# Fungal Infections of the Central Nervous System

## Pathogens, Diagnosis, and Management

Mehmet Turgut
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ISBN 978-3-030-06087-9 ISBN 978-3-030-06088-6 (eBook)
https://doi.org/10.1007/978-3-030-06088-6



This Springer imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

# Preface I

Fungal infections of the central nervous system, once considered rare, have become more frequent and pose a diagnostic and therapeutic challenge in the day-to-day practice. Better awareness of the epidemiological features and elucidation of the risk factors along with advancements in technology in imaging and molecular diagnostics contributed to better understanding of the disease mechanisms and diagnosis. However, geographic variations due to environmental factors, emerging fungi in different clinical scenarios, and genetic factors influence the incidence of fungal infections. Though there is a wealth of information on fungal infections of the central nervous system, textbook like this provides a comprehensive and rapid access to the various aspects of these diseases and serves as a ready reference for the trainee and practicing neuroscientists.

The book has six sections with each section dedicated to one aspect of the disease. The authors were chosen from various parts of the world, based on their contributions and special interest in that subspecialty. Each chapter was edited by an expert in the field to provide concise and up-to-date information on the subject. The chapters were well-illustrated with tables and figures and provided with extensive references to guide further reading for residents, neurologists, internists, and neurological surgeons.

We are grateful to all the authors for their contributions and support to complete this book project in time. We especially wish to thank Springer Nature for their support in ensuring quality publication of the book. We are truly humbled by this experience. We hope this book will be a unique and important addition to the existing books on this subject.

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# Preface II

Fungi are ubiquitous organisms found in the soil, water, and environment. Infections of humans are uncommon with only a few species being pathogenic. However, with changes in the environmental factors and immune status of individuals, fungal infections are on the rise. The incidence of fungal infections of the central nervous system (CNS) parallels that of the systemic fungal infections. Fungal infections of the CNS are being increasingly diagnosed in the past few decades due to steady increase in the number of immunosuppressed individuals, better awareness, and improved diagnostic modalities. Infections of the CNS are associated with high morbidity and mortality, but the diagnosis and treatment remain a challenge. Understanding the pathogenesis and host pathogen interactions helps in devising new diagnostic modalities and therapeutic interventions.

The etiologic agents include yeasts, filamentous fungi, and dimorphic fungi. The common yeast fungi include *Cryptococcus* and *Candida*, whereas filamentous fungi with hyaline septate hyphae include *Aspergillus*, *Fusarium*, and *Mucorales* and the pigmented fungi include dematiaceous fungi. The dimorphic fungi include *Blastomyces*, *Histoplasma*, *Coccidioides*, and *Paracoccidioides*. *Aspergillus* and *Mucorales* are usually opportunistic, but *Aspergillus* can cause infections in immunocompetent hosts in certain geographical regions. Dematiaceous fungi are neurotropic and cause infection in immunocompetent hosts, and dimorphic fungi cause infections which are geographically restricted.

The portal of entry is usually by inhalation and subsequent hematogenous dissemination to the CNS. The infection may spread from contiguous structures like paranasal sinuses, orbit, mastoid, or skull bone and by direct inoculation from surgery or trauma.

The size of the conidia or yeast, the virulence factors, and angioinvasiveness of the fungus are important in the pathogenesis. The interplay between host defenses and the strategy of the pathogen to evade immune attack, acquire nutrients, degrade extracellular matrix, and disseminate are not yet completely understood.

The immune status, portal of entry, type of the fungus, and virulence of the organism determine the pathology which in turn manifests as the clinical syndrome. The clinical syndromes include meningitis, intracranial space-occupying lesion, stroke-like manifestation, or spinal syndrome. The pathology includes abscess, granuloma, meningitis, infarct with or without

hemorrhage, or subarachnoid hemorrhage. Imaging provides important clues to diagnosis in appropriate clinical setting.

Diagnosis is established by cerebrospinal fluid examination or tissue obtained at surgery along with culture. Histopathology is useful for delineation of fungal morphology, but species confirmation by culture is needed. Molecular tests, especially in disseminated disease, are warranted. Serum galactomannan is widely used but has several limitations. High index of clinical suspicion in appropriate clinical setting, along with epidemiological consideration, is important for early diagnosis. Management includes neurosurgical intervention, especially for intracranial space-occupying lesions, administration of antifungal treatment, and correction of immune impairment or risk factors.

In this textbook, in several chapters contributed by experts in the field, the epidemiological, clinical, diagnostic, and management aspects of various fungal infections of the CNS are addressed.

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# Contents

# Part I

# General Considerations

# Historical Aspects of Fungal Infections

1

Nikolaos Ch. Syrmos, Vaitsa Giannouli, and Mehmet Turgut

## Abbreviations

CNS Central nervous system
CSF Cerebrospinal fluid
USA United States of America

## 1.1 Introduction

Scientific research documented in the particular field of fungal infections should be explored through the perspectives of continuously changing biological, medical, and public profiles. In this chapter, a brief review of ancient to modern approaches to manage the central nervous system (CNS) infections caused by fungal pathogens will be given according to the historical references in the following subheadings of the history of medicine: "Ancient Greece," "Mid Modern Period," and "Contemporary Period."

## 1.2 Ancient Greece

The description and the scientific study of fungal infections remains an interesting and attractive topic since the antiquity. The father of the documented medicine, Hellenic Hippocrates of Kos, was the first physician who observed (Ancient Greek word παρατήρισις) and described the candidiasis phenomenon with white patches into the oral cavity in a weak and infirm patient. His main contribution initiated the human society's development of medicine through a well-documented and delicate blending of the art of healing and scientific observations and studies (Fig. 1.1) (Syrmos et al. 2010; Giannouli and Syrmos 2011; Syrmos 2011).

## 1.3 Mid Modern Period

Pier Antonio Micheli (1679–1737 AD) (Fig. 1.2), a catholic priest from Pisa, Central Italy, in his observations and studies, described *Aspergillus* (Schaechter 2011). Initially, his aim was to study the nine different fungal species that resembled aspergillum (Sumbali and Johri 2005). This was very often used, perforated, to sprinkle the holy water during Christian ceremonies (Schaechter 2000). Antonio also became a well-known academic botanist, a ranking professor, and also a curator of the Orto Botanico di Firenze, in Central Italy (Giardino dei Semplici). He made various

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M. Turgut et al. (eds.), *Fungal Infections of the Central Nervous System*,
https://doi.org/10.1007/978-3-030-06088-6_1

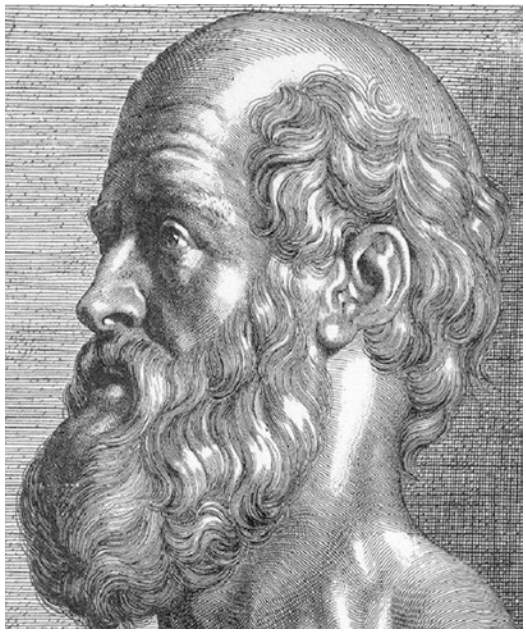

**Fig. 1.1** A photograph of Hippocrates of Kos


**Fig. 1.2** A photograph of Pier Antonio Micheli (1679–1737 AD)

well-documented projects and wrote a paper entitled "Nova plantarum genera: iuxta Tournefortii methodum disposita" (Geronimus 2007). Over the years, he performed profound research about mushroom spores, managed to become an undisguised authority on cryptogams, and became a widely recognized figure in the scientific community of his era (Geronimus 2007). His main achievement was the connection between generations of microfungi such as *Aspergillus*, *Botrytis*, and others (Schaechter 2000; Geronimus 2007).

**Fig. 1.3** A photograph of Alejandro Posadas (1870–1902 AD)

Later, around 1840, the fungal etiology of these manifestations was documented, thanks to the Berg-Bennett studies (Gholami-Shabani et al. 2018). Kurchenmeister in 1855 was the first who described human zygomycetes after isolation of nonseptate hyphae from a cancerous lung (Guého et al. 1992). Twenty one years later in 1861, Zenkar described the first case of human intracerebral candidiasis (McPartland and Goff 1991).

In 1892, Alejandro Posadas (1870–1902 AD) (Fig. 1.3), an Argentinian surgeon specializing in the general and pediatric surgery, started his scientific collaboration with Carl Wernicke (1848–1905 AD). Wernicke was at the same time an anatomist and a psychiatrist, from Germany (Fig. 1.4) (Sharpton et al. 2009; Miranda 2015). Together, they performed a series of well-documented neurological, biological, and specific pathological studies about human coccidioidomycosis.

