BMJ Best Practice

Fungal meningitis

Straight to the point of care

Last updated: Nov 10, 2022

Table of Contents

Summary

Typically presents as a progressive, life-threatening, chronic or subacute meningitis.

Occurs most commonly in immunosuppressed individuals and is often accompanied by systemic involvement.

Cerebrospinal fluid (CSF) typically shows lymphocytic pleocytosis, elevated protein, and low glucose.

The most common type of fungal meningitis is caused by *Cryptococcus neoformans* .

A rapid aetiological diagnosis is required to guide antifungal therapy.

Complications include seizures, cerebral infarction, hydrocephalus, and elevated CSF pressure without hydrocephalus.

Definition

Meningitis is an inflammatory disease of the leptomeninges. All major fungal pathogens have the capacity to cause meningitis. The incidence of fungal meningitis is increasing worldwide due to the increasing number of patients immunosuppressed by pharmacological agents and the ongoing burden of HIV-associated cryptococcal meningitis in resource-limited countries.[1] Cryptococcal, histoplasmal, coccidioidal, candidal, *Exserohilum rostratum* , *Aspergillus* , and mucormyocosal meningitis will be discussed in this topic.[2] [3] [4] [5] [6] [7]

THEORY

Epidemiology

Many opportunistic fungal pathogens such as *Candida* species and *Cryptococcus neoformans* cause disease worldwide. In contrast, the endemic mycoses such as histoplasmosis and coccidioidomycosis, and, to a lesser extent, *Cryptococcus gattii* , are confined to certain geographical areas.[8] [9] [10] [11] [12] [13] *C neoformans* is a phenotypically heterogeneous pathogen and genetic lineage plays an important role in cryptococcal virulence during human infection.[14]

Cryptococcal meningitis

In the 1980s, *C neoformans* emerged as an important opportunistic infection in the US, Europe, and Australia, occurring in 5% to 10% of all people with AIDS.[15] Since the 1990s, the incidence of HIV-associated cryptococcosis has decreased in the US, largely due to early and effective antiretroviral therapy. The annual incidence in people with AIDS in Atlanta decreased from 66 per 1000 in 1992 to 7 per 1000 in 2000.[16]

Cryptococcosis remains a major cause of morbidity and mortality in people with AIDS in developing countries.[17] [18] [1] In one study of patients with HIV-associated cryptococcal meningitis (in Thailand, Uganda, Malawi, and South Africa), mortality was 17% at 2 weeks and 34% at 10 weeks.[19] Risk of death was associated with low body weight, older age, anaemia (haemoglobin <75 g/L [<7.5 g/dL]), high peripheral white cell count, high fungal burden, and altered mental status.[19]

HIV-associated cryptococcal meningitis carries a significant burden in sub-Saharan Africa and is considered as a measure of HIV treatment programme failure.[1] In 2014, an estimated 73% of all cryptococcal meningitis cases were reported in sub-Saharan Africa.[1] Tuberculosis and cryptococcosis co-infection causing dual meningitis has been reported in China, and could be easily overlooked or misdiagnosed.[20]

Organ transplantation and developments in immunosuppressive therapies for cancer and other systemic diseases have contributed to the increasing incidence of fungal meningitis. An estimated 8% of invasive fungal infections in solid organ transplant recipients are due to cryptococcosis.[21] Fungal meningitis causes complications in up to 10% of patients with cancer, although they may not develop typical symptoms of meningitis.[22] Risk of cryptococcosis is higher in haematological malignancies than solid tumours.[23]

Between 1999 and the 2004, an outbreak of over 100 cases of *C gattii* infection occurred on Vancouver Island, Canada, predominantly in immunocompetent individuals.[24] [25]

