Interim Recommendations for Diagnosis and Management of Cases of Suspected Fungal Meningitis Associated with Epidural Anesthesia Administered in Matamoros, Mexico

Background

On May 8, 2023, U.S. public health officials were notified of an outbreak of suspected fungal meningitis among U.S. patients hospitalized after undergoing epidural anesthesia in Matamoros, Tamaulipas, Mexico. This outbreak currently involves patients from multiple U.S. states and has led to several patient deaths. A fungal etiology is suspected based on elevated cerebrospinal fluid (CSF) levels of the fungal biomarker (1,3)-beta-D-glucan in at least one patient. In addition, the Mexican national laboratory (InDRE) has reported that 4 patients in Mexico have had spinal fluid test positive by a DNA test for the fungus *Fusarium solani.* All known affected patients received epidural anesthesia during January–May 2023, generally for cosmetic procedures, in at least two clinics in Matamoros, Mexico, including River Side Surgical Center and Clinica K-3. The Mexican government halted all procedures at these clinics on Saturday, May 13, 2023.

Document Scope & Purpose

This document provides diagnostic and management recommendations for clinicians caring for patients who underwent a procedure under epidural anesthesia in the city of Matamoros, state of Tamaulipas, Mexico during January 1–May 13, 2023, and therefore may be at risk of developing healthcare-associated meningitis of suspected fungal origin. These recommendations are based on the clinical experience of clinicians caring for patients during the current outbreak or during previous outbreaks of healthcare-associated fungal meningitis in Durango, Mexico, and the United States. **This document will be updated based on new information learned during the ongoing investigation.**

Infectious Diseases Physician Consultation

It is recommended to consult an infectious diseases physician to assist with patient diagnosis, management, and follow-up. Optimal therapy for these infections has not been established and may be complex and prolonged. Expert consultation is particularly important because overall clinical experience with these infections is highly limited. Clinicians who do not have access to infectious diseases consultation can reach out to your state/local health department and CDC (fungaloutbreaks@cdc.gov).

Consultation with local health department

Providers should contact their local health department if they have patients presenting for care. They can also contact CDC (fungaloutbreaks@cdc.gov). Public health officials can connect clinicians with experts in fungal meningitis management.

Which diagnostic tests should be performed for patients presenting for care?

For both symptomatic and asymptomatic patients, the following tests are recommended:

- Brain imaging, ideally an MRI with and without contrast, to assess for meningeal enhancement, vasculitis, stenosis, hemorrhage, or ischemia
    - In patients with back pain or paresthesia, spine imaging, ideally an MRI with and without contrast, to assess for local infection or meningeal enhancement.
- Diagnostic lumbar puncture (LP), unless contraindicated (e.g., because of because of skin infection over the puncture site, brain mass causing increased intracranial pressure). **During a recent healthcare-associated fungal meningitis in Durango, Mexico, patients with mild or no symptoms were found upon LP to have fungal meningitis; given the high case fatality rates associated with fungal meningitis and the importance of early treatment to improving outcomes, LPs are currently recommended even in patients without symptoms.**
    - The following CSF tests should be performed/sent:
        - Opening pressure
        - Other routine CSF testing (e.g., color, cell counts [WBC with differential, RBC], protein, lactate, glucose)
        - Bacterial, mycobacterial, and fungal stains and cultures
        - Beta-d-glucan (Fungitell®)
        - *Aspergillus* galactomannan (until etiology of outbreak has been determined)
        - Molecular testing by multiplex PCR (if available) (e.g., Biofire ME panel)
    - Extra CSF should be collected and stored for further testing
    - If available, clinicians should also strongly consider sending CSF for pan-fungal PCR testing or metagenomic testing. If not available, reach to state or local health department and CDC (fungaloutbreaks@cdc.gov)
        - CLIA-approved pan-fungal PCR testing: this is available through the University of Washington (email: molmicdx@uw.edu; phone: (206) 685-6066 or (800) 713-5198)
        - CLIA-approved metagenomic testing that can detect fungal CSF pathogens (including fungus) is available through the University of California – San Francisco (information about testing: https://nextgendiagnostics.ucsf.edu/technology/; important instructions: https://www.testmenu.com/UCSFClinLab/Tests/812266)
    - When collecting CSF, it is important to communicate with the testing laboratory for guidance on shipping and storage.
- Serum Beta-d-glucan (Fungitell®) and *Aspergillus* galactomannan

What treatment recommendations exist for patients who are asymptomatic and have normal LP results?