**Fig. 1.4** A photograph of Carl Wernicke (1848–1905 AD)

Invaluable studies were performed by Abraham Buschke (1868–1943 AD) from Nakel, Posen, Germany (Fig. 1.5) (Sharpton et al. 2009). He was actually a dermatologist (Miranda 2015). In 1894, in collaboration with Otto Busse (1867–1922 AD), they described the "Busse-Buschke disease," an infectious pathological situation caused by the fungus *Cryptococcus neoformans*.

Around 1897, Oppe presented in the scientific community the first case of cerebral aspergillosis extending from sphenoid sinusitis (Antoniades et al. 2008). In 1905, Von Hansemann demonstrated *Cryptococcus* in cerebrospinal fluid (CSF) (Genkal et al. 2011). The name *Cryptococcus* was derived from the Greek word *kryptus* meaning "hidden." It was used to describe a specific group of yeasts that lacked the ability to produce endospores by Friedrich Traugott Kützing (1807–1893 AD), a German pharmacist, botanist, and phycologist (Fig. 1.6) (McPartland and Goff 1991; Sharpton et al. 2009).

In the same time period, cerebral *Cryptococcus* and the blast mycosis were described, and the organism was successfully grown in culture

**Fig. 1.5** A photograph of Abraham Buschke (1868–1943 AD)

**Fig. 1.6** A photograph of Friedrich Traugott Kützing (1807–1893 AD)

(Miranda 2015). The triple scientific collaboration between Smith, Sano, and Miale reported the instances of meningeal implication caused by

*Candida albicans* (Antoniades et al. 2008; Genkal et al. 2011). They also described *Candida* meningitis for the first time (Gavito-Higuera et al. 2016; Pappas et al. 2016; Correia and Campos 2003).

## 1.4 Contemporary Period

Ophuls made the first human report of a coccidioidal brain lesion during his studies around 1905 (Huntington 1976, 1985). The next huge step in understanding the disease was made by William Ophuls (Patrick Ophuls) (1871–1933 AD) (Fig. 1.7), an academic pathologist in 1921, in Stanford Medical School, USA. Ophuls managed to clearly identify the fungal nature of this organism with mice transmission (Huntington Jr. 1986). He performed clinical studies of the disease in a documented series of cases of coccidioidomycosis in a patient who died because of disseminated coccidioidomycosis, the first documented case of the disease in the history (Hirschmann 2007). After decades of studies and many efforts, the researchers made the clear definition and manifestation of coccidioidomycosis in scientific publications. Further description of the disease was reported by Evans in 1909. The first case with both coccidioidal meningitis and hydrocephalus was described by Ryfkogel. He managed also to perform an accurate description of coccidioidal meningitis (Veterans Affairs Armed Forces, 1955–1958) (Correia and Campos 2003).

Adolfo Lutz (1855–1940 AD), a Brazilian physician and pioneer tropical medical doctor, was the first to describe paracoccidioidomycosis in 1908 (Fig. 1.8). He performed zoological studies, epidemiological investigations, and infectious diseases research (Correia and Campos 2003).

**Fig. 1.7** A photograph of William Ophuls (1871–1933 AD)


**Fig. 1.8** A photograph of Adolfo Lutz (1855–1940 AD)

Morris was the first to report coccidioidomycosis as the only site of dissemination outside of the pulmonary area in 1924 (Morris 1924). Abbott and Cutler made review studies regarding 14 cases in 1936 with description of the typical CSF findings (Correia and Campos 2003). Subsequent pathological reports were very important in order to clarify the association between meningeal involvement and CNS coccidioidal infection (Spellberg et al. 2005).

Edmond Isidore Etienne Nocard (1850–1903 AD) performed studies in Provins (Seine-et-Marne, France) (Fig. 1.9) (Haas 2000). He was the first scientist who managed to describe the acid-fast aerobic cattle actinomycetes (Mathijsen 2003). Trevisan called them by the name *Nocardia farcinica* in 1889 (Pospischil 2002). An essential step was performed in 1891 by Eppinger with the first documented report of metastatic human cerebral nocardiosis from the lung (Pospischil 2002).

Histoplasmosis was described by Darling around 1906: the report was about a documented disseminated granulomatous infection in a patient (Beolens et al. 2011). About 18 years later in 1924, Morris reported a unique case of coccidioidomycosis outside the pulmonary function as a result of dissemination (Smit et al. 2003). Then, a total of 14 cases of typical CSF findings were reviewed by Abbott and Cutler in 1936 (Abbott and Cutler 1936). The association of meningeal involvements with coccidioidal infections of the CNS was documented in an accurate pathological report.

**Fig. 1.9** A photograph of Edmond Isidore Etienne Nocard (1850–1903 AD)

In general, histiocytes were studied with *Histoplasma capsulatum.* On the other hand, rhinocerebral zygomycosis was accurately described and presented in a series of three cases by Gregory Binford in Maryland, USA, in 1943 (Chiller 2016). In 1952, he published a case report of brain abscess attributed to *Cladosporium* (Chiller 2016).

Moreover, we have to mention that before the use of the antifungal drugs, such cases with combination of fungal infections of the CNS and later improvement following surgical removal of cerebral abscess and evacuation of granulomatous lesion were rarely published in the current literature. In 1903, antifungal chemotherapy started successfully using potassium iodide in cases of cutaneous or subcutaneous sporotrichosis (Chiller 2016). The next decades involved with the introduction of mucosal and systemic mycoses: in 1953, nystatin, the first useful polyene drug, and in 1956, amphotericin B, the second useful polyene drug. Amphotericin B remains till today the best option about these infection types (Moen et al. 2013). Although these infections have been recognized for over a century, until the use of amphotericin B, fungal infections of the CNS remained a pathological situation with difficult effective treatment.

During the next few years, in 1964, flucytosine (5-fluorocytosine); in 1970, azole drugs; in 1978, miconazole; in 1981, ketoconazole; in 1990, fluconazole; in 1992, itraconazole; and in 2000–2010, other drugs against the fungal infections of the CNS were developed (Chiller 2016; Moen et al. 2013). In order to avoid the toxicity of amphotericin B, the following were introduced: liposomal amphotericin B with/without lipids, triazoles like voriconazole and posaconazole, and echinocandins like anidulafungin,

caspofungin, and micafungin (Chiller 2016). The use of these combinations in situations such as cases of patients with severe invasive mycoses provided good results and in this way improved the outcome and ameliorated the health-related quality of life of these patients (Moen et al. 2013).

Finally, Fragoyannis, van Wyk, and de Beer reported of North American blastomycosis in South Africa (Fragoyannis et al. 1977). Gonyea (1978) reported a three-patient series with blastomycosis meningitis without extracranial infection (Schlech et al. 1985; Hurwitz et al. 1986).

## 1.5 Conclusion

Fungal infections have been known since early times, in particular since the nineteenth century. Although many fungal infections of the CNS are rare, there is no doubt further research is still needed in order to describe their formation in detail. Microbiologically, there are some morphologic similarities in various fungi, and therefore there is a difficulty in differential diagnosis of these complex forms but also the functional deficits that may cause.

## References


Abbott KH, Cutler OI. Chronic coccidioidal meningitis: review of the literature and report of seven cases. Arch Pathol. 1936;21:320–30.

Antoniades D, Hamilton PB, Douglas MSV, Smol JP. Diatoms of North America: the freshwater floras of Prince Patrick, Ellef Ringnes and northern Ellesmere Islands from the Canadian Arctic Archipelago. Iconogr Diatomol. 2008;17:1–64.

Beolens B, Watkins M, Grayson M. The eponym dictionary of reptiles. Baltimore, MD: Johns Hopkins University Press; 2011.

Chiller TM. Histoplasmosis. CDC yellow book: CDC Health Information for International Travel. 2016.

Correia MI, Campos AC. Prevalence of hospital malnutrition in Latin America: the multicenter ELAN study. Nutrition. 2003;19:823–5.

Fragoyannis S, van Wyk G, de Beer M. North American blastomycosis in South Africa: a case report. S Afr Med J. 1977;51:169–71.

Gavito-Higuera J, Mullins CB, Ramos-Duran L, Olivas Chacon C, Hakim N, Enrique Palacios E. Fungal infections of the central nervous system: a pictorial review. J Clin Imaging Sci. 2016;6:24.

Genkal SI, Bondarenko NA, Schur LA. Diatoms in the lakes of the Southern and Northern Eastern Siberia. Rybinsk: Rybinsky Dom Pechati; 2011. p. 71.

Geronimus D. Piero di Cosimo: visions beautiful and strange. New Haven, CT: Yale University Press; 2007.