Histoplasmal meningitis

Histoplasmosis is endemic to Ohio and the Mississippi Valley in the US. However, it also occurs widely in Central and South America, Africa, Asia, and parts of southern Europe.[8] Studies using histoplasmin skin tests in tuberculin-negative individuals to determine areas of endemicity have concluded that more than 80% of young adults from states bordering the Ohio and Mississippi rivers have been previously infected with *Histoplasma capsulatum* .[26] Low-level exposure to *H capsulatum* in healthy individuals is largely asymptomatic. Central nervous system (CNS) involvement is clinically recognised in 5% to 10% of cases of progressive disseminated histoplasmosis, for which HIV infection is a risk factor.[27]

Coccidioidal meningitis

Coccidioidomycosis is found only in the Western hemisphere, predominantly the southwest of the US and northwest Mexico.[10] [28] [29] An estimated 100,000 to 150,000 cases of coccidioidomycosis occur annually in the US. The incidence of primary disease and consequent dissemination continues to increase,

in part due to population growth, migration and increasing numbers of immunocompromised hosts.[30] [31] [32] The advent of early, potent antiretroviral therapy has reduced the incidence of HIV-associated coccidioidomycosis.[33] [34]

Candidal meningitis

The prevalence of all types of invasive candidiasis is increasing. Candidal meningitis is a relatively common cause of meningitis in premature infants and infants younger than 1 month of age.[35] [36] Neonatal candidal meningitis represented 0.4% of admissions to a neonatal intensive care unit in a 10-year retrospective US study.[37] Candidaemia in adults is rarely associated with meningitis, and meningeal involvement has been found in less than 15% of cases of disseminated candidiasis in autopsy series.[38] [39] Candidal meningitis is the most common fungal meningitis following CNS shunt or ventriculostomy placement.[40] [41] The highest rates are seen in infants less than 1 year old. Neurosurgery-related CNS candidiasis may be increasing,[42] perhaps related to prescription of prophylactic antibiotics for neurosurgical procedures.

Exserohilum rostratum meningitis

An outbreak of fungal infections and fatal fungal meningitis, due to *E rostratum* from therapeutic use of contaminated pharmaceutical product (vials of methylprednisolone), was reported in the US from September 2012.[43] This was investigated by the Centers for Disease Control and Prevention and local health departments. The investigation traced the primary fungal pathogen, *E rostratum* , isolated from patient specimens, to three lots of contaminated methylprednisolone acetate produced by a single compounding pharmacy. A total of 753 cases have been reported in 20 states, with 64 deaths.[44]

Aspergillus and mucormycosal meningitis

Aspergillus meningitis is rare and much more frequently observed among immunocompetent patients.[45] Mucormycosal meningitis occurs rarely, as a manifestation of rhinocerebral mucormycosis.[46]

Aetiology

Cryptococcus neoformans and *Cryptococcus gattii* are environmental saprophytes, found as budding yeasts in clinical specimens.[47] *C neoformans* is found worldwide and has been isolated from soil contaminated by birds, especially pigeon excreta. *C neoformans* (serotypes A and D) usually causes infection in immunocompromised individuals. In contrast, *C gattii* (serotypes B and C) predominantly causes infection in apparently immunocompetent individuals, and is found primarily in tropical and subtropical regions, notably Australia and Papua New Guinea. *C gattii* has been found in association with several species of eucalyptus trees.

Histoplasma capsulatum is a thermally dimorphic fungus that exists as a mould in the environment, and as small intracellular yeasts in clinical specimens.[8] *H capsulatum* contaminates soil and has been isolated from poultry house litter, caves, and areas harbouring bats and bird roosts.

Coccidioides species are also thermally dimorphic fungi.[28] [29] *Coccidioides immitis* and *Coccidioides posadii* cause clinically indistinguishable disease. In the soil of the semi-arid and desert endemic areas, septate hyphae give rise to thick-walled, airborne arthroconidia. In susceptible hosts, multinucleate spherules develop, which mature and rupture, releasing endospores that give rise to further spherules.

