REVIEW ARTICLE

Mold Infections of the Central Nervous System

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THE RECENT OUTBREAK OF *EXSEROHILUM ROSTRATUM* MENINGITIS LINKED TO epidural injections of methylprednisolone acetate has brought renewed attention to mold infections of the central nervous system (CNS).[1] Although uncommon, these infections are often devastating and difficult to treat. This focused review of the epidemiologic aspects, clinical characteristics, and treatment of mold infections of the CNS covers a group of common pathogens: aspergillus, fusarium, and scedosporium species, molds in the order Mucorales, and dematiaceous molds. Infections caused by these pathogen groups have distinctive epidemiologic profiles, clinical manifestations, microbiologic characteristics, and therapeutic implications, all of which clinicians should understand.

COMMON FEATURES

Molds are ubiquitous organisms found in soil, water, and decaying vegetation.[2] All have septate, angular, branching hyphae in tissue, with the exception of those in the order Mucorales, which have broad, ribbonlike, nonseptate or hyposeptate hyphae (Fig. 1). The respiratory tract is usually the portal of entry, with subsequent hematogenous dissemination to the CNS. However, direct inoculation of CNS or paraspinal tissue as a result of surgery, trauma, intravenous drug use, or contaminated medical supplies may also occur in immunocompetent persons, including those infected with *Exophiala dermatitidis* (formerly known as *Wangiella dermatitidis*) and *E. rostratum*.[3] Organisms may also spread to the CNS from adjacent structures, including the sinuses, mastoid, and orbit. Infection of the ethmoid sinuses may lead to cavernous sinus thrombosis as a result of invasion of the emissary veins that drain the sinuses. Hyphae can invade from the ethmoid sinuses through the lamina papyracea and into the periorbital space, thus threatening the eye, extraocular muscles, and posterior apical structures, including the optic nerve.

Angioinvasion is common in immunocompromised patients and accounts for the hematogenous dissemination from the lungs that causes focal neurologic deficits (Fig. 2). Histopathological examination of involved brain tissue reveals hyphal angioinvasion with thrombosis in small and large vessels, hemorrhagic infarction, and coagulative necrosis, as well as vasculitis and granuloma formation. Susceptibility to angioinvasion also confers a predisposition to the formation of mycotic aneurysms. Without effective management, mold infections of the CNS carry poor prognoses, particularly in immunocompromised patients; such patients may present with isolated brain abscesses that simulate tumors of the CNS.

There are four cornerstones of the management of mold infections of the CNS: early diagnosis, administration of antifungal chemotherapy, neurosurgical assessment and intervention, and management of immunologic impairment. Figure 1 outlines the comparative epidemiologic profiles, clinical characteristics, laboratory features,

and neuroimaging features of mold infections of the CNS. Early diagnosis may allow for timely therapeutic intervention and prevention of neurologic sequelae. Computed tomography (CT) and magnetic resonance imaging (MRI) are important adjuncts in the detection of infection and in monitoring the course of therapy. Patients who are at risk or who have documented invasive mold infection of the lungs or sinuses should be evaluated with the use of neuroimaging if they have any neurologic signs or symptoms. Patients with intracranial lesions suggestive of fungal abscesses or granulomas may be candidates for stereotactic biopsy.

Two distinct patterns characterize mold infections of the CNS. In some patients, the disease arises by direct extension from the paranasal sinuses, eye, or middle ear, causing a single abscess or a few abscesses.[4,5] These lesions usually occur in the frontal or temporal lobe. Other patients have hematogenous infection, which may lead to solitary or multiple small abscesses that are often seen at the junction of cerebral gray and white matter and in the putamen–striatal arterial distribution. Mycotic aneurysms may form and rupture, which creates the potential for hemorrhagic strokes, subarachnoid hemorrhage, and empyema formation.

EARLY DIAGNOSIS

Detection of galactomannan antigen and 1,3-β-D-glucan in cerebrospinal fluid (CSF) may be helpful in establishing the diagnosis of CNS aspergillosis or other mold infections, such as fusariosis.[6,7] However, because galactomannan antigen and 1,3-β-D-glucan can also be expressed by fusarium species, its presence in CSF does not constitute a definitive diagnosis of CNS aspergillosis[8]; 1,3-β-D-glucan may also be expressed by scedosporium species and *Exserohilum rostratum*. A polymerase-chain-reaction assay that is specific for aspergillus also may prove useful, but standardized platforms are lacking.[9]