Gholami-Shabani M, Zamani S, Moosa H, Ghahfarokhi M, Jamzivar F, Mehdi Razzaghi-Abyaneh M. Recent advances in fungal infections of the central nervous system: from etiology to diagnosis and management. In: Kon K, Rai M, editors. The microbiology of central nervous system infections. Volume 3 in clinical microbiology: diagnosis, treatments and prophylaxis of infections. Cambridge, MA: Academic Press; 2018. p. 215–59.

Giannouli V, Syrmos N. Information about Macedonian medicine in ancient Greece. Hell J Nucl Med. 2011;14:324–5.

Guého E, de Hoog GS, Smith MT. Neotypification of the genus Trichosporon. Antonie Van Leeuwenhoek. 1992;61:285–8.

Haas L. Edmond Isidore Etienne Nocard (1850–1903). J Neurol Neurosurg Psychiatry. 2000;69:1.

Hirschmann JV. The early history of coccidioidomycosis: 1892–1945. Clin Infect Dis. 2007;44:1202–7.

Huntington RW. William Ophuls, pioneer coccidioidomycologist. Sabouraudia. 1976;14:231–5.

Huntington RW. Four great coccidioidomycologists: William Ophuls (1871–1933), Myrnie Gifford (1892–1966), and Charles Edward Smith (1904–1967) and William A. Winn (1903–1967). Sabouraudia. 1985;23:361–70.

Huntington RW Jr. Coccidioidomycosis—a great imitator disease. Arch Pathol Lab Med. 1986;110:182.

Hurwitz MD, Kallenbach JM, Behr A, Chun R, Baynes RD. Blastomycosis: a case report. S Afr Med J. 1986;70:622–4.

Mathijsen AH. Predecessors: veterinarians from earlier times (51). Edmond Isidore Etienne Nocard (1850–1903). Tijdschr Diergeneeskd. 2003;128:488–9.

McPartland JM, Goff JP. Neotypification of Trichosporon beigelii: morphological, pathological and taxonomic considerations. Mycotaxon. 1991;41:173–8.

Miranda E. Coccidioides posadasii. The encyclopedia of life (EOL) the earliest account of human cryptococcosis (Busse-Buschke disease) in a woman with chronic osteomyelitis of the tibia. Pediatr Infect Dis J. 2015;34:1278.

Moen MD, Lyseng-Williamson KA, Scott LJ. Liposomal amphotericin B. Drugs. 2013;69:361–92.

Morris M. Coccidioides of the central nervous system. California West Med. 1924;22:483–5.

Pappas PG, Kauffman CA, Andes DR, Clancy CJ, Marr KA, Ostrosky-Zeichner L, Reboli AC, Schuster MG, Vazquez JA, Walsh TJ, Zaoutis TE, Sobel JD, Kauffman CA, Andes DR. Clinical practice guideline

for the management of Candidiasis: 2016 update by the Infectious Diseases Society of America. Clin Infect Dis. 2016;62(4):e1–50.

Pospischil A. Chlamydia, if it exists, is everywhere. Edmond Nocard (1850–1903). Schweiz Arch Tierheilkd. 2002;144(9):461.

Schaechter M. Pier Antonio Micheli, the father of modern mycology: a paean. In: McIlvainea. Official organ of the NAMA, vol. 14 2000.

Schaechter M. Eukaryotic microbes. Amsterdam: Academic Press; 2011. p. 19.

Schlech WF, Ward JI, Band JD, Hightower A, Fraser DW, Broome CV. Bacterial meningitis in the United States, 1978 through 1981. The national bacterial meningitis surveillance study. JAMA. 1985;253:1749–54.

Sharpton TJ, Stajich JE, Rounsley SD, Gardner MJ, Wortman JR, Jordar VS, Maiti R, Kodira CD, Neafsey DE, Zeng Q, Hung CY, McMahan C, Muszewska A, Grynberg M, Mandel MA, Kellner EM, Barker BM, Galgiani JN, Orbach MJ, Kirkland TN, Cole GT, Henn MR, Birren BW, Taylor JW. Comparative genomic analyses of the human fungal pathogens Coccidioides and their relatives. Genome Res. 2009;19:1722–31.

Smit LHM, Leemans R, Overbeek BP. Nocardia farcinica as the causative agent in a primary psoas abscess in a previously healthy cattle inspector. Clin Microbiol Infect. 2003;9:445–8.

Spellberg B, Edwards J Jr, Ibrahim A. Novel perspectives on mucormycosis: pathophysiology, presentation, and management. Clin Microbiol Rev. 2005;18:556–69.

Sumbali G, Johri BM. The fungi. Oxford: Alpha Science International Limited; 2005. p. 11.

Syrmos N. Microcephaly in ancient Greece—the Minoan Microcephalus of Zakros. Childs Nerv Syst. 2011;27:685–6.

Syrmos N, Ampatzidis G, Fachantidou A, Mouratidis A, Syrmos C. Historical back training in most important points of neurosurgery. Ann General Psychiatry. 2010;9(Suppl 1):S89.

# 2 Epidemiology of Central Nervous System Fungal Infections

Sanjeet Singh Dadwal

## Abbreviations

| | |
|---|---|
| CARD9 | Caspase recruitment domain-containing protein 9 deficiency |
| CGD | Chronic granulomatous disease |
| CNS | Central nervous system |
| GvHD | Graft-versus-host disease |
| HCT | Hematopoietic cell transplantation |
| HIV/AIDS | Human immunodeficiency virus/acquired immunodeficiency syndrome |
| ICU | Intensive care unit |
| IFI | Invasive fungal infection |
| SOT | Solid organ transplantation |
| TNF-α | Tumor necrosis factor-alpha |

## 2.1 Introduction

The burden of invasive fungal infection (IFI) has been increasing in both immunocompetent and the immunocompromised hosts (Vallabhaneni et al. 2016). This phenomenon is due to multiple factors that include increased awareness of fungal infections leading to an increased diagnostic testing, improvements in the diagnostic capabilities, and an ever-increasing pool of at-risk population: cancer, hematopoietic cell transplantation (HCT), solid organ transplantation (SOT), newer immunosuppressive therapies, and neonatal and elderly patients (Powers-Fletcher and Hanson 2016; Vallabhaneni et al. 2016). The spectrum includes fungi that are opportunistic pathogens and true pathogens (latter can lead to fungal infection without any apparent immunodeficiency). This chapter will discuss general considerations of central nervous system (CNS) IFI epidemiology and epidemiology of specific class of fungi: yeasts and molds that are most commonly associated with CNS infection.

## 2.2 General Considerations of Epidemiology of CNS Fungal Infection

In the absence of an immunocompromising condition, fungal infection of the CNS is uncommon as the host defense and the anatomy of the CNS (functional and structural) help prevent invasion of their CNS (Chakrabarti 2007; Marra et al. 2014). Although this protects vast majority of mankind, exposures related to diverse environmental/ecological niches of various fungal pathogens can lead to IFI in the context of their endemic distribution: *Coccidioides* (Brown et al. 2013), *Cryptococcus gattii* (Chen et al. 2014; Datta et al. 2009), *Histoplasma* (Chu et al. 2006; Hammerman et al. 1974), and *Blastomyces*

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M. Turgut et al. (eds.), *Fungal Infections of the Central Nervous System*,
https://doi.org/10.1007/978-3-030-06088-6_2

(Baumgardner et al. 1992; Dworkin et al. 2005). The sinonasal fungal infection when invasive in nature can extend beyond the extracranial compartment into the brain (Kourkoumpetis et al. 2012; McCarthy et al. 2014) and may manifest as meningitis or space-occupying lesions/abscess. Certain epidemiologic exposures such as drowning have led to infection of the CNS with *Scedosporium apiospermum* (Kantarcioglu et al. 2008) and *Aspergillus* spp. (Kowacs et al. 2004). Diabetic ketoacidosis, steroid use, and iron overload are known risk factors for mucormycosis (Spellberg et al. 2005). Furthermore, iatrogenic fungal infections have occurred in the setting of outbreaks such as with *Exserohilum rostratum* due to contaminated compounded methylprednisolone for spinal injections in 2013 (Chiller et al. 2013), *Exophiala* infection from contaminated injectable steroids (From the Centers for Disease Control and Prevention 2003), and *Aspergillus* meningitis after spinal anesthesia in pregnant women (Gunaratne et al. 2007).

Perhaps, the most significant group that contributes to the burden of IFI is the immunocompromised patient. The high-risk group include, neutropenia in patients undergoing cytotoxic chemotherapy for hematologic malignancy, those who have undergone allogeneic HCT (Kontoyiannis et al. 2010), especially those with graft-versus-host disease (GVHD) requiring immunosuppressive therapy, SOT (Pappas et al. 2010; Singh 2003; Singh and Paterson 2005), use of biologic agents such as TNF-α (Warris et al. 2001), use of Bruton tyrosine kinase inhibitor, ibrutinib (Bercusson et al. 2018; Peri et al. 2018), congenital immunodeficiency such as chronic granulomatous disease (CGD) (Alsultan et al. 2006; Dotis et al. 2007; Henriet et al. 2013), and caspase recruitment domain-containing protein 9 deficiency (CARD9) (Gavino et al. 2014; Lanternier et al. 2015; Rieber et al. 2016). Within the SOT recipients, the type of organ transplant has an impact on the risk of IFI (Munoz et al. 2016). ICU patients are also at high risk for IFI: mainly candida and aspergillus (Denning 2004; Pittet et al. 1994). Patients with human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) are at high risk for cryptococcal infection (Rajasingham et al. 2017), and the risk correlates with the status of the cell-mediated immunity.