Candida species are part of the normal human flora, causing disease only when the skin or mucosal barriers to infection and/or protective immune responses are impaired. *Candida albicans* is to date the most

commonly recognised cause of candidal meningitis, although other, non-albicans *Candida* species may be increasing as causes of neurocandidiasis.[48] [49] [50]

Aspergillus meningitis is rare. Invasive *Aspergillus* disease of paranasal sinuses may cause hypertrophic cranial pachymeningitis. Rare cases of spinal arachnoiditis and meningitis have been reported after discitis from epidural corticosteroid injection or spinal anaesthesia as an iatrogenic complication in immunocompetent subjects.[51] [52] Acute and chronic meningitis as well as meningoencephalitis have been reported in case studies of which nearly half did not have known cause of immunosuppression.[53]

Mucormycosis (zygomycosis) is an aggressive and lethal mycosis that may complicate sinus infection in immunosuppressed patients leading to local angioinvasion, tissue necrosis, and spread to orbits, cavernous sinus, and brain; chronic meningitis is rarely reported with focal intracerebral mucormycosis.[46]

Pathophysiology

With the notable exception of *Candida* species, many fungal pathogens are thought to be acquired through inhalation. Meningeal involvement, either isolated or associated with widely disseminated infection, results from haematogenous dissemination from the lungs. This may occur either following primary infection, or after a period of controlled, latent infection, when host immunity is compromised. Protection from *Cryptococcus neoformans* and the endemic mycoses is associated with an active granulomatous inflammatory response, and depends on intact cell-mediated immunity involving both CD4 and CD8 T cells (Th1 pattern of cytokine release).[54]

Cryptococcal infection is probably acquired through the inhalation of small yeasts or basidiospores. The primary pulmonary infection is often asymptomatic. Reactivation of latent infection may be important in HIV-associated cryptococcal meningitis.[55] The organism has a particular predilection for dissemination to the brain. This may relate to the production of melanin (that may interfere with oxidative killing by phagocytes) from L-dopa in the brain by a cryptococcal laccase enzyme.[56]

In histoplasmosis, haematogenous dissemination may occur throughout the reticuloendothelial system via parasitised macrophages. There are numerous reports of histoplasmosis in patients who have not returned to endemic areas for many years. This suggests the importance of reactivation of latent infection. In endemic areas, the relative importance of reactivation versus progressive primary infection is less clear.[57]

Coccidioidal meningitis occurs in approximately half of individuals with disseminated disease. Following the initial primary infection, dissemination to the brain, when it occurs, typically takes weeks to months. In high-risk, symptomatic populations, the dissemination rate may be >15%.[11]

Candidal meningitis may occur as a complication of candidaemia, especially in neonates and premature infants. It is also associated with head trauma and neurosurgical procedures. In contrast to cryptococcosis and the endemic mycoses, the major risk factor for invasive candidiasis in adults is neutropenia.[54]

Classification

Primary and secondary fungal pathogens

There is no formal classification of fungal meningitides.

Fungal meningitides are commonly classified according to the aetiological agent involved. Fungal pathogens that cause meningitis may be classified into primary and secondary pathogens, although this distinction is not clear cut. Cryptococcal meningitis is the most common type of fungal meningitis.

Primary pathogens are capable of causing disease in apparently immunocompetent patients, although most frequently cause disease in immunosuppressed individuals.

Primary pathogens include:

- *Cryptococcus neoformans*
- *Coccidioides immitis*
- *Histoplasma capsulatum* .

Secondary or opportunistic pathogens that occur in the setting of obvious immune dysfunction or of anatomical abnormalities include:

- *Candida*
- *Aspergillus*
- Other moulds (e.g., *Fusarium*).

Case history

Case history #1

A 35-year-old man originally from sub-Saharan Africa presents with a 3-week history of headache and fever. On questioning, he has had intermittent diarrhoea and weight loss of 10 kg over the last year. The patient's Glasgow Coma Scale score is 15, he is haemodynamically stable, and the only positive findings on examination are a fever of 38.5°C (100.4°F) and oral candidiasis.

