

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

**Last updated:** July 18, 2023

**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](#).
- Approximately 185 residents in 23 U.S. states and jurisdictions have been identified as potentially 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.
- A highly-resistant strain of *Fusarium solani* was isolated from one patient’s tissue culture specimen (see **Table 1** at end of this document for antifungal susceptibility testing results)

## 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](mailto: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 50%) 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 for all patients:
  - 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
- The following CSF tests should be performed for patients with abnormal LP results:
  - Beta-d-glucan (Fungitell®).
  - 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](mailto:fungaloutbreaks@cdc.gov)).
    - CLIA-approved pan-fungal PCR is available through the University of Washington (email: [molmicdx@uw.edu](mailto: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://nextgendiagnosics.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 recommended for all patients with abnormal LP results** (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 CSF WBC >5 (accounting for the presence of red cells (i.e., subtracting 1 white cell for every 500 RBCs present))**

- **Aggressive combination antifungal treatment with liposomal amphotericin B (Ambisome®), voriconazole, and fosmanogepix is recommended** because of the high case-fatality rate seen during previous outbreaks of fungal meningitis involving *Fusarium* and the highly-resistant profile (Table 1) of *Fusarium solani* isolated from a patient during the current outbreak. Antifungal therapy should be started as soon as possible after collection of CSF.
  - Providers should give **liposomal amphotericin B (Ambisome®)**
    - Liposomal amphotericin B should be given at a dose of 10 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.

- Intrathecal amphotericin B formulations has been used in certain refractory cases during the current outbreak. Consultation with an infectious diseases expert with previous experience on intrathecal amphotericin B administration is recommended if that therapeutic modality is recommended. If an expert is not locally available, please contact the CDC or local health department to arrange for a consultation.
- Providers should give **voriconazole**, preferably at an initial dose of 6 mg/kg IV every 12 hours for two doses. 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 5<sup>th</sup> 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 minimum trough level range of 4 to 5 micrograms per milliliter (mcg/ml) or a higher trough level if the patient can tolerate it.
- 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 minimum range of 4 to 5 mcg/ml, or higher if the patient can tolerate it.
  - In most situations it is suggested that patients should be started on intravenous (IV) voriconazole.
  - 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 (minimum of 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.
- **Fosmanogepix**, which is an experimental antifungal drug in phase II clinical trials, is recommended based on the antifungal susceptibility profile of a *Fusarium solani* isolate that was collected from a patient's tissue specimen during the current outbreak. The dose of fosmanogepix should be as high as Pfizer allows in their compassionate use protocol.
  - Obtaining fosmanogepix requires a two-step approval process:
    1. Contact Pfizer at [FMGXExpandedaccess@pfizer.com](mailto:FMGXExpandedaccess@pfizer.com) and ask for compassionate use of fosmanogepix; include in this email that fosmanogepix will be used for a patient in the ongoing fungal meningitis outbreak.
      - Pfizer will respond with the next steps, which include a case report form and instructions to contact the IRB for expedited compassionate use approval and consent requirements.
    2. After Pfizer grants approval, contact FDA at: (888) 463-6332 or (301) 796-3400 and request an **emergency IND** (investigational new drug application). More information can be found here: [Emergency Use of an Investigational Drug or Biologic | FDA](#)
- **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. Some sites managing these patients repeat imaging on a weekly basis.

### Length of treatment and when to step down therapy

- The optimal duration of combination treatment is unknown.
- Decreasing CSF beta-D-glucan levels can suggest the infection is improving. Decisions about patient disposition after hospitalization will depend on clinical improvement, 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 neurologic imaging may be warranted.
- However, it is important to note that radiologic abnormalities may persist for several months after clinical symptoms have resolved.
  - **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, or with lumbar drains and external ventricular derivation devices.
- 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.

- **Table 1: Antifungal Susceptibility Testing Results of One *Fusarium solani* isolate from the Outbreak of Fungal Meningitis among U.S. Residents who Received Epidural Anesthesia at Two Clinics in Matamoros, Mexico<sup>a</sup>**

<b>Antifungal</b>	<b>Results (mcg/mL)</b>
<b>Amphotericin B</b>	<b>2</b>
<b>Anidulafungin</b>	<b>&gt;8</b>
<b>Caspofungin</b>	<b>&gt;8</b>
<b>Micafungin</b>	<b>&gt;8</b>
<b>Ibrexafungerp</b>	<b>&gt;8</b>
<b>Rezafungin</b>	<b>8</b>
<b>Itraconazole</b>	<b>&gt;16</b>
<b>Posaconazole</b>	<b>&gt;16</b>
<b>Voriconazole</b>	<b>8</b>
<b>Isavuconazole</b>	<b>&gt;16</b>
<b>Olorofim</b>	<b>&gt;4</b>
<b>Manogepix</b>	<b>≤0.008</b>

<sup>a</sup>Methodology used: [Clinical and Laboratory Standards Institute's reference method](#) for broth dilution antifungal susceptibility testing of filamentous fungi. Testing performed by the Fungus Testing Laboratory, University of Texas San Antonio, San Antonio, Texas, USA.