Fungal brain infections

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Current Opinion in Neurology 2008, 21:347–352

Purpose of review

Fungal infections of the central nervous system, once a relatively rare occurrence, are increasingly common due to the expansion of immunocompromised populations at risk, and therefore are important to recognize early and manage appropriately.

Recent findings

The specific infectious risk posed by novel immune-modifying therapies can, in most cases, be predicted on the basis of the immune target and medication timing. In addition, major advances in noninvasive diagnostic tests (e.g. serum beta glucan and galactomannan assays), and the recent introduction of more effective antifungal therapies, have led to a dramatic improvement in clinical outcomes.

Summary

The current review provides approaches to patients with suspected central nervous system fungal infections based on host-risk factors, clinical syndromes and specific pathogens.

Keywords

aspergillus, candida, central nervous system, fungi, mycoses

Curr Opin Neurol 21:347–352

1350-7540

Introduction to pathogenic fungi

Clinically relevant fungi include yeasts, filamentous fungi and dimorphic fungi. Yeasts are unicellular organisms and include the relatively common *Candida* spp. and *Cryptococcus* spp., and less common pathogens such as *Trichosporon* spp. The filamentous fungi (molds) are characterized by branching hyphae, which are either septate or aseptate and are further subdivided into the hyalinized and the dematiaceous (darkly pigmented) groups. These classes include the more common *Aspergillus* spp. and the zygomycetes, including *Rhizopus*, *Rhizomucor* and *Mucor*. Less common pigmented molds that infect the central nervous system (CNS) include *Pseudallescheria* and *Fusarium* species. Finally, the dimorphic, or so-called 'endemic', fungi are filamentous at 25°C and yeasts or spherules in host tissue or when incubated at 35°C, and include *Blastomyces* (south-eastern and south-central North America), *Histoplasma* (United States and Africa), *Coccidioides* (American southwest), *Paracoccidioides* (Brazil, Venezuela, Colombia) and *Penicillium marneffei* (south-east Asia) [1••,2•,3].

Host populations at risk

With the exception of the endemic fungi and trauma-induced inoculation, invasive fungal infections are largely confined to immunocompromised patients, with variations in patterns of susceptibility based on the degree and category of immune dysfunction. Frequently cited risk factors for fungal brain infections are HIV/AIDS, hematopoietic stem cell transplant (HSCT), lymphoid malignancies, neutropenia, hereditary immune defects, immunosuppressive medications, diabetes mellitus, intravenous drug abuse and mechanical breakdown of the blood brain barrier via surgery or trauma (Table 1). Indwelling catheters are a risk factor for developing candidemia [4], which in turn increases the risk of CNS seeding [5].

Classically, neutropenia is associated with infection with *Aspergillus* and other molds, highlighting the importance of circulating phagocytes in controlling these pathogens. The duration and depth of the neutropenia are directly related to the risk, and patients with prolonged neutropenia, such as those with aplastic anemia or other causes of bone marrow failure, are at the highest risk. Although less common, *Candida* spp. brain infections are also associated with profound neutropenia. In a series of invasive filamentous fungal infections among patients with hematologic malignancies, CNS disease represented 9.4% of cases [6]. HSCT patients exhibit a bimodal susceptibility to invasive mold infections, particularly *Aspergillus* – first in the early posttransplant neutropenic phase, and later during the postengraftment period when high levels of immunosuppression are given for graft versus host disease (GvHD) [7].

Infectious complications of nonmyeloablative allogeneic transplantation are beginning to be defined. This population frequently has high-risk characteristics including

Table 1 Major risk factors for fungal central nervous system infections

Risk factor	Immune defect	Principal susceptibility
HIV/AIDS	T-cell	*Cryptococcus neoformans* *Coccidioides immitis* *Histoplasma capsulatum* *Penicillium marneffei* *Aspergillus* spp.
Leukemia/ neutropenia	Granulocyte	*Aspergillus* spp.
HSCT	Combined T, B and granulocyte; barrier breakdown Indwelling catheters Immune suppressive medications	*Aspergillus* spp.
Corticosteroids	Monocyte and macrophage	*Cryptococcus neoformans*
	Complement and immunoglobulin receptors	*Candida* spp
TNF inhibitors	Cytokine T-cell and B-cell signaling	*Cryptococcus neoformans* *Histoplasma capsulatum* *Aspergillus* spp. Zygomycetes *Fusarium* spp. *Pseudallescheria boydii* Pigmented molds