ANTIFUNGAL THERAPY

Table 1 outlines therapeutic interventions for mold infections of the CNS. The arsenal against these infections includes three classes of antifungal agents: polyenes (amphotericin B formulations), triazoles (voriconazole, itraconazole, and posaconazole), and echinocandins (caspofungin, micafungin, and anidulafungin). Voriconazole is
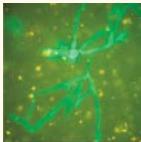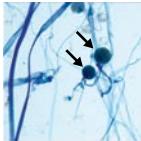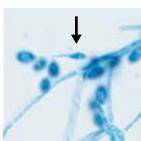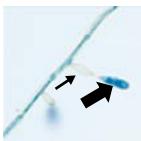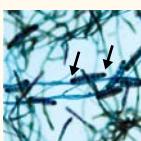
the primary agent for the treatment of CNS aspergillosis.[12] Amphotericin B and its lipid formulations are first-line agents for the treatment of mucormycosis. The roles of other triazoles and echinocandins in the treatment of mold infections of the CNS have not been well defined.

Antifungal agents vary widely in their distribution in the CSF.[13] Voriconazole is a relatively small (349-dalton), moderately lipophilic molecule with a concentration in CSF that is approximately 50% of its concentration in plasma, in both animals and humans. Other antimold triazoles, such as posaconazole and itraconazole (708 and 705 daltons, respectively), are highly lipophilic molecules with negligible concentrations in CSF. Amphotericin B (923 daltons) and its lipid formulations have relatively limited distribution in the CSF, but they do have detectable concentrations that are at or above inhibitory concentrations within brain parenchyma. Echinocandins are larger cyclic hexapeptide molecules (1140 to 1292 daltons) with relatively low or undetectable concentrations in CSF. The administration of antifungal agents through a ventriculostomy or by the intrathecal route is not recommended because of local toxic effects and a lack of proven efficacy.

NEUROSURGICAL ASSESSMENT AND INTERVENTION

The clinical characteristics of mold infections of the CNS warrant assessment for possible biopsy and neurosurgical intervention (Table 2). A definitive diagnosis almost invariably requires a biopsy, with prompt inspection of the specimen by means of wet-mount preparation with calcofluor white stain, culture, and histologic analysis (with Gomori methenamine silver stain and periodic acid–Schiff stain). In situ hybridization and immunohistochemical analysis may be helpful if cultures of biopsy specimens are negative. Because brain biopsies are highly invasive and may lead to neurologic deficits, they are often not feasible; therefore, diagnosis of a mold infection of the CNS is more often made by inference based on the recovery of the pathogen from a pulmonary or sinus source in a patient who has a CNS lesion that is radiologically consistent with a mold infection.

If the patient has a hemispheric ischemic stroke that is thought to be due to invasive fungal infection, and if the patient's clinical condition — that is, coexisting conditions, coagulation status, and overall health status — permits,

Mold	Mold Taxon and Common Features Used for Identification	Common Host Factors	Common Symptoms and Signs	Diagnostic Tests	Neuroimaging
	Aspergillus fumigatus Calcofluor–potassium hydroxide fluorescent stain: Thin, septate hyphae of *A. fumigatus* are seen on this direct smear of a brain-biopsy sample.	Neutropenia, solid-organ or hematopoietic stem-cell transplantation	Focal deficits	Galactomannan in serum, bronchoalveolar-lavage specimen, or CSF; $1,3\text{-}\beta\text{-D-}$glucan in serum or CSF; positive PCR assay	Cerebral infarcts, parenchymal hemorrhage, mycotic aneurysms, abscess
	Mucor circinelloides LPCB: The hyphae are broad, ribbonlike, and hyposeptate. Two large, round sporangia (arrows) contain many spores. Rhizoids are absent.	Diabetes mellitus, neutropenia, solid-organ or hematopoietic stem-cell transplantation, iron-overload conditions	Sino-orbital mucormycosis; cranial-nerve palsies, cavernous sinus infection, focal deficits	Positive PCR assay	Cerebral infarcts, parenchymal hemorrhage, mycotic aneurysms, cavernous sinus thrombosis
	Scedosporium apiospermum Front of inhibitory mold agar plate showing dark, "mouse-gray" colonies.	Drowning, trauma, neutropenia, solid-organ or hematopoietic stem-cell transplantation	Focal deficits	$1,3\text{-}\beta\text{-D-}$glucan in serum or CSF; positive PCR assay	Cerebral infarcts and abscesses
	Scedosporium prolificans LPCB: Hyphae are septate, and the conidiogenous cell has a swollen base (arrow) and elongated neck. Conidia with truncated bases form in clusters at the apex of the conidiogenous cell.	Trauma, neutropenia, solid-organ or hematopoietic stem-cell transplantation	Focal deficits	Positive blood culture; $1,3\text{-}\beta\text{-D-}$glucan in serum or CSF; positive PCR assay	Cerebral infarcts and abscesses
	Fusarium species Sabouraud dextrose agar showing yellow-orange colonies.	Neutropenia, hematopoietic stem-cell transplantation	Focal deficits, nodular cutaneous lesions, bilateral endophthalmitis	Positive blood culture; galactomannan in serum, bronchoalveolar-lavage specimen, or CSF; $1,3\text{-}\beta\text{-D-}$glucan in serum; positive PCR assay	Cerebral infarcts, parenchymal hemorrhage, mycotic aneurysms
Dematiaceous Mold					
	Cladophialophora bantiana LPCB: Long, wavy chains of smooth, oval conidia (arrow) extend from the conidiophore. The brown pigment of the conidia and hyphae is apparent.	Immunocompetent host, trauma	Focal deficits	None developed	Solitary encapsulated masses simulating a brain tumor, abscess with satellite lesions
	Ochroconis gallopava LPCB: The conidiophore (thin arrow) extends from a septate hypha. The two-celled, oval conidium (wide arrow) extends from the conidiophore by means of a threadlike attachment.	Neutropenia, solid-organ or hematopoietic stem-cell transplantation	Focal deficits	None developed	Cerebral infarcts, parenchymal hemorrhage, brain abscess
	Exserohilum rostratum LPCB: Dark hyphae with brown septate conidia. At both ends of the conidia, the septa are dark and conspicuous bands (arrows).	Immunocompetent host, history of injection of methylprednisolone	Focal deficits, meningitis, arachnoiditis	$1,3\text{-}\beta\text{-D-}$glucan; positive PCR assay	Cerebral infarcts, mycotic aneurysm, brain abscess, epidural abscess, arachnoiditis