The CNS IFI can manifest as meningitis, which is the inflammation of the meninges. The symptoms are often protean and can vary from acute onset to subacute and chronic in nature. Patients often present with headaches that are subacute to chronic and may have visual changes, cranial nerve abnormalities, and other symptoms of elevated intracranial pressure. Nuchal rigidity may or may not exist. At times, patients may present with the symptoms/signs of cerebritis suggesting parenchymal involvement. The inflammatory component can result in endarteritis that may result in stroke manifesting with focal neurologic defects. In patients with immunocompromised state, symptoms and signs may be minimal or atypical that often result in delayed diagnosis. Intracranial abscess-/mass-like lesions are mostly encountered with invasive mold infections. Mold infections of the CNS are mostly encountered in the immunocompromised patients and typically present with space-occupying parenchymal lesions/abscesses and less likely to be associated with meningitis.

This chapter will provide an outline of the epidemiology for CNS infections related to common fungal pathogens (true and opportunistic), and the description will be centric to the specific organism.

## 2.3 Yeast Infections of the CNS

### 2.3.1 *Cryptococcus neoformans*

This pathogen belongs to basidiomycetous fungi and is the leading cause of CNS fungal infection manifesting as meningitis and may be accompanied by brain abscesses "cryptococcomas." Its distribution is worldwide and is ubiquitously found in soil, bird droppings, and animals. Humans can be colonized with it as well. There are eight genotypes, with the most common being *C. neoformans* var. *neoformans* in the USA and Europe. *C. neoformans* var. *grubii* is most common in the rest of the world. The most significant burden from this pathogen is in the

HIV/AIDS patient population, and the risk of developing this infection is directly correlated with the cell-mediated immunity that increases with the declining CD4 count (most cases occur when CD4 is <100 cells/μl) (Rajasingham et al. 2017). With the availability of HAART, the incidence of cryptococcal CNS infection has decreased in the USA, although it is still a major cause for morbidity and mortality in the developing world (Rajasingham et al. 2017). After HIV/AIDS, SOT recipients have the highest rate of CNS infection (Pappas et al. 2010), but it is rare in recipients of HCT (with more cases observed in autologous than allogeneic) (Kontoyiannis et al. 2010). In the SOT, *Cryptococcus* contributed to 8% of all IFI in a large prospective study (Pappas et al. 2010), and the CNS is the most common extrapulmonary site of infection. Increased risk for CNS involvement was correlated with abnormal mental status, late-onset disease, and high serum cryptococcal antigen titer (Osawa et al. 2010).

*C. gattii* is an emerging pathogen worldwide that was previously described primarily in tropical and subtropical areas such as Australia, New Guinea, Hawaii, Southern California, Central Africa, and Southeast Asia (Maziarz and Perfect 2016). Originally described with eucalyptus trees, the recent outbreaks noted association with trees such as oaks and firs. There has been an evolving epidemic in the Vancouver Island and Pacific Northwest, USA, and cases have been described in multiple states across the USA (Harris et al. 2011). This pathogen primarily affects the healthy individuals although there is an association with anti-GM-CSF antibodies and *C. gattii* infection (Rosen et al. 2013; Saijo et al. 2014). The disease process is frequently severe with meningitis and cryptococcomas in the immunocompetent patients (Chen et al. 2014).

### 2.3.2 *Candida*

*Candida* species are an important cause of healthcare-associated infection presenting as disseminated infection (candidemia). They are found in soil, on inanimate objects, and on hospital surfaces and colonize the respiratory/GI tract of normal and immunocompromised hosts. The risk factors for candidemia include critically ill neonates associated with prematurity, low APGAR score, shock, intubation and congenital malformations, neutropenic host, HCT recipients with mucositis or graft-versus-host disease (GVHD) of the gut, SOT, use of broad-spectrum antibiotics, central venous catheter, intravenous drug use, total parenteral nutrition, gastrointestinal surgery, diabetes, sepsis, pancreatitis, ICU stay, and dialysis (Blumberg et al. 2001). *C. albicans* is the most frequent cause of infection in the USA followed by *C. glabrata* (Matsumoto et al. 2014), and there is variability in the distribution of species based on geography and patient population (Pfaller et al. 2012); *C. glabrata* is more frequently isolated from SOT and elderly patients. Additionally, there has been emergence of drug-resistant *Candida* spp. such as triazole and echinocandin resistance in *C. glabrata* (Pfaller et al. 2010; Pfaller et al. 2011). *Candida auris*, a multidrug-resistant candida species, has gained notoriety in recent years as a cause of outbreaks associated with high morbidity and mortality (Sarma and Upadhyay 2017).

*Candida* used to be the most common cause of fungal meningitis, but that has been replaced by *C. neoformans*. *Candida* meningitis/brain abscesses occur in the context of disseminated candida infection in premature infants and neonates (Faix 1984; Fernandez et al. 2000) and patients with AIDS (Casado et al. 1997), neutropenia from chemotherapy (Flynn et al. 1993), CGD (Cohen et al. 1981), and SCID (Smego Jr et al. 1984). Direct inoculation may occur with traumatic injuries (Brenier-Pinchart et al. 1999), CNS ventricular shunts (Baradkar et al. 2009; Shapiro et al. 1989) and polymer wafers used in local chemotherapy are additional risk factors (Glick et al. 2010).

### 2.3.3 *Coccidioides*

The disease caused by *Coccidioides* is commonly referred to as coccidioidomycosis or "valley fever," named after the common

occurrence of this endemic fungal infection in the San Joaquin Valley in California. *C. immitis* and *C. posadasii* are the two species that cause disease in humans. It is a dimorphic fungus that is able to survive in dry and arid environment. It is highly infectious and inhalation of even a few arthroconidia can lead to infection (Kong et al. 1964). Endemic areas include California, with particularly high rates in Kern and Fresno counties, Arizona, New Mexico, Nevada, Utah, Washington, Texas, Mexico, Central America, Honduras and Guatemala, and South America: Brazil, Venezuela, Argentina, and Paraguay (Stevens 1995). Changing environmental and human factors in the endemic area, changes in surveillance and definitions, diagnostic methods, and increasing pool of immunocompromised patients may be affecting the increase of rates in California and Arizona (Stockamp and Thompson 3rd 2016). Certain natural disasters such as major earthquakes (Schneider et al. 1997), digging/excavation activities, and dust storms may lead to local epidemics. Coccidioidal meningitis is a dreaded complication that is associated with significant morbidity and mortality. Basilar meningitis with its inflammatory exudate is commonly complicated with obstructive hydrocephalus that requires ventricular shunt. Patients with coccidioidomycosis with headache, visual changes, or any CNS symptom or sign should undergo spinal tap.

In a study of allogeneic HCT recipients living in endemic areas with prior history of exposure/infection, 11/426 (2.6%) were noted to develop active coccidioidomycosis post-HCT (Mendoza et al. 2015). In a study with SOT recipients with prior history of coccidioidomycosis, reactivation was observed in 5% despite antifungal prophylaxis (Keckich et al. 2011). Mortality rates of up to 55% have been reported in allogeneic HCT (Mendoza et al. 2015) and 28% in SOT (Mendoza and Blair 2013). Other risk factors include the use of TNF-α blockers (Bergstrom et al. 2004) and HIV/AIDS (CD4 less than 250) (Masannat and Ampel 2010), pregnant women, and race. It is more frequently observed in African Americans and Filipinos with the propensity to develop CNS involvement.

### 2.3.4 *Blastomyces*

*Blastomyces dermatitidis* is a dimorphic fungus that is endemic in the Midwestern states of the USA, Canadian provinces along the great lakes, and the Mississippi and Ohio river valleys (Castillo et al. 2016). Cases have been reported from other states and countries too. Even though surveys from Wisconsin show high rates of endemicity, the true prevalence is unknown, secondary to a lack of mandatory reporting. The infection has been associated with exposure to decaying wood or disturbing the soil. The most common site of infection is the skin and lungs with the propensity to develop disseminated disease. CNS involvement occurs in about a third of all infected patients. In a pediatric study that reviewed 114 children with *Blastomyces* infection, 21% had extrapulmonary disease, and only 2 had CNS involvement. The majority of the infections were due to *B. gilchristii* followed by *B dermatitidis*, and the latter was associated with more extrapulmonary disease (Frost et al. 2017). In a study of 22 patients with CNS involvement, 22.7% had isolated involvement of the CNS (Bariola et al. 2010). Presentation varies from symptoms/signs of acute meningitis to chronic meningitis and brain abscess. AIDS patients have high burden from CNS disease developing in 40% of patients (Grim et al. 2012), while it is of rare occurrence in SOT and HCT recipients (Kauffman et al. 2014). Furthermore, the use of corticosteroids and TNF-α blockers also increases the risk (Pappas et al. 1993; Smith and Kauffman 2009).