Case history #2

A 25-year-old woman presents with increasing headache for 3 to 4 weeks together with confusion, nausea and vomiting, and diplopia for 1 week. On examination she is drowsy, but is able to cooperate with the medical examination. On neurological examination she has a left 6th cranial nerve palsy and has reduced visual acuity and papilloedema. There are no further positive findings on examination.

Other presentations

Patients with fungal meningitis may also present with altered personality, drowsiness, seizures, nausea and/or vomiting, hearing loss, and fever without prominent headache. In particular, patients with cryptococcal meningitis may present with signs and symptoms of raised intracranial pressure such as severe headache, nausea or vomiting, visual loss, and altered mental status. Symptoms and signs of hydrocephalus commonly occur in patients diagnosed with coccidioidal meningitis either at presentation or as a late complication.

Approach

Diagnosis involves collation of symptoms, signs, and investigation results. Often, empirical treatment may need to be initiated before definitive diagnosis is made.

Key tests include brain imaging, cerebrospinal fluid (CSF) analysis, and blood cultures. If repeated examination of the CSF, blood, and urine remains inconclusive, histopathological examination for fungi and culture of the brain, meninges, and cisternal or ventricular fluid may be considered.[27]

Clinical history

Cryptococcal meningitis

- May present in a variety of ways; clinical features are not specific.
- Meningoencephalitis is the most frequent manifestation of cryptococcosis.
- HIV-infected individuals and organ transplant recipients are the major risk groups, but it can also present in immunocompetent adults and children.
- Typically presents with progressive headache (70% to 90%), and fever (50% to 90%) of several weeks' duration.[58] [60]
- Symptoms may progress to include nausea, vomiting, behavioural change, drowsiness, and seizures.
- Diplopia and subsequently reduced visual acuity reflect the development of raised intracranial pressure.
- Cough and dyspnoea are not infrequent and may reflect pulmonary involvement.
- The rate of progression of symptoms may depend on host immunity so that some patients without major immune deficits present a more chronic course.
- Significant incidence and higher mortality when associated with immune reconstitution inflammatory syndrome after initiation of antiretroviral therapy.[76]

Histoplasmal meningitis

- Fever, headache, and neck stiffness due to a subacute or chronic meningitis.[27]
- Focal neurological symptoms due to focal brain or spinal cord lesions and stroke syndromes.[27]
- Behavioural and mental status changes secondary to encephalitis.[27]
- Patients with central nervous system (CNS) involvement associated with disseminated infection may also report high fevers, weight loss, and mouth ulcers.

Coccidioidal meningitis

- Headache, fever, nausea, vomiting, and behavioural changes.[77]
- The most common complication of coccidioidal meningitis is hydrocephalus, which can occur as a presenting feature or as a late complication.[11]
- Symptoms of hydrocephalus include headache, nausea, blurred or double vision, coordination or gait disturbance, memory loss, confusion, changes in personality, and urinary incontinence.
- May also present with focal neurological symptoms secondary to cerebral infarction due to arteritis of small- to mid-sized blood vessels.

Candidal meningitis

- Adult candidal meningitis may present with acute or subacute symptoms of meningitis, with fever and headache being the most common reported symptoms.[78]

- Neonates with candidal meningitis are often premature and present initially with symptoms of respiratory distress.[35] [36] [37]

Mucormycosis

- Rhino-orbito-cerebral disease commonly presents with facial pain, sinusitis, eye pain, blurred vision, and proptosis. Any of these clinical findings in a patient with diabetes necessitates prompt investigation for mucormycosis.[46]

Clinical signs

Cryptococcal meningitis

- Signs may be absent or minimal.
- Meningismus is present in only 20% to 50% of patients on presentation.[58] [60]
- Additional signs may include: altered mental status, reduced visual acuity, papilloedema, cranial nerve palsies, and other focal neurological deficits.
- In children, headache and fever are most common symptoms.[79]
- Atypical features include subacute dementia and visual loss.