Figure 1 (facing page). Comparative Features of Mold Infections of the Central Nervous System.

The use of a polymerase-chain-reaction (PCR) assay of cerebrospinal fluid (CSF) remains investigational and has not been approved by the Food and Drug Administration. The host factors listed here are the most common; however, other hosts may be susceptible. LPCB denotes lactophenol cotton blue stain.

early selective decompressive hemicraniectomy and durotomy may prevent devastating secondary brain herniation. Selective stereotactic decompression of edematous intracerebral lesions may prevent herniation while sparing functionally critical areas. Bulk excision of either intracranial abscesses or granulomas should be avoided, especially within critical functional regions.

Compressive and intramedullary spinal cord syndromes caused by intradural, extradural, or vertebral fungal infections necessitate prompt neurosurgical decompression, drainage, and resection. Surgical drainage or excision, tailored to the location and size of the lesion, is the first-line treatment for intramedullary abscess or granuloma formations. In contrast, localized meningitis, arachnoiditis, radiculopathy, radiculomyelopathy, and anterior-spinal-artery infarction are treated conservatively.

MANAGEMENT OF IMMUNOLOGIC IMPAIRMENTS

Because innate host defenses play a critical role in protection from and eradication of mold infections of the CNS, the reversal of immunosuppression is essential for a successful outcome. The intrinsic immune responses within the brain, involving microglia and the complement system, appear to be inadequate as a host defense against invasive *Aspergillus fumigatus*.[14] In transplant recipients, for whom reversal of immunosuppression may not be feasible, immunosuppressive therapy should be minimized in close coordination with the patient's primary care team.

Strategies that can augment the innate host response against mold infection of the CNS include the use of growth factors to accelerate recovery from neutropenia, provision of granulocyte transfusions with sustained circulating neutrophils until the patient recovers from neutropenia, and discontinuation or reduction in the dose of glucocorticoids.[15,16] The correction of metabolic acidosis and hyperglycemia is a cornerstone of the treatment of CNS mucormycosis.

SPECIFIC PATHOGENS

The management of mold infections of the CNS is individualized for each patient on the basis of the host response, neuroanatomical involvement, and the specific pathogen involved.