- At this time, empiric antifungal therapy is not recommended for asymptomatic patients with normal CSF profiles and symptomatic patients who have 5 or fewer white blood cells (WBC) in the cerebrospinal fluid (CSF) at the time of diagnostic lumbar puncture. All patients, especially those with symptoms, should be closely monitored and re-evaluated for new or persistent symptoms.

- Clinicians may consider a second diagnostic lumbar puncture two weeks after the original to re-evaluate the CSF.
- Symptoms to monitor include fever, headache, stiff neck, nausea/vomiting, photophobia, altered mental status
- Should the patient have new or persistent symptoms, a lumbar puncture should be repeated.

What recommendations exist for the treatment of patients who present with <u>symptoms</u> of meningitis <u>and/or have CSF WBC >5</u> (*accounting for the presence of red cells (i.e., subtracting 1 white cell for every 500 RBCs present*)

Although the infectious etiology of this outbreak is unknown, aggressive, **broad-spectrum, dual antifungal treatment using drugs with adequate CNS penetration is recommended** because of the high case-fatality rate seen during previous outbreaks of fungal meningitis. Antifungal therapy should be started as soon as possible after collection of CSF.

- Providers should give **liposomal amphotericin B**
  - Liposomal amphotericin B should be given at a dose of 5 milligrams per kilogram (mg/kg) IV daily. The liposomal preparation of amphotericin B [AmBisome®] is preferred over other lipid formulations because of better CNS penetration. Nephrotoxicity is a common complication of amphotericin B therapy, including therapy with lipid formulations of amphotericin B.
    - Kidney function and electrolytes should be monitored closely in patients receiving any amphotericin B formulation. Administration of 1 liter of normal saline IV before amphotericin B infusion may be considered to minimize risk of nephrotoxicity. Providers and patients should also be aware of and monitor for other potential adverse effects of amphotericin B formulations.
  - Higher doses of liposomal amphotericin B (7.5-10 mg/kg IV daily) may be considered for patients who are not improving, recognizing the potential for increased nephrotoxicity on this higher dose.
  - Avoid the routine use of intrathecal amphotericin B formulations, because of limited data on their use and associated toxicities.
- Providers should give **voriconazole in addition to liposomal amphotericin B**, preferably at an initial dose of 6 mg/kg every 12 hours for two doses, then 4mg/kg every 12 hours thereafter. These doses are recommended because ensuring adequate penetration of voriconazole into the CNS is critical.
  - Therapeutic drug monitoring for voriconazole is recommended to ensure appropriate dosing.
    - A blood specimen for serum voriconazole trough level measurement should be collected on the 5th day of voriconazole treatment, and the dose of voriconazole should be adjusted based on this trough level, aiming for a trough level range of 4 to 5 micrograms per milliliter (mcg/ml). Serum voriconazole trough levels greater than 5 mcg/ml should be avoided because of the risk of neurotoxicity and other drug-related adverse events.
    - Regular monitoring of serum voriconazole trough levels once per week should occur for the initial 4 to 6 weeks of voriconazole treatment and when dose adjustments are made. Dose adjustments should be made as needed to maintain serum voriconazole trough levels within the range of 4 to 5 mcg/ml.