HSCT, hematopoietic stem cell transplant; TNF, tumor necrosis factor.

advanced age, previously treated and refractory disease and comorbid conditions that direct them toward the nonmyeloablative approach. Although initial case series found lower rates of invasive fungal infection compared with HSCT, a recent series including 30 patients documented 33% prevalence of invasive fungal infection that directly contributed to mortality, including at least three cases with CNS involvement. Risk factors for CNS infection included high-grade GvHD, corticosteroid use, recurrent neutropenia, and refractory or relapsed disease prior to transplant [8].

Solid-organ transplant recipients treated with immunosuppressive agents, including corticosteroids and calcineurin inhibitors, are also at significant risk for CNS fungal infections, including *Candida* (liver, pancreas and small bowel) and *Aspergillus* (lung and liver). Cryptococcal disease, frequently involving the CNS, has a reported incidence of approximately 2.8% in this population [9]. Invasive fungal infections tend to occur later in solid-organ transplant recipients (mean 1.6 years after transplant), with later presentations in renal graft recipients who require lower levels of prolonged immunosuppression. Renal transplant recipients from endemic areas also have high rates of *Coccidioides* spp. (6.9%), and present with disseminated and CNS disease that can be prevented by targeted prophylaxis [10].

Although the most well known infectious complication of anti-tumor necrosis factor (TNF)-α therapy may be tuberculosis, there is a growing evidence of an increased incidence of invasive fungal infections, including cryptococcosis, histoplasmosis, candidiasis and aspergillosis [11–14]. However, to date there are relatively few cases reported of CNS disease.

HIV-infected patients have a clearly enhanced risk for CNS cryptococcal disease, supporting the role of T-cell mediated immunity in the control of this infection [15]. A population-based surveillance program documented a declining rate of infection and emphasized the strong association with effective HIV treatment, with 89% of infections occurring in patients known to be HIV-infected. In contrast to HIV patients who primarily develop cryptococcal meningitis, patients on TNF inhibitors are more likely to present with pulmonary disease or isolated fungemia [14,16]. CNS *Aspergillus* infections in HIV patients occur at a rate higher than the general population, and the clinical presentation can vary from abscess to meningitis/meningoencephalitis/arachnoiditis. There is evidence to suggest that defects in T-cell immunity, as is seen with HIV infection, predispose to progressive or more widespread CNS disease when patients are infected with endemic fungi such as blastomycosis, histoplasmosis and *P. marneffei* [17–19].

Clinical syndromes

Clinical syndromes of CNS infection have been reviewed elsewhere [1••,2•,3,20]. The most important CNS fungal syndromes that bring patients to medical attention are meningitis and brain abscess with or without vascular invasion (Table 2).

Meningitis generally presents with headache, meningismus, photophobia, papilledema, diminished consciousness, and, in advanced cases, seizure or complications from increased intracranial pressure (e.g. 6th nerve palsy). The cardinal features may be variably present in immunocompromised patients; thus high clinical suspicion is required. Fungal meningitis can have a variable pace and severity and may be clinically indistinguishable from bacterial causes of a chronic meningitis.

Fungal brain abscesses typically present with a focal neurological abnormality, headache and/or seizure, which is the consequence of local destruction or compression of adjacent brain tissue. Certain fungal pathogens, in particular *Aspergillus*, will often have a degree of angioinvasion that can produce simultaneous infarction and/or meningitis. Clinical evidence for angioinvasive disease includes the presence of a new stroke-like syndrome and/or meningeal signs. Other presentations of brain abscesses include direct extension to the CNS from preexisting sinusitis or osteomyelitis and infections associated with foreign bodies including shunts or prior head trauma. As fungal and