ASPERGILLUS SPECIES

The risk factors for CNS aspergillosis include neutropenia, systemic glucocorticoid treatment, mastoidectomy, spinal anesthesia, and paraspinal glucocorticoid injections.[17] *A. fumigatus* was isolated from the index patient in the 2012 outbreak of fungal meningitis.[18]

Focal neurologic deficits and seizures caused by stroke or mass effect are the most common clinical manifestations of CNS aspergillosis.[19] Meningeal signs are uncommon, and their presence is indicative of a subarachnoid hemorrhage.[20] CNS aspergillosis should be high on the list of disorders in the differential diagnosis for patients with immunosuppression and focal brain lesions, especially those with characteristic pulmonary infiltrates in whom focal neurologic deficits or focal seizures develop. Recovery of aspergillus from pulmonary lesions with the use of bronchoalveolar lavage or fine-needle aspiration should be pursued when possible. An enzyme immunoassay for detection of galactomannan in serum or bronchoalveolar lavage fluid should be performed when feasible.[21] As described above, galactomannan and 1,3-β-D-glucan may be found in the serum or CSF of patients with CNS aspergillosis.[6,7]

Voriconazole is the first-line treatment for CNS aspergillosis.[12] Although there are no formal guidelines regarding therapeutic drug monitoring in CNS aspergillosis, we recommend maintaining trough concentrations of 2 to 5 μg per milliliter in serum. Drug-related adverse events may necessitate a reduction in dosage. Because voriconazole has approximately 50% penetration through the blood–brain barrier, measurement of concentrations in CSF is not necessary. For patients in whom voriconazole as primary therapy might have unacceptable adverse effects, liposomal amphotericin B is an alternative.[12] Monitoring of the therapeutic response of CNS aspergillosis and other mold infections of the CNS should include careful bedside evaluation and serial CT or MRI scans. The frequency of scanning should vary directly with the severity of the infection, but a reasonable interval is a
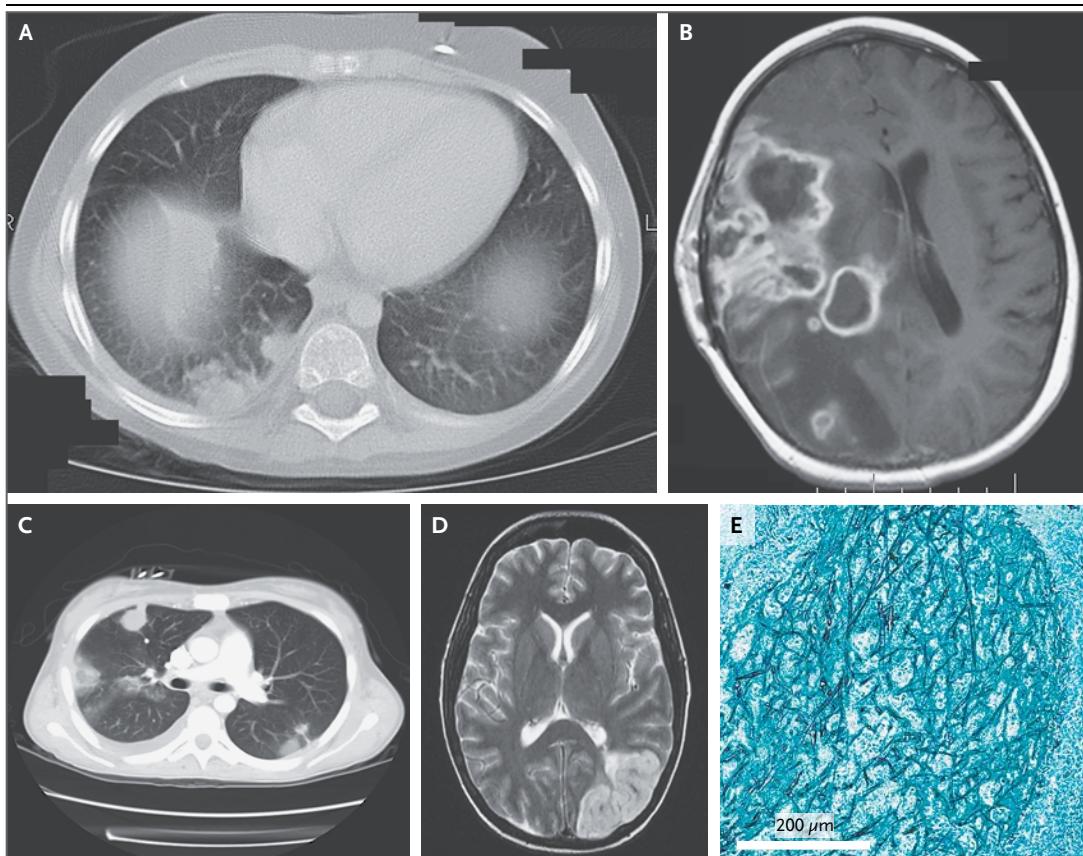
Figure 2. Characteristic Findings Associated with Mold Infections of the Central Nervous System.