*Blastomyces helicus* is an emerging fungus that has been reported to be associated with disseminated disease with CNS involvement in 20% of the infected patients. The primary route of acquisition is inhalational and skin involvement is rare. In a case series of ten patients, six had underlying immunocompromising condition, and 50% had fungemia which is extremely uncommon with *B. dermatitidis* (Schwartz et al. 2018).

### 2.3.5 *Histoplasma*

*Histoplasma capsulatum* leads among the other causes for endemic mycoses (Chu et al. 2006; Hammerman et al. 1974). In the USA, it is most

prevalent in the Ohio and Mississippi river valleys. Outside of the USA, it has been reported from Mexico, South American countries, parts of Asia, and Southeast Asia. Exposure to soil rich in bird or bat guano is a risk factor for the acquisition of *Histoplasma* (Wheat et al. 2016). The activities that are mostly reported to be significant exposures include farming, cave exploration, remodeling of old buildings, clearing brushes, or cutting trees at sites that had supported blackbird roosting. The highest numbers were seen in the context of HIV/AIDS epidemic (Assi et al. 2007; Kaur and Myers 1983) and, subsequently, exposure in the immunocompromised patients with T cell dysfunction, exposure to TNF-α blockers, SOT, and HCT (Wheat et al. 2016). It is encountered more commonly in the SOT group, while a lower incidence is observed in HCT recipients (Kauffman et al. 2014). Dissemination to the CNS is infrequent and is mostly observed in the immunocompromised patient with development of meningitis or focal lesions in 5–10% of the cases (Chen et al. 2014). A recent retrospective study reviewing 77 cases noted male predominance with most frequent underlying diagnosis of HIV/AIDS in 44% followed by transplantation in 13%, and 14% had other immunocompromising conditions (Wheat et al. 2018). Morbidity and mortality are high in patients with CNS involvement.

### 2.3.6 *Sporothrix schenckii*

*S. schenckii* is a dimorphic fungus that is most commonly found in the tropical and subtropical areas. It has been reported mostly from Japan, India, Mexico, Brazil, Uruguay, and Peru. In the USA, outbreaks related to pine seedlings and manipulation of the moss have been reported from the Mississippi Valley (Barros et al. 2011). The activities associated with risk for acquisition of *Sporothrix* are agriculture, floriculture, wood exploration, mining, and exposure to cats that are infected with this fungus (veterinarians, owners, and caretakers of cats) (Barros et al. 2004; Vilela et al. 2007). The most common site of infection is the skin although it can be acquired via inhalation and has the propensity to disseminate in the immunocompromised patients (Barros et al. 2011). CNS involvement has been reported in patients with underlying immunodeficiency (Gullberg et al. 1987; Hardman et al. 2005) and mostly manifests as meningitis.

## 2.4 Mold Infections of CNS

### 2.4.1 *Aspergillus*

The increase in the number of at-risk patients undergoing transplantation, chemotherapy for hematologic malignancies, and use of novel immunosuppressive medications has led to a spurt in invasive aspergillosis. *Aspergillus* spp. have a ubiquitous distribution in the nature and are commonly found in soil, decaying vegetation, and food material. The primary route of acquisition is inhalational, although infection related to skin patch dressing and trauma has been observed.

Risk factors for invasive aspergillosis include neutropenia in patients undergoing induction chemotherapy for hematologic malignancy and HCT especially in the context of GVHD that requires treatment with steroids or agents such as infliximab, and ibrutinib (bruton tyrosine kinase inhibitor) and in SOT (Bercusson et al. 2018; Kourkoumpetis et al. 2012; McCarthy et al. 2014; Pappas et al. 2010; Peri et al. 2018; Singh and Paterson 2005). Inherited conditions such as CGD and CARD9 deficiency are also associated with increased risk of *Aspergillus* infection (Alsultan et al. 2006; Dotis et al. 2007; Henriet et al. 2013; Rieber et al. 2016). Patients with diabetes, recent CNS surgery, lumbar puncture, paranasal sinusitis, chronic steroid use, intravenous drug use, pulmonary tuberculosis, and alcoholic liver disease are also at risk.

*Aspergillus* is now the most common cause of IFI in the allogeneic HCT patients having surpassed *Candida* as reported in a large prospective database (Kontoyiannis et al. 2010). In SOT, the highest incidence is noted in lung, lung-heart transplant (about 6%), and liver and kidney transplants (Pappas et al. 2010). CNS involvement occurred in 15.4% of cases in the context of disseminated disease from a large study in Europe

(Gavalda et al. 2005). *A. fumigatus*, *A. terreus*, *and A. flavus* are the most common species associated with CNS disease. CNS aspergillosis can manifest as meningitis, infarction, or a brain abscess with the latter two presentations being more common.

### 2.4.2 Non-*Aspergillus* Mold Infections

#### 2.4.2.1 *Mucormycosis*

Mucormycosis is an infection caused by fungi from the *Mucorales* order (Mendoza et al. 2014), with *Rhizopus* spp. the most common offending agent. The organism is found in the decaying organic matter such as vegetables, seeds, fruits, manure, and compost. It releases spores that when airborne can be inhaled.

The incidence of this devastating illness has been increasing over the last decade, in the HCT and SOT, patients with hematologic malignancy (HM) undergoing cytotoxic chemotherapy, uncontrolled diabetes mellitus with acidosis, burns, and trauma (Roden et al. 2005; Walsh et al. 2012). Voriconazole and echinocandin prophylaxis has been associated with increased risk of mucormycosis, while tacrolimus is protective (Singh et al. 2009).

The spread to CNS is primarily via the hematogenous route, although direct extension from the sinuses to the intracranial compartment is well known. In a large retrospective study of 929 patients, CNS involvement was described in one-third of the patients, and of that 69% were related to sinonasal source (Roden et al. 2005). Injection drug users manifest predominantly with cerebral involvement—abscesses or infarcts (Fong et al. 1990; Stave et al. 1989).

#### 2.4.2.2 *Phaeohyphomycoses* (*Dematiaceous Fungi*)

This is a diverse group of pigmented fungi that are emerging as a cause of CNS fungal infections. Many of the fungi in this group are neurotropic, such as *Cladophialophora bantiana*, *Exophiala dermatitidis*, and *Rhinodadeiella mackenziei* (Chakrabarti 2007).

Although *Cladophialophora* infections are reported worldwide, the majority are in areas that have a warm and humid climate (Kantarcioglu et al. 2017). A systematic review of *C. bantiana* cases reported that the majority of cases are from India, the USA, Brazil, Canada, France, Spain, South Africa, and Italy, with sporadic cases from various other countries. The majority of patients were immunocompetent (58.3%) and 97% had brain abscess. Regardless of the immune status, mortality was high at 65% (Kantarcioglu et al. 2017).

*Exophiala dermatitidis* notoriously causes brain abscesses and is mostly reported from the Asian countries. CARD9 deficiency has been identified as a risk factor (Lanternier et al. 2015). Other molds such as *Lomentospora prolificans*, *Alternaria* spp., *Exserohilum rostratum*, *Scopulariopsis* spp., *Curvularia* spp., *Bipolaris* spp., *Chaetomium*, and *Ochroconis gallopava* are more often encountered in immunocompromised hosts (Kontoyiannis et al. 2010; Pappas et al. 2010). In a review of 72 cases of phaeohyphomycosis (Revankar et al. 2002), the majority of patients (76%) had underlying immunodeficiency, and CNS involvement was identified in 22/72 (30.5%). Only three of the patients with CNS infection did not have an underlying immunologic deficit (two caused by *Curvularia* spp. and one by *Wangiella dermatitidis*). A case series of 12 SOT patients with *Ochroconis gallopava* infection described high mortality rate in those with CNS involvement that reached 80% (Shoham et al. 2008).

From an iatrogenic standpoint, a large outbreak of fungal meningitis due to *Exserohilum rostratum* in the USA resulted in patients who had received contaminated compounded methylprednisolone used for spinal/epidural injections (Chiller et al. 2013).

## 2.5 Miscellaneous Fungi

*Scedosporium apiospermum* is ubiquitously found in the environment, especially polluted environment of high human activity, agricultural soil, and polluted water (Ramirez-Garcia et al. 2018). *Scedosporium* and *Lomentospora* accounted for

the majority of non-*Aspergillus* mold infections in both HCT and SOT, 71% and 29%, respectively (Husain et al. 2005).