Table 2 Fungi that cause central nervous system infections

	Meningitis	Brain abscess
Common	*Cryptococcus neoformans*	*Aspergillus* spp.
	Histoplasma capsulatum	*Candida* spp.
	Coccidioides immitis	Zygomycetes
Uncommon	*Aspergillus* spp.	*Blastomyces dermatitidis*
	Blastomyces dermatitidis	*Coccidioides immitis*
	Candida spp.	*Fusarium* spp.
	Paracoccidioides brasiliensis	*Histoplasma capsulatum*
	Sporothrix schenckii	*Paracoccidioides brasiliensis*
	Zygomycetes	*Penicillium* spp.
		Pseudallescheria boydii
		Sporothrix schenckii
		Ustilgo spp.
Rare	*Blastoschizomyces capitatus*	*Acrophialophora fusispora*
	Rhodotorula rubra	*Bipolaris* spp.
		Blastochizomyces capitatus
		Chaetomium atrobrunneum
		Chaetomium strumarium
		Cladophialophora bantiana
		Curvularia clavate
		Metarrhizium anisopliae
		Microascus cinereus
		Paecilomyces spp.
		Ramichloridium spp.
		Schizophyllum commune
		Trichoderma longibrachiatum
		Trichophyton spp.
		Trichosporon spp.

Adapted with permission from [2•].

bacterial syndromes overlap, a careful review of host risk factors should raise suspicion for a fungal cause that will direct appropriate evaluation and management.

Specific pathogens

The likelihood of CNS fungal infection is generally underestimated because of the nonspecific symptoms and the difficulty in diagnosis [5]. Cryptococcal meningitis is the most common CNS fungal infection and has recently been reviewed [21,22]. Two important CNS fungal pathogens will be discussed briefly.

Aspergillosis

Aspergillus brain abscess is a severe complication of hematological malignancies and cancer chemotherapy, and, until recently, was almost uniformly fatal [23]. The Transplant Associated Infections Surveillance Network demonstrated that the incidence of proven or probable invasive *Aspergillus* at 12 months was 0.5% for autologous HSCT, 2.3% for allogeneic, human leukocyte antigen (HLA)-matched donor, 3.2% after an HLA-mismatched related donor and 3.9% from an unrelated donor [24•]. Additional specific risk factors for CNS fungal infection include solid-organ transplant, GvHD, HIV, liver disease and sarcoidosis.

Of more than 100 *Aspergillus* species that are known, the most virulent pathogen is *A. fumigatus*, but *A. niger*, *A. flavus* and *A. terrus* (which is relatively amphotericin resistant) can cause human disease. CNS infections with *Aspergillus* are typically seeded hematogenously but may also occur via direct spread from the anatomically adjacent sinuses, favoring the frontal and temporal lobes. In a series of 71 cases of invasive aspergillosis, 94% involved the CNS, the vast majority of which were brain abscesses. Uncommon presentations of *Aspergillus* CNS infection include basilar meningitis, myelitis, carotid artery invasion, dural abscesses and mycotic aneurysm [25].

Pathologic features of *Aspergillus* CNS infection include a necrotizing vasculitis, consistent with the species' vasocentric tropism. The radiological appearance of lesions is variable, with frequently associated edema, hemorrhage and ring enhancement. Given the vascular tropism, multiple areas of infarction with or without associated hemorrhage may be suggestive [26,27]. Cerebrospinal fluid (CSF) findings are generally nondiagnostic [28].

Candida

Candida species have emerged as important pathogens that are currently the fourth most common cause of hospital-acquired blood stream infections. CNS infections include the following:

(1) cerebral microabscesses, which typically manifest with diffuse encephalopathy, often below the limits of detection by computed tomography (CT) and occult on lumbar puncture;
(2) cerebral abscesses, which are uncommon, present with focal neurological signs, seizures and biopsy is required for diagnosis;
(3) meningitis, which occurs in less than 15% of cases, and presents with subacute fever and headache, and head imaging demonstrating hydrocephalus; and
(4) vascular complications manifest by infarcts, mycotic aneurysms and subarachnoid hemorrhage, which have been found in up to 23% of necropsy after candidemia [5].

In patients with an indwelling catheter and a fever unresponsive to antibacterial agents, consideration and investigation for invasive *Candida* infection may occur including fundoscopic examination of the retina. Culture data from urine, sputum and skin have little diagnostic value, but positive blood and CSF cultures are highly suggestive of infection.

Of the greater than 200 *Candida* species, five are responsible for the majority of all infections: *C. albicans*, *C. glabrata*, *C. tropicalis* (particularly important in patients with hematologic malignancies and HSCT), *C. parapsilosis* and *C. krusei*. Therapy should be directed by local susceptibility data.