Patient 1, a 7-year-old girl with newly diagnosed, high-risk, pre–B-cell acute lymphocytic leukemia, presented with neutropenia and cough, paralysis of the left arm, and left homonymous hemianopsia. Computed tomography (CT) of the chest (Panel A) revealed nodular densities in the lower lobe of the right lung. Magnetic resonance imaging (MRI) of the head (Panel B) showed numerous cortical and subcortical infarcts with surrounding edema leading to mass effects; stereotactically guided brain biopsy yielded a specimen for culture that was positive for *Aspergillus fumigatus*. Patient 2, a 24-year-old woman with acute myeloid leukemia, was admitted for fever and neutropenia followed by rapid deterioration of mental status; CT of the chest (Panel C) showed nodular pneumonia. MRI of the head (Panel D) revealed multiple bilateral infarcts, the largest of which shown in the left parietal–occipital region. Examination of a brain-biopsy specimen (Panel E, Gomori methenamine silver stain) revealed numerous acutely branching septate hyphae. No organisms were grown in culture, because the biopsy specimen was obtained while the patient was receiving antifungal therapy. The histologically compatible organisms include aspergillus, fusarium, scedosporium, and other hyaline molds. The use of immunohistochemical and molecular diagnostic procedures, such as a PCR assay and in situ hybridization, may make it possible to further identify the causative organism.

minimum of every 1 to 2 weeks until the patient's condition is stable.

MUCORALES

Cerebral mucormycosis, which is perhaps the most aggressive mold infection of the CNS, constitutes a medical emergency. Early cases were uniformly fatal. However, recent studies have shown improved survival, possibly as the result of earlier diagnosis and better control of underlying diseases.[22] Diabetes mellitus and iron-overload conditions are distinctive risk factors for the development of mucormycosis.[23] In patients with neutropenia or patients receiving glucocorticoid therapy, mold infections of the CNS develop as sino-orbital infections or through hematogenous dissemination of pulmonary mucormycosis.[24] In contrast, patients with diabetes mellitus usually present with sino-orbital mucormycosis and seldom present with pulmonary or disseminated infection.[23,25] Among intravenous drug users, CNS mucormycosis is a relatively common cause of

intracerebral fungal abscesses.[25] Treatment with the iron-chelating agent deferoxamine is a well-recognized risk factor for disseminated mucormycosis.[26]

Perhaps more than any other infection, mucormycosis of the ethmoid sinuses may involve all structures along its invasive path, including the orbit and eye, bone, and brain tissue.[25,27] Because venous drainage of the ethmoid sinuses extends into the cavernous sinuses, ethmoidal mucormycosis carries a high risk of cavernous sinus thrombosis. Impairment of cranial nerves III, IV, V_1, V_2, and VI may be the initial signs of cavernous sinus thrombosis. Sinus opacification, bony erosions, and obliteration of deep fascia planes can be detected with the use of CT and MRI. The organism may be identified by swabbing, scraping, or biopsy of an involved area to obtain samples for analysis, such as "black pus" from the nasal turbinates, fluid from a surgically drained sinus, or brain tissue. Wet-mount preparations reveal ribbonlike, broad, nonseptate or hyposeptate hyphae, which are highlighted with the use of calcofluor white. Because it can be difficult to detect hyphae in frozen sections stained with hematoxylin and eosin, some institutions have introduced calcofluor-stained homogenates of intraoperative specimens as a rapid means of determining whether Mucorales organisms are present.[28]

Successful management of rhinocerebral mucormycosis depends not only on early diagnosis but also on primary antifungal therapy with amphotericin B, reversal of host impairments — particularly diabetes mellitus, neutropenia, and glucocorticoid exposure — and timely surgical intervention, when indicated. Posaconazole, which has in vitro activity against some isolates of Mucorales, particularly species of mucor, may have a role in follow-up therapy.[29] Although iron chelation with deferasirox has been shown to improve the outcome in a diabetic murine model of disseminated mucormycosis, a randomized trial of this agent did not show a benefit.[30] Adjunctive treatments, such as hyperbaric oxygen, granulocyte–macrophage colony-stimulating factor, and interferon-γ, require further study.[31]

FUSARIUM SPECIES

CNS fusariosis develops predominantly in patients with prolonged neutropenia. These organisms are highly angioinvasive and cause hemorrhagic infarction with strokelike events.[32] Portals of entry include the lungs, sinuses, vascular catheters, and distinctively, periungual lesions (paronychia in patients with neutropenia).[33] Fusarium species are also most frequently associated with fungemia, multiple erythematous nodular cutaneous lesions, and septic arthritis. A positive blood culture growing a hyaline (i.e., colorless or lightly pigmented) mold in a patient with persistent neutropenia is most likely to indicate the presence of fusarium. A definitive mycologic diagnosis can be rapidly established by biopsy and culture of these cutaneous lesions. As compared with other mold infections of the CNS, disseminated fusariosis is more commonly associated with bilateral endophthalmitis, which may lead to blindness. Hematogenously disseminated fusarium infections cause chorioretinitis at a rate that is disproportionally higher than that seen with other organisms causing mold infections of the CNS.[34] Because disseminated fusariosis commonly causes fungemia and cutaneous lesions, early diagnosis and therapy may prevent progression to encephalitis and endophthalmitis.