*Paracoccidioides brasiliensis* is the main cause for paracoccidioidomycosis that is endemic in South America, and chronic disease is a risk factor for CNS involvement (Shikanai-Yasuda et al. 2017). *Fusarium* spp., *Acremonium* spp., and *Paecilomyces* spp. have also been associated with CNS involvement in patients with disseminated disease. Dermatophytes such as *Trichophyton* and *Microsporum* have also been described in immunocompromised patients leading to CNS infection. *Emmonsia* is another emerging fungus that has the ability to cause disseminated disease.

## 2.6 Conclusion

Fungi are ubiquitous in the environment and exposure to them is inevitable. The epidemiologic trends of CNS yeast and mold infections demonstrate varying risk based on the host immune status and environmental exposures especially in the context of endemic fungi, as well as non-endemic fungi. With the advancement in the care of very ill patients and neurosurgical interventions, these infections may occur more frequently. Increased awareness coupled with diagnostic advances over time should result in the timely establishment of diagnosis and intervention with a potential improvement in outcomes. The CNS IFI carries high morbidity and mortality and is a challenging medical/surgical condition.

## References


Alsultan A, Williams MS, Lubner S, Goldman FD. Chronic granulomatous disease presenting with disseminated intracranial aspergillosis. Pediatr Blood Cancer. 2006;47:107–10.

Assi MA, Sandid MS, Baddour LM, Roberts GD, Walker RC. Systemic histoplasmosis: a 15-year retrospective institutional review of 111 patients. Medicine (Baltimore). 2007;86:162–9.

Baradkar VP, Mathur M, Sonavane A, Kumar S. Candidal infections of ventriculoperitoneal shunts. J Pediatr Neurosci. 2009;4:73–5.

Bariola JR, Perry P, Pappas PG, Proia L, Shealey W, Wright PW, Sizemore JM, Robinson M, Bradsher RW Jr. Blastomycosis of the central nervous system: a multicenter review of diagnosis and treatment in the modern era. Clin Infect Dis. 2010;50:797–804.

Barros MB, Schubach Ade O, do Valle AC, Gutierrez Galhardo MC, Conceicao-Silva F, Schubach TM, Reis RS, Wanke B, Marzochi KB, Conceicao MJ. Cat-transmitted sporotrichosis epidemic in Rio de Janeiro, Brazil: description of a series of cases. Clin Infect Dis. 2004;38:529–35.

Barros MB, de Almeida Paes R, Schubach AO. Sporothrix schenckii and Sporotrichosis. Clin Microbiol Rev. 2011;24:633–54.

Baumgardner DJ, Buggy BP, Mattson BJ, Burdick JS, Ludwig D. Epidemiology of blastomycosis in a region of high endemicity in north central Wisconsin. Clin Infect Dis. 1992;15:629–35.

Bercusson A, Colley T, Shah A, Warris A, Armstrong-James D. Ibrutinib blocks Btk-dependent NF-kB and NFAT responses in human macrophages during Aspergillus fumigatus phagocytosis. Blood. 2018;132(18):1985–8.

Bergstrom L, Yocum DE, Ampel NM, Villanueva I, Lisse J, Gluck O, Tesser J, Posever J, Miller M, Araujo J, Kageyama DM, Berry M, Karl L, Yung CM. Increased risk of coccidioidomycosis in patients treated with tumor necrosis factor alpha antagonists. Arthritis Rheum. 2004;50:1959–66.

Blumberg HM, Jarvis WR, Soucie JM, Edwards JE, Patterson JE, Pfaller MA, Rangel-Frausto MS, Rinaldi MG, Saiman L, Wiblin RT, Wenzel RP. Risk factors for candidal bloodstream infections in surgical intensive care unit patients: the NEMIS prospective multicenter study. The National Epidemiology of Mycosis Survey. Clin Infect Dis. 2001;33:177–86.

Brenier-Pinchart MP, Leclercq P, Mallie M, Bettega G. Candida meningitis possibly resulting from a harpoon injury. Eur J Clin Microbiol Infect Dis. 1999;18:454–5.

Brown J, Benedict K, Park BJ, Thompson GR 3rd. Coccidioidomycosis: epidemiology. Clin Epidemiol. 2013;5:185–97.

Casado JL, Quereda C, Oliva J, Navas E, Moreno A, Pintado V, Cobo J, Corral I. Candidal meningitis in HIV-infected patients: analysis of 14 cases. Clin Infect Dis. 1997;25:673–6.

Castillo CG, Kauffman CA, Miceli MH. Blastomycosis. Infect Dis Clin North Am. 2016;30:247–64.

Chakrabarti A. Epidemiology of central nervous system mycoses. Neurol India. 2007;55:191–7.

Chen SC, Meyer W, Sorrell TC. Cryptococcus gattii infections. Clin Microbiol Rev. 2014;27:980–1024.

Chiller TM, Roy M, Nguyen D, Guh A, Malani AN, Latham R, Peglow S, Kerkering T, Kaufman D, McFadden J, Collins J, Kainer M, Duwve J, Trump D, Blackmore C, Tan C, Cleveland AA, MacCannell T, Muehlenbachs A, Zaki SR, Brandt ME, Jernigan JA. Clinical findings for fungal infections caused by methylprednisolone injections. N Engl J Med. 2013;369:1610–9.

Chu JH, Feudtner C, Heydon K, Walsh TJ, Zaoutis TE. Hospitalizations for endemic mycoses: a population-based national study. Clin Infect Dis. 2006;42:822–5.

Cohen MS, Isturiz RE, Malech HL, Root RK, Wilfert CM, Gutman L, Buckley RH. Fungal infection in chronic granulomatous disease. The importance of the phagocyte in defense against fungi. Am J Med. 1981;71:59–66.

Datta K, Bartlett KH, Baer R, Byrnes E, Galanis E, Heitman J, Hoang L, Leslie MJ, MacDougall L, Magill SS, Morshed MG, Marr KA. Spread of Cryptococcus gattii into Pacific Northwest region of the United States. Emerg Infect Dis. 2009;15:1185–91.

Denning DW. Aspergillosis in "nonimmunocompromised" critically ill patients. Am J Respir Crit Care Med. 2004;170:580–1.

Dotis J, Iosifidis E, Roilides E. Central nervous system aspergillosis in children: a systematic review of reported cases. Int J Infect Dis. 2007;11:381–93.

Dworkin MS, Duckro AN, Proia L, Semel JD, Huhn G. The epidemiology of blastomycosis in Illinois and factors associated with death. Clin Infect Dis. 2005;41:e107–11.

Faix RG. Systemic Candida infections in infants in intensive care nurseries: high incidence of central nervous system involvement. J Pediatr. 1984;105:616–22.

Fernandez M, Moylett EH, Noyola DE, Baker CJ. Candidal meningitis in neonates: a 10-year review. Clin Infect Dis. 2000;31:458–63.

Flynn PM, Marina NM, Rivera GK, Hughes WT. Candida tropicalis infections in children with leukemia. Leuk Lymphoma. 1993;10:369–76.

Fong KM, Seneviratne EM, McCormack JG. Mucor cerebral abscess associated with intravenous drug abuse. Aust N Z J Med. 1990;20:74–7.

From the Centers for Disease Control and Prevention. Exophiala infection from contaminated injectable steroids prepared by a compounding pharmacy—United States, July–November 2002. JAMA. 2003;289:291–3.

Frost HM, Anderson J, Ivacic L, Meece J. Blastomycosis in children: an analysis of clinical, epidemiologic, and genetic features. J Pediatric Infect Dis Soc. 2017;6:49–56.

Gavalda J, Len O, San Juan R, Aguado JM, Fortun J, Lumbreras C, Moreno A, Munoz P, Blanes M, Ramos A, Rufi G, Gurgui M, Torre-Cisneros J, Montejo M, Cuenca-Estrella M, Rodriguez-Tudela JL, Pahissa A. Risk factors for invasive aspergillosis in solid-organ transplant recipients: a case-control study. Clin Infect Dis. 2005;41:52–9.

Gavino C, Cotter A, Lichtenstein D, Lejtenyi D, Fortin C, Legault C, Alirezaie N, Majewski J, Sheppard DC, Behr MA, Foulkes WD, Vinh DC. CARD9 deficiency and spontaneous central nervous system candidiasis: complete clinical remission with GM-CSF therapy. Clin Infect Dis. 2014;59:81–4.

Glick JA, Graham RS, Voils SA. Candida meningitis post Gliadel wafer placement successfully treated with intrathecal and intravenous amphotericin B. Ann Pharmacother. 2010;44:215–8.

Grim SA, Proia L, Miller R, Alhyraba M, Costas-Chavarri A, Oberholzer J, Clark NM. A multicenter study of histoplasmosis and blastomycosis after solid organ transplantation. Transpl Infect Dis. 2012;14:17–23.

Gullberg RM, Quintanilla A, Levin ML, Williams J, Phair JP. Sporotrichosis: recurrent cutaneous, articular, and central nervous system infection in a renal transplant recipient. Rev Infect Dis. 1987;9:369–75.