Diagnostic considerations

The appropriate presentation in at-risk hosts should spur testing to identify a fungal pathogen. Fungemia is seen with a few species, including *Candida* spp., *Histoplasma capsulatum*, *Cryptococcus neoformans* and *Aspergillus terreus* but rarely with other *Aspergillus* spp. such as *Aspergillus fumigatus* [29]. CSF sampling is indicated in all patients with meningitis and may show a lymphocytic pleocytosis (*Cryptococcus*, *Candida*), neutrophilic predominance (*Aspergillus*, *Blastomycosis*) or eosinophilia (*Coccidioides*) [20]. Care is required prior to sampling the CSF to ensure that increased intracranial pressure does not place the patient at undue risk from the lumbar puncture (e.g. noncommunicating hydrocephalus). In cases of neurosurgery or device-related *Candida* meningitis, pleocytosis may be absent. CSF glucose is generally low and protein high, with exceptionally high levels seen in cryptococcal infections [20]. CSF antigen testing is available for *Cryptococcus* and *Histoplasma*, with sensitivity and specificity rates reported in some series above 90% [20,30].

Testing for serum beta glucan may be useful for identifying the presence of an invasive fungal infection (with the notable exceptions of *Cryptococcus* and zygomycetes) with sensitivity rates, in some series, of 64–77%, although specificity may be decreased in the presence of concurrent bacteremia [31,32]. Serum assay for galactomannan is reported in some series to have a 95% sensitivity and specificity for invasive *Aspergillus* infections. CSF assays for galactomannan are under investigation and may prove to have clinical utility [33]. A positive serum galactomannan assay in the setting of a radiographic brain lesion should prompt empiric antifungal therapy targeted to treat invasive aspergillosis. If noninvasive methods fail to define a pathogen, the risks and benefit of brain biopsy should be weighed against empiric antifungal therapy.

Pharmacologic therapy for central nervous system fungal infections

Primary issues in the successful treatment of a CNS fungal infection are maintaining a high index of clinical suspicion and establishing a specific pathogen identification through antigen detection, histopathology or fungal culture obtained by lumbar puncture or biopsy. Effective empiric antifungal regimens are limited by significant toxicities and narrow therapeutic range. In addition, the patients at highest risk for fungal brain infections are often on a variety of other medications, including antiretrovirals or immunosuppressants, which have multiple drug–drug interactions. Antifungal therapy for CNS fungal infections typically requires a prolonged period, often months to years; thus, it is imperative to define the etiologic agent [34]. The classes and toxicities of available antifungal agents will be reviewed.

Polyene antibiotics

The class of polyene antibiotics includes intravenous amphotericin B preparations and topical nystatin. Polyenes bind to ergosterol, the principal component of fungal cell membranes, leading to pore formation and cell death. The agents also bind, albeit with lower avidity, to the cholesterol in mammalian cell membranes, accounting for their significant toxicity. There may also be antifungal activity via oxidation and the generation of free radicals [35].

CSF levels of amphotericin B are generally undetectable, although it has been shown to have efficacy in treatment of CNS infections. The lipid formulations of amphotericin preferentially distribute to the mononuclear phagocytic system, reducing their toxicity. Renal failure, the most common treatment-limiting toxicity, is reduced with lipid-based formulations that allow higher doses to be administered [36]. Potentiation of nephrotoxicity may occur with calcineurin inhibitors (e.g. cyclopsporine, tacrolimus) and aminoglycosides commonly used in bone marrow and organ transplant recipients [34].

Amphotericin B or a lipid-based preparation is indicated for treatment of severe infections caused by *Candida*, *Blastomyces*, *Coccidioidies*, *Cryptococcus*, and *Histoplasma*. Of note, a retrospective series of patients with CNS aspergillosis treated with amphotericin B alone or in combination with itraconazole or fluctyosine showed no clinical efficacy, leading the authors [37] to conclude that voriconazole may be the preferred agent in this setting.