Fusarium species vary in their susceptibility to antifungal agents.[35] Voriconazole is licensed for second-line therapy; however, amphotericin B also has been used successfully.[36] A rational approach for treating patients with CNS fusariosis, pending determination of susceptibility, is the administration of voriconazole plus a lipid formulation of amphotericin B.

SCEDOSPORIUM SPECIES

Scedosporium apiospermum is readily isolated from soil, polluted water, and sewage. Mold infections of the CNS caused by *S. apiospermum* are strongly associated with drowning events in immunocompetent hosts, when the organism invades through the cribriform plate or disseminates from pneumonic foci.[37,38] Among immunocompromised patients, the features of CNS scedosporiosis resemble those of aspergillosis, including hematogenous dissemination from pulmonary lesions or by extension from the sinuses. Although scedosporium species form branching septate hyphae that are similar to those of aspergillus, in rare cases, terminal annelloconidia are seen in tissue. Nonetheless, culture is required for a definitive diagnosis. Voriconazole is licensed as second-line therapy for *S. apiospermum* infections

Table 1. Therapeutic Options for Mold Infections of the Central Nervous System (CNS).*

Mold	First-Line Therapy		Second-Line Therapy		Adjunctive Therapy and Comments†
	Adults	Children	Adults	Children	
Aspergillus species	Voriconazole: loading dose, 6 mg/kg IV every 12 hr; maintenance dose, 4 mg/kg IV every 12 hr‡; Liposomal amphotericin B: 5–7.5 mg/kg/day IV	Voriconazole: loading dose, 9 mg/kg IV every 12 hr; maintenance dose, 8 mg/kg IV every 12 hr‡; Liposomal amphotericin B: 5–7.5 mg/kg/day IV	Amphotericin B lipid complex: 5 mg/kg/day IV; Caspofungin: loading dose, 70 mg/day IV; maintenance dose, 50 mg/day IV; Posaconazole: 200 mg 4 times a day initially, then 400 mg PO twice a day§; Itraconazole: dosage depends on formulation	Amphotericin B lipid complex: 5 mg/kg/day IV; Caspofungin: loading dose, 70 mg/m²/day IV; maintenance dose, 50 mg/m²/day IV	Reversal of neutropenia, surgical resection, and discontinuation of glucocorticoids should be used as adjunctive therapy; Combination therapy with voriconazole plus echinocandin may be more effective than voriconazole alone in pulmonary aspergillosis, but its effectiveness has not been determined for CNS aspergillosis
Mucorales	Liposomal amphotericin B: 5–7.5 mg/kg/day IV; Amphotericin B lipid complex: 5 mg/kg/day IV	Liposomal amphotericin B: 5–7.5 mg/kg/day IV; Amphotericin B lipid complex: 5 mg/kg/day IV			Reversal of neutropenia, surgical resection, discontinuation of glucocorticoids, and control of diabetes mellitus should be used as adjunctive therapy; use of hyperbaric oxygen remains controversial; Combination therapy with liposomal amphotericin B and echinocandin may be synergistic, but its role in CNS disease is not well defined
Scedosporium apiospermum	Voriconazole: loading dose, 6 mg/kg IV every 12 hr; maintenance dose, 4 mg/kg IV every 12 hr‡	Voriconazole: loading dose, 9 mg/kg IV every 12 hr; maintenance dose, 8 mg/kg IV every 12 hr‡	Posaconazole: 200 mg orally 4 times a day initially, then 400 mg orally twice a day§; Itraconazole: dosage depends on formulation		Reversal of neutropenia, surgical resection, and discontinuation of glucocorticoids should be used as adjunctive therapy
Scedosporium prolificans	Surgical resection	Surgical resection			Reversal of neutropenia, surgical resection, discontinuation of glucocorticoids should be used as adjunctive therapy; This organism is resistant to all licensed antifungal agents.