Gunaratne PS, Wijeyaratne CN, Seneviratne HR. Aspergillus meningitis in Sri Lanka—a post-tsunami effect? N Engl J Med. 2007;356:754–6.

Hammerman KJ, Powell KE, Tosh FE. The incidence of hospitalized cases of systemic mycotic infections. Sabouraudia. 1974;12:33–45.

Hardman S, Stephenson I, Jenkins DR, Wiselka MJ, Johnson EM. Disseminated Sporothrix schenckii in a patient with AIDS. J Infect. 2005;51:e73–7.

Harris JR, Lockhart SR, Debess E, Marsden-Haug N, Goldoft M, Wohrle R, Lee S, Smelser C, Park B, Chiller T. Cryptococcus gattii in the United States: clinical aspects of infection with an emerging pathogen. Clin Infect Dis. 2011;53:1188–95.

Henriet S, Verweij PE, Holland SM, Warris A. Invasive fungal infections in patients with chronic granulomatous disease. Adv Exp Med Biol. 2013;764:27–55.

Husain S, Munoz P, Forrest G, Alexander BD, Somani J, Brennan K, Wagener MM, Singh N. Infections due to Scedosporium apiospermum and Scedosporium prolificans in transplant recipients: clinical characteristics and impact of antifungal agent therapy on outcome. Clin Infect Dis. 2005;40:89–99.

Kantarcioglu AS, Guarro J, de Hoog GS. Central nervous system infections by members of the Pseudallescheria boydii species complex in healthy and immunocompromised hosts: epidemiology, clinical characteristics and outcome. Mycoses. 2008;51:275–90.

Kantarcioglu AS, Guarro J, De Hoog S, Apaydin H, Kiraz N. An updated comprehensive systematic review of Cladophialophora bantiana and analysis of epidemiology, clinical characteristics, and outcome of cerebral cases. Med Mycol. 2017;55:579–604.

Kauffman CA, Freifeld AG, Andes DR, Baddley JW, Herwaldt L, Walker RC, Alexander BD, Anaissie EJ, Benedict K, Ito JI, Knapp KM, Lyon GM, Marr KA, Morrison VA, Park BJ, Patterson TF, Schuster MG, Chiller TM, Pappas PG. Endemic fungal infections in solid organ and hematopoietic cell transplant recipients enrolled in the Transplant-Associated Infection Surveillance Network (TRANSNET). Transpl Infect Dis. 2014;16:213–24.

Kaur J, Myers AM. Homosexuality, steroid therapy, and histoplasmosis. Ann Intern Med. 1983;99:567.

Keckich DW, Blair JE, Vikram HR, Seville MT, Kusne S. Reactivation of coccidioidomycosis despite antifungal prophylaxis in solid organ transplant recipients. Transplantation. 2011;92:88–93.

Kong YC, Levine HB, Madin SH, Smith CE. Fungal multiplication and histopathologic changes in vaccinated

mice infected with coccidioides immitis. J Immunol. 1964;92:779–90.

Kontoyiannis DP, Marr KA, Park BJ, Alexander BD, Anaissie EJ, Walsh TJ, Ito J, Andes DR, Baddley JW, Brown JM, Brumble LM, Freifeld AG, Hadley S, Herwaldt LA, Kauffman CA, Knapp K, Lyon GM, Morrison VA, Papanicolaou G, Patterson TF, Perl TM, Schuster MG, Walker R, Wannemuehler KA, Wingard JR, Chiller TM, Pappas PG. Prospective surveillance for invasive fungal infections in hematopoietic stem cell transplant recipients, 2001–2006: overview of the Transplant-Associated Infection Surveillance Network (TRANSNET) Database. Clin Infect Dis. 2010;50:1091–100.

Kourkoumpetis TK, Desalermos A, Muhammed M, Mylonakis E. Central nervous system aspergillosis: a series of 14 cases from a general hospital and review of 123 cases from the literature. Medicine (Baltimore). 2012;91:328–36.

Kowacs PA, Monteiro de Almeida S, Pinheiro RL, Fameli H, Piovesan EJ, Correia A, Werneck LC. Central nervous system Aspergillus fumigatus infection after near drowning. J Clin Pathol. 2004;57:202–4.

Lanternier F, Barbati E, Meinzer U, Liu L, Pedergnana V, Migaud M, Heritier S, Chomton M, Fremond ML, Gonzales E, Galeotti C, Romana S, Jacquemin E, Angoulvant A, Bidault V, Canioni D, Lachenaud J, Mansouri D, Mahdaviani SA, Adimi P, Mansouri N, Jamshidi M, Bougnoux ME, Abel L, Lortholary O, Blanche S, Casanova JL, Picard C, Puel A. Inherited CARD9 deficiency in 2 unrelated patients with invasive Exophiala infection. J Infect Dis. 2015;211:1241–50.

Marra CM, Whitley RJ, Scheld WM. Approach to the patient with central nervous system infection. In: Infections of the central nervous system. Philadelphia: Wolters Kluwer Health; 2014.

Masannat FY, Ampel NM. Coccidioidomycosis in patients with HIV-1 infection in the era of potent antiretroviral therapy. Clin Infect Dis. 2010;50:1–7.

Matsumoto E, Boyken L, Tendolkar S, McDanel J, Castanheira M, Pfaller M, Diekema D. Candidemia surveillance in Iowa: emergence of echinocandin resistance. Diagn Microbiol Infect Dis. 2014;79:205–8.

Maziarz EK, Perfect JR. Cryptococcosis. Infect Dis Clin North Am. 2016;30:179–206.

McCarthy M, Rosengart A, Schuetz AN, Kontoyiannis DP, Walsh TJ. Mold infections of the central nervous system. N Engl J Med. 2014;371:150–60.

Mendoza N, Blair JE. The utility of diagnostic testing for active coccidioidomycosis in solid organ transplant recipients. Am J Transplant. 2013;13:1034–9.

Mendoza L, Vilela R, Voelz K, Ibrahim AS, Voigt K, Lee SC. Human fungal pathogens of Mucorales and Entomophthorales. Cold Spring Harb Perspect Med. 2014;5 https://doi.org/10.1101/cshperspect.a019562.

Mendoza N, Noel P, Blair JE. Diagnosis, treatment, and outcomes of coccidioidomycosis in allogeneic stem cell transplantation. Transpl Infect Dis. 2015;17:380–8.

Munoz P, Giannella M, Vena A. Mold infections in solid transplant recipients. In: Transplant infections. Switzerland: Springer; 2016.

Osawa R, Alexander BD, Lortholary O, Dromer F, Forrest GN, Lyon GM, Somani J, Gupta KL, Del Busto R, Pruett TL, Sifri CD, Limaye AP, John GT, Klintmalm GB, Pursell K, Stosor V, Morris MI, Dowdy LA, Munoz P, Kalil AC, Garcia-Diaz J, Orloff S, House AA, Houston S, Wray D, Huprikar S, Johnson LB, Humar A, Razonable RR, Fisher RA, Husain S, Wagener MM, Singh N. Identifying predictors of central nervous system disease in solid organ transplant recipients with cryptococcosis. Transplantation. 2010;89:69–74.

Pappas PG, Threlkeld MG, Bedsole GD, Cleveland KO, Gelfand MS, Dismukes WE. Blastomycosis in immunocompromised patients. Medicine (Baltimore). 1993;72:311–25.

Pappas PG, Alexander BD, Andes DR, Hadley S, Kauffman CA, Freifeld A, Anaissie EJ, Brumble LM, Herwaldt L, Ito J, Kontoyiannis DP, Lyon GM, Marr KA, Morrison VA, Park BJ, Patterson TF, Perl TM, Oster RA, Schuster MG, Walker R, Walsh TJ, Wannemuehler KA, Chiller TM. Invasive fungal infections among organ transplant recipients: results of the Transplant-Associated Infection Surveillance Network (TRANSNET). Clin Infect Dis. 2010;50:1101–11.

Peri AM, Bisi L, Cappelletti A, Colella E, Verga L, Borella C, Foresti S, Migliorino GM, Gori A, Bandera A. Invasive aspergillosis with pulmonary and central nervous system involvement during ibrutinib therapy for relapsed chronic lymphocytic leukaemia: case report. Clin Microbiol Infect. 2018;24:785–6.

Pfaller MA, Castanheira M, Messer SA, Moet GJ, Jones RN. Variation in Candida spp. distribution and antifungal resistance rates among bloodstream infection isolates by patient age: report from the SENTRY Antimicrobial Surveillance Program (2008–2009). Diagn Microbiol Infect Dis. 2010;68:278–83.

Pfaller MA, Moet GJ, Messer SA, Jones RN, Castanheira M. Geographic variations in species distribution and echinocandin and azole antifungal resistance rates among Candida bloodstream infection isolates: report from the SENTRY Antimicrobial Surveillance Program (2008 to 2009). J Clin Microbiol. 2011;49:396–9.