Histoplasmal meningitis

- Meningismus and focal neurological signs.
- Signs of disseminated histoplasmosis include splenomegaly, hepatomegaly, and lymphadenopathy.
- Histoplasmosis is the most endemic mycosis in Europe.[80]

Coccidioidal meningitis

- Meningismus (about 50%).[81]
- Signs of hydrocephalus (altered mental status and gait).
- Focal neurological signs related to cerebral infarction.

Candidal meningitis

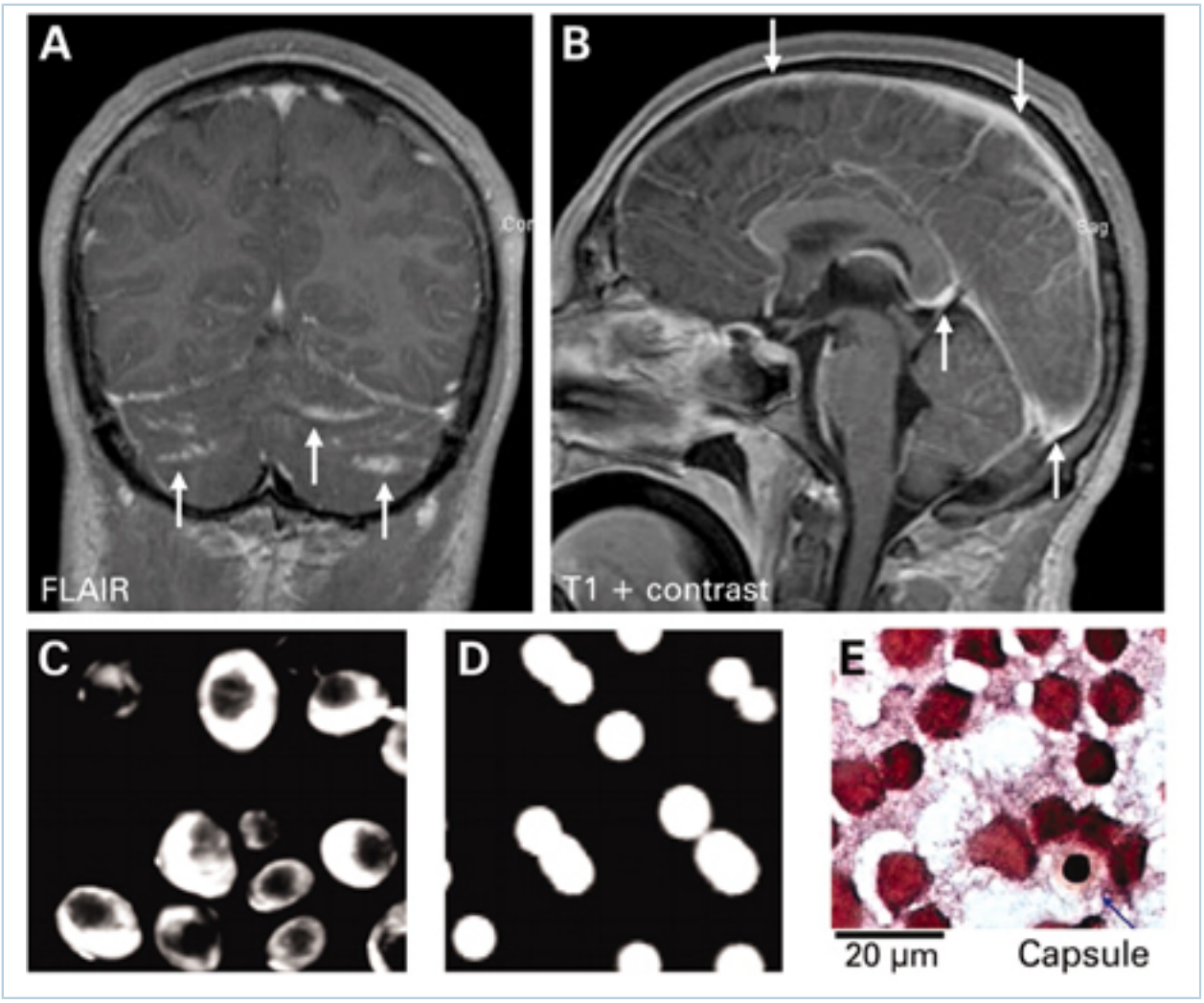
- Meningismus may be found, although it is not common in neurosurgical patients with candidal meningitis.
- Patients commonly present with altered mental status.
- Focal clinical presentations, cranial nerve involvement, papilloedema, and seizures are uncommon manifestations of candidal meningitis.
- An examination of the patient should be performed looking for signs of disseminated candidiasis. For example, fundoscopy may reveal invasion of the retina; the Infectious Diseases Society of America recommends at least one ophthalmological examination in patients with suspected disseminated candidiasis.[74]