Organism			Comments
Fusarium species¶	Voriconazole: loading dose, 6 mg/kg IV every 12 hr; maintenance dose, 4 mg/kg IV every 12 hr‡ Liposomal amphotericin B: 5–7.5 mg/kg/day IV Amphotericin B lipid complex: 5 mg/kg/day IV	Voriconazole: loading dose, 9 mg/kg IV every 12 hr; maintenance dose, 8 mg/kg IV every 12 hr‡ Liposomal amphotericin B: 5–7.5 mg/kg/day IV Amphotericin B lipid complex: 5 mg/kg/day IV	Posaconazole: 200 mg orally 4 times a day initially, then 400 mg orally twice a day§ — Reversal of neutropenia, surgical resection, and discontinuation of glucocorticoids should be used as adjunctive therapy
Dematiaceous molds			
Cladophialophora bantiana	Voriconazole: loading dose, 6 mg/kg IV every 12 hr; maintenance dose, 4 mg/kg IV every 12 hr‡	Voriconazole: loading dose, 9 mg/kg IV every 12 hr; maintenance dose, 8 mg/kg IV every 12 hr‡	Liposomal amphotericin B: 3–5 mg/kg/day IV	Liposomal amphotericin B: 3–5 mg/kg/day IV — No single antifungal agent or combination of agents has proved to be effective; surgical resection is critical for a successful outcome
Ochroconis gallopava	Voriconazole: loading dose, 6 mg/kg IV every 12 hr; maintenance dose, 4 mg/kg IV every 12 hr‡ Liposomal amphotericin B: 5–7.5 mg/kg/day IV Amphotericin B lipid complex: 5 mg/kg/day IV	Voriconazole: loading dose, 9 mg/kg IV every 12 hr; maintenance dose, 8 mg/kg IV every 12 hr‡ Liposomal amphotericin B: 5–7.5 mg/kg/day IV Amphotericin B lipid complex: 5 mg/kg/day IV		Reversal of neutropenia, surgical resection, and discontinuation of glucocorticoids should be used as adjunctive therapy — Interpretive breakpoints for in vitro antifungal susceptibility tests have not been established for this organism
Exserohilum rostratum	Initial therapy — voriconazole: loading dose, 6 mg/kg IV every 12 hr; maintenance dose, 4 mg/kg IV every 12 hr‡ For severe or refractory infection, add liposomal amphotericin B: 5 mg/kg/day IV	Initial therapy — voriconazole: loading dose, 9 mg/kg IV every 12 hr; maintenance dose, 8 mg/kg IV every 12 hr‡ For severe or refractory infection, add liposomal amphotericin B: 5 mg/kg/day IV		Decompression of spinal epidural abscess should be used as adjunctive therapy

* The most effective duration of treatment for mold infections of the CNS is unknown. However, a reasonable approach is to provide treatment until all lesions have resolved or stabilized. If immunosuppression persists, antifungal therapy should be continued throughout the period of immunosuppression. Premature discontinuation of antifungal therapy may lead to recrudescent infection. IV denotes intravenously.

† Treatment with granulocyte colony-stimulating factor, granulocyte–macrophage colony-stimulating factor, or granulocyte transfusions can be used to promote recovery from neutropenia.

‡ Because trough levels may vary, therapeutic drug levels should be monitored, with dosage adjustment as warranted.

§ The pediatric dosage of posaconazole has not been well defined. The limited experience with posaconazole for the treatment of mold infections of the CNS comes from the use of the posaconazole suspension; the newer formulations of posaconazole (intravenous agents and extended-release tablets) appear to have improved pharmacokinetic properties, but there are no data available on their use for treating these infections.

¶ The in vitro antifungal susceptibility of voriconazole varies over a wide range for these organisms.[10,11] Initial therapy with both voriconazole and liposomal amphotericin B, pending the availability of data on minimum inhibitory concentrations, may be warranted.

Table 2. Criteria for Neurosurgical or Neuroradiologic Intervention.

Indication	Intervention	Comments
CNS space-occupying lesion with mass effects	Surgical decompression with debulking of lesion or stereotactic drainage	Choice of approach depends on lesion size, location, and severity; large masses with evidence of brain or spinal cord compression or herniation syndromes (with or without increases in intracranial pressure) should immediately be decompressed, especially in patients with a rapid onset of clinical deterioration
Hydrocephalus	Insertion of extraventricular drainage catheter	Clinical deterioration with rostrocaudal brain herniation can occur rapidly as a result of unrecognized hydrocephalus; an external ventricular drain allows monitoring of intracranial pressure and collection of CSF samples
Lesion thought to be fungal in origin but not responding to antifungal therapy	Surgical open biopsy or stereotactic biopsy	Choice of approach depends on lesion location and size
Acute hemispheric stroke with mass effects (ischemic or hemorrhagic)	Hemicraniectomy for large middle-cerebral-artery stroke; hematoma aspiration	Skull bone removal (craniectomy) reduces intracranial pressure and brain herniation
Mycotic aneurysm with subarachnoid hemorrhage	Coiling or surgical aneurysm, parent-artery occlusion, or both	Severe subarachnoid hemorrhage–induced arterial vasospasm may require catheter angioplasty

and, in the absence of alternatives, is used as initial therapy, until the in vitro susceptibility profile is available.[39]