Pfaller M, Neofytos D, Diekema D, Azie N, Meier-Kriesche HU, Quan SP, Horn D. Epidemiology and outcomes of candidemia in 3648 patients: data from the Prospective Antifungal Therapy (PATH Alliance(R)) registry, 2004–2008. Diagn Microbiol Infect Dis. 2012;74:323–31.

Pittet D, Monod M, Suter PM, Frenk E, Auckenthaler R. Candida colonization and subsequent infections in critically ill surgical patients. Ann Surg. 1994;220:751–8.

Powers-Fletcher MV, Hanson KE. Nonculture diagnostics in fungal disease. Infect Dis Clin North Am. 2016;30:37–49.

Rajasingham R, Smith RM, Park BJ, Jarvis JN, Govender NP, Chiller TM, Denning DW, Loyse A, Boulware DR. Global burden of disease of HIV-associated cryptococcal meningitis: an updated analysis. Lancet Infect Dis. 2017;17:873–81.

Ramirez-Garcia A, Pellon A, Rementeria A, Buldain I, Barreto-Bergter E, Rollin-Pinheiro R, de Meirelles JV, Xisto M, Ranque S, Havlicek V, Vandeputte P, Govic YL, Bouchara JP, Giraud S, Chen S, Rainer J, Alastruey-Izquierdo A, Martin-Gomez MT, Lopez-Soria LM, Peman J, Schwarz C, Bernhardt A, Tintelnot K, Capilla J, Martin-Vicente A, Cano-Lira J, Nagl M, Lackner M, Irinyi L, Meyer W, de Hoog S, Hernando FL. Scedosporium and Lomentospora: an updated overview of underrated opportunists. Med Mycol. 2018;56:102–25.

Revankar SG, Patterson JE, Sutton DA, Pullen R, Rinaldi MG. Disseminated phaeohyphomycosis: review of an emerging mycosis. Clin Infect Dis. 2002;34:467–76.

Rieber N, Gazendam RP, Freeman AF, Hsu AP, Collar AL, Sugui JA, Drummond RA, Rongkavilit C, Hoffman K, Henderson C, Clark L, Mezger M, Swamydas M, Engeholm M, Schule R, Neumayer B, Ebel F, Mikelis CM, Pittaluga S, Prasad VK, Singh A, Milner JD, Williams KW, Lim JK, Kwon-Chung KJ, Holland SM, Hartl D, Kuijpers TW, Lionakis MS. Extrapulmonary Aspergillus infection in patients with CARD9 deficiency. JCI Insight. 2016;1:e89890.

Roden MM, Zaoutis TE, Buchanan WL, Knudsen TA, Sarkisova TA, Schaufele RL, Sein M, Sein T, Chiou CC, Chu JH, Kontoyiannis DP, Walsh TJ. Epidemiology and outcome of zygomycosis: a review of 929 reported cases. Clin Infect Dis. 2005;41:634–53.

Rosen LB, Freeman AF, Yang LM, Jutivorakool K, Olivier KN, Angkasekwinai N, Suputtamongkol Y, Bennett JE, Pyrgos V, Williamson PR, Ding L, Holland SM, Browne SK. Anti-GM-CSF autoantibodies in patients with cryptococcal meningitis. J Immunol. 2013;190:3959–66.

Saijo T, Chen J, Chen SC, Rosen LB, Yi J, Sorrell TC, Bennett JE, Holland SM, Browne SK, Kwon-Chung KJ. Anti-granulocyte-macrophage colony-stimulating factor autoantibodies are a risk factor for central nervous system infection by Cryptococcus gattii in otherwise immunocompetent patients. MBio. 2014;5:e00912–4.

Sarma S, Upadhyay S. Current perspective on emergence, diagnosis and drug resistance in Candida auris. Infect Drug Resist. 2017;10:155–65.

Schneider E, Hajjeh RA, Spiegel RA, Jibson RW, Harp EL, Marshall GA, Gunn RA, McNeil MM, Pinner RW, Baron RC, Burger RC, Hutwagner LC, Crump C, Kaufman L, Reef SE, Feldman GM, Pappagianis D, Werner SB. A coccidioidomycosis outbreak following the Northridge, Calif, earthquake. JAMA. 1997;277:904–8.

Schwartz IS, Wiederhold NP, Hanson KE, Patterson TF, Sigler L. Blastomyces helicus, a new dimorphic fungus causing fatal pulmonary and systemic disease in humans and animals in Western Canada and United States. Clin Infect Dis. 2018; https://doi.org/10.1093/cid/ciy483.

Shapiro S, Javed T, Mealey J Jr. Candida albicans shunt infection. Pediatr Neurosci. 1989;15:125–30.

Shikanai-Yasuda MA, Mendes RP, Colombo AL, Queiroz-Telles F, Kono ASG, Paniago AMM, Nathan A, Valle A, Bagagli E, Benard G, Ferreira MS, Teixeira MM, Silva-Vergara ML, Pereira RM, Cavalcante RS, Hahn R, Durlacher RR, Khoury Z, Camargo ZP, Moretti ML, Martinez R. Brazilian guidelines for the clinical management of paracoccidioidomycosis. Rev Soc Bras Med Trop. 2017;50:715–40.

Shoham S, Pic-Aluas L, Taylor J, Cortez K, Rinaldi MG, Shea Y, Walsh TJ. Transplant-associated Ochroconis gallopava infections. Transpl Infect Dis. 2008;10:442–8.

Singh N. Fungal infections in the recipients of solid organ transplantation. Infect Dis Clin North Am. 2003;17:113–34., viii.

Singh N, Paterson DL. Aspergillus infections in transplant recipients. Clin Microbiol Rev. 2005;18:44–69.

Singh N, Aguado JM, Bonatti H, Forrest G, Gupta KL, Safdar N, John GT, Pursell KJ, Munoz P, Patel R, Fortun J, Martin-Davila P, Philippe B, Philit F, Tabah A, Terzi N, Chatelet V, Kusne S, Clark N, Blumberg E, Julia MB, Humar A, Houston S, Lass-Florl C, Johnson L, Dubberke ER, Barron MA, Lortholary O. Zygomycosis in solid organ transplant recipients: a prospective, matched case-control study to assess risks for disease and outcome. J Infect Dis. 2009;200:1002–11.

Smego RA Jr, Devoe PW, Sampson HA, Perfect JR, Wilfert CM, Buckley RH. Candida meningitis in two children with severe combined immunodeficiency. J Pediatr. 1984;104:902–4.

Smith JA, Kauffman CA. Endemic fungal infections in patients receiving tumour necrosis factor-alpha inhibitor therapy. Drugs. 2009;69:1403–15.

Spellberg B, Edwards J Jr, Ibrahim A. Novel perspectives on mucormycosis: pathophysiology, presentation, and management. Clin Microbiol Rev. 2005;18:556–69.

Stave GM, Heimberger T, Kerkering TM. Zygomycosis of the basal ganglia in intravenous drug users. Am J Med. 1989;86:115–7.

Stevens DA. Coccidioidomycosis. N Engl J Med. 1995;332:1077–82.

Stockamp NW, Thompson GR 3rd. Coccidioidomycosis. Infect Dis Clin North Am. 2016;30:229–46.

Vallabhaneni S, Mody RK, Walker T, Chiller T. The global burden of fungal diseases. Infect Dis Clin North Am. 2016;30:1–11.

Vilela R, Souza GF, Fernandes Cota G, Mendoza L. Cutaneous and meningeal sporotrichosis in a HIV patient. Rev Iberoam Micol. 2007;24:161–3.

Walsh TJ, Gamaletsou MN, McGinnis MR, Hayden RT, Kontoyiannis DP. Early clinical and laboratory diagnosis of invasive pulmonary, extrapulmonary, and disseminated mucormycosis (zygomycosis). Clin Infect Dis. 2012;54(Suppl 1):S55–60.

Warris A, Bjorneklett A, Gaustad P. Invasive pulmonary aspergillosis associated with infliximab therapy. N Engl J Med. 2001;344:1099–100.

Wheat LJ, Azar MM, Bahr NC, Spec A, Relich RF, Hage C. Histoplasmosis. Infect Dis Clin North Am. 2016;30:207–27.

Wheat J, Myint T, Guo Y, Kemmer P, Hage C, Terry C, Azar MM, Riddell J, Ender P, Chen S, Shehab K, Cleveland K, Esguerra E, Johnson J, Wright P, Douglas V, Vergidis P, Ooi W, Baddley J, Bamberger D, Khairy R, Vikram HR, Jenny-Avital E, Sivasubramanian G, Bowlware K, Pahud B, Sarria J, Tsai T, Assi M, Mocherla S, Prakash V, Allen D, Passaretti C, Huprikar S, Anderson A. Central nervous system histoplasmosis: multicenter retrospective study on clinical features, diagnostic approach and outcome of treatment. Medicine (Baltimore). 2018;97:e0245.