Mucormycosis

- A specific sign in the later stages of mucormycosis infection is necrotic eschar on the skin, palate, or nasal turbinates.[46]

Investigations

Brain imaging with computed tomography (CT) or magnetic resonance imaging is performed in all patients with suspected fungal meningitis.



Cryptococcal meningoencephalitis. (A) Cranial magnetic resonance imaging (MRI) shows cerebellar hyperintensities (arrows) in FLAIR sequences (fluid-attenuated inversion recovery) and (B) meningeal contrast enhancement (arrows) in T1 weighted MRI. (C) Indian ink stain, (D) fungal culture, and (E) Gram stain of cerebrospinal fluid were positive

Braun J. Headache, personality changes and fine motor disturbances. BMJ Case Reports. 2009; doi:10.1136/bcr.06.2008.0093. Used with permission.

If cryptococcal meningitis is suspected, imaging should always precede lumbar puncture.[82] Imaging may be normal or may demonstrate, for example, communicating hydrocephalus (also common with coccidioidal meningitis), fungal granuloma, or vasculitic complications. The role of 18F-fluorodeoxyglucose positron emission tomography (PET)/CT in the diagnosis and management of fungal meningitis is being explored.[83] [84]

Lumbar puncture is part of the routine evaluation. CSF is tested for glucose, white blood cell count and differential, protein, culture, antibodies/antigens, India ink stain (*Cryptococcus*), and opening pressure. However, repeated sampling of large volumes of CSF is often required for the diagnosis of non-HIV-associated cryptococcal meningitis, coccidioidal meningitis, histoplasmosis, candidal meningitis, and *Aspergillus* meningitis. Culture positivity of *Aspergillus* meningitis is reported in less than one third of all cases but galactomannan antigen test in CSF has a higher sensitivity.[53] [85] Cryptococcal meningitis by non-capsulated forms of cryptococci is rare but would be difficult to diagnose without CSF culture.[86]

Up to three sets of blood cultures should be taken in all patients; they may be positive when candidal, histoplasmal, or cryptococcal meningitis is associated with disseminated disease.

Specific tests include:

- CSF cryptococcal antigen test.
- Serum antibody and antigen testing for histoplasmosis.
- Urine antigen testing for histoplasmosis.
- Immunodiffusion tests (IgM and IgG) and the complement fixation test (IgG) for coccidioidomycosis: positive results support the diagnosis of coccidioidal meningitis when other causes of meningitis are excluded, and the presence of coccidioidal IgG antibody in the CSF is virtually diagnostic of coccidioidal meningitis.[11] Negative results from an experienced laboratory in patients with untreated disseminated disease are rare.