In contrast, *S. prolificans* is resistant experimentally and clinically to the three major classes of antifungal agents. *S. prolificans* infects the CNS through hematogenous dissemination in immunocompromised patients and through traumatic inoculation in immunocompetent hosts.[37] Unlike *S. apiospermum*, *S. prolificans* may be recovered from blood cultures. Therapy consists of surgical resection and reversal of immunosuppression.

DEMATIACEOUS MOLDS

Dematiaceous fungi are a group of molds characterized by the presence of melanin-like pigment within the cell wall that is pale brown to black.[40] These organisms can be pathogens to plants or livestock and may cause chromoblastomycosis and black-grain mycetoma. Dematiaceous molds may also cause deeply invasive infections (phaeohyphomycosis), including infections of the CNS. Most of the agents causing phaeohyphomycosis grow very slowly, so classic mycologic identification can take 3 weeks or longer. In comparison

with aspergillus, Mucorales, and fusarium, dematiaceous molds commonly cause infections of the CNS in immunocompetent hosts. Some dematiaceous molds within a narrow geographic range cause cerebral phaeohyphomycosis.[41]

Until October 2012, most known cases of CNS phaeohyphomycosis were caused by *Cladophialophora bantiana* (also called *Xylohypha bantiana*), *Rhinocladiella mackenziei*, and *Ochroconis gallopava* (also called *Dactylaria gallopava*).[40] *E. rostratum* has since emerged as a cause of meningitis in a nationwide outbreak associated with tainted epidural glucocorticoid injections.[42,43] Prolonged receipt of antifungal chemotherapy, surgical resection of abscesses, and reversal of immunosuppression are mainstays of the treatment of CNS phaeohyphomycosis. Persistence or recurrence of disease is common.

Mold infections of the CNS caused by *C. bantiana* are manifested as a slowly expanding, space-occupying lesion causing headache, seizure, and localizing neurologic signs that simulate a brain tumor.[40] Among immunocompetent patients, CNS infection may occur in the absence of pulmonary lesions. Patients who have survived had easily resectable, encapsulated masses on CT or MRI

scans, whereas those who have died had a solitary lesion that was not entirely resected, poorly demarcated abscess borders, or multiple satellite lesions.[44] There is no clearly effective antifungal therapy.[45] Surgical resection remains the most definitive treatment.

O. gallopava is a neurotropic dematiaceous mold that causes pulmonary and CNS infection in domestic poultry and in immunocompromised humans.[46] Exposure to infested aerosolized warm water may be a risk factor. In one study involving transplant recipients, the CNS was involved in 50% of patients (6 of 12) with *O. gallopava* infection and a poor outcome.[47] The most effective antifungal regimen for treatment of this infection is not known. Interpretive breakpoints for in vitro antifungal susceptibility tests have not been established for this organism. Combination antifungal therapy with voriconazole and a lipid formulation of amphotericin B, pending the availability of in vitro susceptibility data, is recommended in conjunction with surgery and reversal of immunosuppression.

E. rostratum is an opportunistic mold that until recently was an uncommon cause of disease in immunocompromised and immunocompetent human hosts.[48] On September 18, 2012, health officials began to react to a large, multistate outbreak of fungal meningitis traceable to three lots of preservative-free methylprednisolone from one compounding pharmacy in Massachusetts. This outbreak resulted in 751 cases of CNS infection and 64 deaths across the United States. Three molecular assays and assays for 1,3-β-D-glucan in serum and CSF have been developed and may serve as adjunctive diagnostic tools.[49-52] Most of the infected patients in the outbreak presented with signs and symptoms that were consistent with fungal meningitis; however, cases of spinal osteomyelitis or epidural abscess and septic arthritis or osteomyelitis were also reported.[1] In vitro susceptibility data indicate that voriconazole and amphotericin B have activity against *E. rostratum*; this has led to recommendations that voriconazole, liposomal amphotericin B, or both be used for initial management in conjunction with neurosurgical consultation, when appropriate.[42,43] A more detailed review of the management of *E. rostratum* meningitis is reported elsewhere.[42,53] A comparison of the clinical features of less common mold infections of the CNS is provided in Table S1 of the Supplementary Appendix, available with the full text of this article at NEJM.org.

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