better CSF penetration compared to other formulations. The geometric mean MIC values for nonoutbreak Exserohilum isolates are amphotericin 0.326 μg/mL (range, 0.03–1 μg/mL), and voriconazole 0.733 μg/mL (range, 0.06–4 μg/mL; data courtesy of A. Fothergill and N. Wiederhold, University of Texas Health Science Center at San Antonio Fungus Testing Laboratory).

Testing of a limited number of outbreak strains also reflects these values. CSF concentrations of voriconazole range from 22% to 100% of blood levels [14]. Regular monitoring of voriconazole blood levels should be done, aiming to achieve trough serum levels of 2–5 μg/mL. Avoidance of drug interactions and careful monitoring for side effects such as hepatotoxicity and neurotoxicity are also needed.

Interim guidance on treatment of joint infections recommends voriconazole 6 mg/kg every 12 hours for 2 doses, then 4 mg/kg every 12 hours [15]. Recommendations for monitoring are similar to those in CNS infections. Oral voriconazole is very well absorbed but it may take higher dosages to consistently achieve target blood levels. In cases of severe joint infection, consideration should be given to the addition of a lipid formulation of amphotericin at a dose of 5 mg/kg daily. For patients unable to tolerate voriconazole, alternatives can include itraconazole or posaconazole, whose geometric mean MIC values for nonoutbreak Exserohilum isolates are 0.168 μg/mL (range, 0.015–16 μg/mL) and 0.127 μg/mL (range, 0.015–8 μg/mL), respectively (data courtesy of T.F.P.). Absorption of these antifungals is problematic, again emphasizing the need to monitor blood levels. Fluconazole should not be used.

Duration of Therapy

Duration of treatment is unknown but will likely be prolonged (eg, months). Clinical response, development of complications, and presence of bone involvement will need to be taken into account.

Asymptomatic Patients

For those patients who received epidural or joint injections with methylprednisolone or any other product labeled as sterile from New England Compounding Center and who are asymptomatic, routine antifungal prophylaxis has not been recommended.

Additional data now suggest that the 6 weeks following epidural or paraspinal injection with the contaminated methylprednisolone product may be the period of greatest risk for the subsequent development of meningitis. Two approaches to this situation are now given [16]. Option 1 is the same as previous guidance, which is to monitor patients closely and
perform LP for symptoms even if mild. LP is recommended to be performed at a site separate from that used for the original injection if possible. Option 2 (derived from a decision analysis model using outbreak data) is to perform an LP even if the patient is asymptomatic if <6 weeks have elapsed from their epidural or paraspinal injection. Close clinical monitoring, possibly with repeat weekly LP, can be done through the remainder of the 6-week interval from injection. Patients with >5 WBCs in CSF should be treated for fungal meningitis. Patients with ≤5 WBCs in CSF should be monitored clinically for development of, or change in baseline, symptoms and also considered for weekly LP until 6 weeks have elapsed from injection. After 6 weeks all patients should be monitored for symptoms but still with a low threshold for LP. The estimated decrease in risk of stroke or death using option 2 is from 0.4% to 0.3% compared with option 1. The benefit of presumably early diagnosis must be weighed against the risk of LP for the individual patient.

For persons who received intra-articular injections with contaminated methylprednisolone product, or with other potentially contaminated steroid product, routine fungal prophylaxis is not recommended. Joint aspiration or other diagnostic evaluation such as arthroscopy or synovial biopsy should be done if patients develop new or worsening joint symptoms [17]. These recommendations may change as additional findings emerge in this ongoing outbreak investigation.

Infectious Diseases Society of America Support to Clinicians

The CDC and the Infectious Diseases Society of America (IDSA) are exploring how additional expert clinical advice could be made available to clinicians involved in the care of cases in this outbreak. IDSA members can receive CDC Health Alerts on this outbreak and other important developments by signing up on the IDSA web site. IDSA members are encouraged to post their experiences and questions to the list-serv of the Emerging Infections Network, to which IDSA members can subscribe (also through the IDSA web site). Subsequent email updates will be sent as the situation warrants.

Supplementary Data

Supplementary materials are available at Clinical Infectious Diseases online (http://www.oxfordjournals.org/our_journals/cid/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyrighted. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Note

Potential conflicts of interest. T. S. has had travel expenses and presidency salary paid by IDSA. C. K. has been paid by Merck as chair of DSMB and by NERI to be on panel of NHLBI study. T. P. has received consultant fees from Astellas, Merck, Pfizer, Toyama, and Viamet, has received grants from Astellas and Merck, and has received speakers’ bureau fees from Merck and Pfizer. M. N. has no potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

13. Centers for Disease Control and Prevention. Interim treatment guidelines for central nervous system (CNS) and parameningeal infections associated with injection of contaminated steroid products. Available in abstract form at Clinical Infectious Diseases online.


