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

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Disclaimer about these interim recommendations: These interim recommendations serve as a reference and do not supplant the individual judgment and expertise of treating clinicians. Clinicians should consider each patient's unique circumstances when applying these recommendations.

Background

- Public health officials are responding to a multistate outbreak of fungal meningitis among patients who received procedures under epidural anesthesia at River Side Surgical Center or Clinica K-3 in Matamoros, Mexico during January 1–May 13, 2023. The most updated information about this outbreak is available on CDC's website.
- More than 200 residents in 25 U.S. states and jurisdictions have been identified who might be at risk for fungal meningitis because they received epidural anesthesia at the clinics of interest in 2023. Several of these patients have died.
- Three U.S. laboratories (CDC Mycotic Diseases Branch's Laboratory, UCSF Clinical Microbiology Laboratory, and University of Washington Medicine Molecular Microbiology Laboratory) and the Mexican national laboratory (InDRE) have detected fungal signals consistent with the ***Fusarium solani*** species complex from the cerebrospinal fluid of patients receiving follow-up care in Mexico or the United States.

Document Scope & Purpose

- This document provides interim diagnostic and management recommendations for clinicians caring for patients who underwent procedures under epidural anesthesia at River Side Surgical Center and Clinica K-3 in Matamoros, Tamaulipas, Mexico, between January 1–May 13, 2023, and therefore are at risk of developing healthcare-associated fungal meningitis.
- 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 and Neurology Specialty Consultation

- If available, consultation with an infectious diseases physician and a neurologist is recommended to assist with diagnosis, management, and follow-up for patients diagnosed with fungal meningitis.
- Optimal therapy for these infections has not been established, varies between patients, and may be complex and prolonged.
- Expert consultation is particularly important because overall clinical experience with these infections is highly limited.

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 reach out to CDC to connect clinicians with experts in fungal meningitis management.

Diagnostic testing for all exposed patients

- Exposed patients include those who underwent a procedure under epidural anesthesia at River Side Surgical Center and Clinica K-3 in Matamoros, Mexico, during January 1–May 13, 2023.

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

- Diagnostic lumbar puncture (LP), unless contraindicated (e.g., because of because of skin infection over the puncture site, brain mass causing increased intracranial pressure). Extra CSF should be collected and stored for further testing.
    - Rationale for LP in asymptomatic exposed patients: **During a recent healthcare-associated fungal meningitis due to *Fusarium* 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 *Fusarium* central nervous system infections (>40%) and the importance of early treatment to improve 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®). Performing laboratories include Mayo clinic and MiraVista
        - CSF for pan-fungal PCR testing or metagenomic testing. If not available, clinicians can reach out to state or local health department and CDC (fungaloutbreaks@cdc.gov).
            - CLIA-approved pan-fungal PCR 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
- **Brain imaging, ideally an MRI with and without contrast, is recommended in patients with symptoms** to assess for meningeal enhancement, vasculitis, stenosis, hemorrhage, or ischemia, but this should not delay obtaining the LP.
- **An MRI with and without contrast is <u>recommended for all patients with abnormal LP results</u>** (see section *Treatment and imaging recommendations for patients who present with CSF WBC >5*)
- In patients with back pain or paresthesia, spine imaging, ideally an MRI with and without contrast, should be considered to assess for local infection or meningeal enhancement.

Treatment recommendations for patients who are asymptomatic and have normal LP results

- At this time, empiric antifungal therapy is not recommended for asymptomatic or symptomatic patients with normal CSF profiles (i.e., 5 or fewer white blood cells [WBC]) in the 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 for at least 4 weeks.
    - Symptoms to monitor include fever, headache, stiff neck, nausea/vomiting, photophobia, altered mental status
- Clinicians may consider a second diagnostic lumbar puncture 2 weeks after the original to re-evaluate the CSF.
- Should the patient have new or persistent symptoms, a lumbar puncture should be repeated.

Treatment and imaging recommendations for patients who present with <u>CSF WBC >5</u> (*accounting for the presence of red cells (i.e., subtracting 1 white cell for every 500 RBCs present*)

- Aggressive, **dual antifungal treatment (liposomal amphotericin B and voriconazole) is recommended** because of the high case-fatality rate seen during previous outbreaks of fungal meningitis involving *Fusarium*. 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 and because it has been used during previous outbreaks to treat fungal meningitis. 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 IV every 12 hours for two doses, then 4mg/kg IV every 12 hours thereafter. These doses are recommended because ensuring adequate penetration of voriconazole into the CNS is critical.
    - Therapeutic drug monitoring for voriconazole serum concentrations 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 at least weekly thereafter), 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 400 mg (6mg/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: *Options for the patients who cannot tolerate amphotericin B or voriconazole*?)

- **Brain imaging is recommended**, 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.

Length of treatment and when to step down therapy

- Patients should receive at least 2 weeks of combination therapy with IV liposomal amphotericin B and voriconazole.
- The decision to discontinue amphotericin B and treat the patient with voriconazole monotherapy depends on multiple factors, including clinical improvement and improvement in CSF parameters. Decreasing CSF beta-D-glucan levels can suggest the infection is improving. Decisions to patient disposition after hospitalization will depend on these factors, as well as the ability to ensure close outpatient follow-up with close monitoring of serum voriconazole levels.
- Prolonged antifungal 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: *Considerations for monitoring clinical status after cessation of antifungal treatment*)

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.

Options for the patients who cannot tolerate amphotericin B or voriconazole

- Alternative therapy to liposomal amphotericin B and voriconazole 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 antifungal therapy should be made in consultation with an infectious disease physician experienced in the treatment of fungal infections.

Potential complications of fungal meningitis and management

- Signs that might indicate clinical decompensation or the need to escalate level of care can include worsening mental status, inability to protect the airway, and focal neurologic deficits.
- 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.
- In consultation with neurology, CT angiography of the head and neck might be considered to assess for vasculitis.
- 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