- In most situations it is suggested that patients should be started on intravenous (IV) voriconazole. If the provider wants to transition patients initially treated with IV voriconazole to oral voriconazole, this should be done only after a patient is clinically stable or improving, as long as no contraindications to oral therapy exist.
- Although it is recommended that most patients with CNS infections be started on IV voriconazole, patients with mild disease who can take oral voriconazole as prescribed and who are able to be monitored closely may be started on oral voriconazole at the provider's discretion. Patients on oral voriconazole should be treated with a dose of 6 mg/kg every 12 hours given on an empty stomach, with monitoring of serum voriconazole trough levels as above and dose adjustment as necessary. The target range for serum voriconazole trough levels (4 to 5 mcg/ml) is readily achievable using the oral form of the drug but may require a slightly higher dose and may take longer to achieve if unforeseen problems with gastrointestinal intolerance or poor absorption are encountered.
- Providers and patients should be aware of and monitor for potential adverse effects of voriconazole, including (but not limited to) hepatic toxicity and neurotoxicity. Liver function tests should be closely monitored. The occurrence of hallucinations is normal in the first 3 days of therapy, but persistence may be an indication of neurotoxicity and elevated serum voriconazole levels, and should prompt collection of a blood specimen for serum voriconazole trough level measurement and voriconazole dose adjustment.
- Providers should carefully consider and manage the potential for voriconazole drug interactions in all patients. Other drugs might be considered in consultation with an infectious diseases expert (see section: *What options should I consider if the patient cannot tolerate amphotericin B or voriconazole*?)

For how long should patients be treated, and when is it reasonable to step down therapy?

- Prolonged therapy is expected and treatment duration should be tailored based on the clinical response to treatment. Individual patient management decisions, including choice of long-term antifungal treatment regimens, should be made in consultation with neurology and infectious diseases specialists.
- A minimum of 3-6 months of antifungal treatment should be considered. Management of these infections will likely vary substantially depending upon individual patient circumstances.
- Treatment will likely need to continue for at least 6 months and longer in patients with more severe disease or underlying immunosuppression.
- Monitoring of symptoms after completion of therapy is important to detect potential relapse of infection (see section: *What are the considerations for monitoring clinical status after cessation of antifungal treatment?*)

What are the considerations for monitoring clinical status after cessation of antifungal treatment?

- Given the potential for relapse of infection, close monitoring of patients in whom anti-fungal therapy has been terminated is essential. Patients with recurrent symptoms or worsening pain should be evaluated promptly.

- Clinicians should have a low threshold for performing lumbar puncture or imaging to diagnose relapsed infection. In the absence of new or worsening symptoms, routine monitoring with lumbar puncture (in the case of meningitis) or neuro imaging may be warranted.
- However, it is important to note that radiologic abnormalities may persist for several months after clinical symptoms have resolved.

What options should I consider if the patient cannot tolerate amphotericin B or voriconazole?

- Alternative therapy to that described above should only be considered if voriconazole and/or amphotericin B are considered too toxic to be used. Consultation with an infectious diseases expert is recommended.
- Mild side effects, such as hallucinations with voriconazole and slight elevations in creatinine with amphotericin B, are to be expected in some patients and should be managed by adjusting doses and not stopping the treatment if possible.
- Some patients may be unable to tolerate voriconazole (because of hepatotoxicity or other severe side effects) or amphotericin B (because of nephrotoxicity or other serious adverse reactions). For patients with contraindications to voriconazole and amphotericin B, some infectious disease clinicians have used other anti-fungal agents such as posaconazole or isavuconazole.
    - These medications have variable pharmacokinetics within the CNS and their effectiveness for treatment of infections associated with this outbreak is not clear. However, use of these drugs merits consideration when first line therapies can no longer be safely administered to the patient. Any decision to change anti-fungal therapy should be made in consultation with an infectious disease physician experienced in the treatment of fungal infections.

What complications might occur in patients who have meningitis in this outbreak, and how should these complications be managed?

- During the ongoing outbreak, several patients have developed elevated intracranial pressure—this has generally been managed through repeated LPs and administration of mannitol.
- Some patients have developed vasculitis or brain edema. During the recent fungal meningitis outbreak in Durango, Mexico, clinicians have reported favorable outcomes when treating these complications using high-dose corticosteroids followed by a slow taper.
- Strokes and intracranial hemorrhage have also been reported and are associated with poor outcomes.

Additional Information on Antifungal Drugs

- Voriconazole label: https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021266s032lbl.pdf
- Liposomal amphotericin B label: https://www.accessdata.fda.gov/drugsatfda_docs/label/2008/050740s016lbl.pdf