Azoles

These are compounds that target ergosterol biosynthesis by inhibiting lanosterol 14-α demethylase, altering cell membrane integrity and causing cell death or growth arrest. The tageted enzyme is cytochrome P-450 dependent and azoles also inhibit other P-450-dependent enzymes in the respiratory cycle of the fungi. Available agents in this class include fluconazole, itraconazole, voriconazole, posaconazole, and the investigational agent – ravuconazole. Itraconazole has limited oral bioavailability and no measurable CSF levels, but does have some penetration into inflamed meninges and brain tissue. Voriconazole is available both orally and parenterally and achieves CSF levels that exceed trough plasma levels. There is a significant individual variability in metabolism, and measurement of serum levels should be considered when treating serious CNS infections. Pharmacokinetic studies [38,39] of posaconazole demonstrated improved oral absorption when coadministered with a fatty meal, although there are no reliable data on CSF penetration. The primary toxicity of the second generation triazoles is related to their cross inhibition of human cytochrome P-450 enzymes and influence on metabolism of other

drugs, which can prolong the QT interval, which may place patients at risk for cardiac arrhythmias. In addition, dose adjustment is required for the coadministration of cyclosporine, tacrolimus and sirolimus [40]. Experience with voriconazole has identified transient elevation of liver enzymes, hallucinations and visual disturbances, which can occur in up to 40% of patients, as the major adverse events, with a relatively low rate of therapy discontinuation [1••]. Voriconazole and posaconazole have been noted to have increased clearance with cimetidine, phenytoin and rifabutin, likely via their common pathway via CYP3A4 [1••].

Fluconazole prophylaxis in the HSCT and cancer population has been associated with increased rates of infection with resistant organisms such as *C. glabrata* and *C. kruseii* strains, although the morbidity of these infections is low [33]. In South Africa, there are reports of increasing cryptococcal resistance to fluconazole, with rates as high as 12.7% in general isolates and above 70% in the setting of clinical relapse [41]. Thus, recent prior antifungal use should be considered when choosing an antifungal therapy. Fluconazole is effective against candidiasis, histoplasmosis, blastomycosis, paracoccidioidomycosis, and mild cases and stable phase treatment of cryptococcosis. Voriconazole is emerging as the first-line therapy for invasive aspergillosis, fusarosis, and scedosporosis. Posaconazole is effective in treating invasive aspergillosis in the setting of resistance to or intolerance of alternate agents and has enhanced activity against zygomycoses and dematiaceous mold infections [42–44].

Echinocandins

The echinocandins are semi-synthetic lipopeptides that noncompetitively inhibit the synthesis of the fungal cell wall polysaccharide 1,3-β glucan. Beta glucan provides a significant part of the cell wall's strength and shape and in maintenance of an osmotic gradient. Echinocandins have fungicidal activity against *Candida*, fungistatic activity against *Aspergillus*, variable activity against endemic and dematiaceous molds and no activity against *Cryptococcus* and the zygomycoses [45,46]. The utility of the echinocandins in CNS infections is not clear given the poor CSF penetration. In one case report, a patient progressed from candidemia to a brain abscess in the setting of active therapy with caspofungin, suggesting that model system data documenting low CSF penetration may be clinically relevant [47]. Successful treatment of CNS aspergillosis with micafungin and caspofungin, however, has been reported [48,49].

Flucytosine

Flucytosine is a fluorinated pyrimidine analogue taken up by the fungal enzyme cytosine permease and incorporated, causing RNA miscoding and inhibiting DNA synthesis. Flucytosine resistance can develop at the level of the cytosine permease or at the cytosine deaminase and develops rapidly in the setting of monotherapy. Flucytosine penetrates the CNS well [50]. Primary side effects are hepatotoxicity and bone marrow suppression, which can be minimized by therapeutic drug-level monitoring [51].

Flucytosine has activity against *Candida*, *Cryptococcus* and *Saccharomyces* and has been demonstrated to have synergistic action with amphotericin B in induction therapy for cryptococcal meningitis [33]. If amphotericin B is not a therapeutic option, flucytosine may be combined with fluconazole for treatment of cryptococcal meningitis or severe candidiasis [33].

Conclusion

With increasing numbers and types of immunocompromised patients, clinicians must maintain a high index of concern for fungal infections of the CNS. Given the nonspecific disease pattern of invasive CNS fungal infection, the pursuit of a specific diagnosis is important and often requires a lumbar puncture or brain biopsy. By defining the specific infecting organism, targeted antifungal therapy can be deployed.

References and recommended reading

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