Positive cultures together with microscopy and immunological testing in serum and CSF remain the current standard for diagnosis of fungal CNS infections. However, specific diagnosis may be delayed due to slow growth in culture, cross-reactivity in case of antigen detection, and inadequate antibody response.

There are early data favouring CSF PCR as an adjunctive diagnostic tool.[87] [88] Emerging data also suggest that CSF (1-3)-beta-D-glucan may play a role in the diagnosis of fungal meningitis.[89] During the 2012 *Exserohilum rostratum* meningitis outbreak from contaminated methylprednisolone, CSF (1-3)-beta-D-glucan also demonstrated potential utility in monitoring treatment response.[90]

Histopathological examination

If repeated examination of the CSF, blood, and urine remains inconclusive, histopathological examination for fungi and culture of the brain, meninges, and cisternal or ventricular fluid may be considered.[27] Meningeal biopsy or stereotactic lesional biopsy of intracranial mass may allow specific pathogen diagnosis in appropriate cases of chronic meningitis.

History and exam

Key diagnostic factors

presence of risk factors (common)

- Key risk factors include immunosuppression; exposure to disturbed soil, chicken guano, or bat caves; neutropenia; impaired phagocytic function; and neurosurgery. Infants and neonates are also at increased risk.

progressive headache (common)

- Typically presents with headache that progresses over several weeks.

severe headache (common)

- Suggests raised intracranial pressure.
- Common finding of cryptococcal meningitis, where raised intracranial pressure probably occurs due to impaired reabsorption of cerebrospinal fluid at the arachnoid villi.

meningismus (common)

- Nuchal rigidity, photophobia, and headache.

symptoms of hydrocephalus (impaired cognitive function, confusion, coordination and gait disturbances, and urinary incontinence) (common)

- Classical signs of hydrocephalus.
- Hydrocephalus is a common early presentation and complication of coccidioidal meningitis.

behavioural or personality change (common)

- Due to meningoencephalitis.

reduced visual acuity and papilloedema (common)

- Signs of raised intracranial pressure.
- Suggestive of cryptococcal meningitis in the appropriate clinical context.

Other diagnostic factors

nausea or vomiting (common)

- Early feature of meningitis.

fever (common)

- Early feature of meningitis.

reduced conscious level (common)

- Common and poor prognostic marker in HIV-associated cryptococcal meningitis.[91]

cranial nerve palsies (common)

- Fungal meningitis commonly affects the basilar meninges and can injure cranial nerves.

seizures (uncommon)

- Inflammation of the meninges can cause seizures.

weight loss (uncommon)

- Symptom of disseminated infection.

mouth ulcers (uncommon)

- Symptom of disseminated infection.

focal neurological signs (uncommon)

- Secondary to cerebral infarction. Coccidioidal infection causes arteritis of small- to mid-sized blood vessels.

lymphadenopathy, hepatosplenomegaly (uncommon)

- Patients with histoplasmal meningitis may demonstrate these signs as a complication of disseminated progressive histoplasmosis.

dyspnoea (uncommon)

- Cough and dyspnoea are associated with pulmonary cryptococcal involvement.
- Neonates with candidal meningitis present with respiratory distress.

papular umbilicated skin lesions (uncommon)

- Occasionally seen in cryptococcal meningitis.

retinal defects (uncommon)

- Retinal involvement may be apparent in central nervous system candidal infection.

nasal or palatal eschar (uncommon)

- A specific sign in the later stages of mucormycosis infection is necrotic eschar on the skin, palate, or nasal turbinates.

Risk factors

Strong

HIV infection

- The progressive loss of CD4+ helper cells in HIV-infected patients correlates with an increasing risk of cryptococcal meningitis. Most patients with cryptococcal meningitis have a CD4 count <100 cells/microlitre, and usually <50 cells/microlitre.[58]

corticosteroid use

- The second most important risk factor for the development of cryptococcal meningitis. Solid-organ transplant recipients and patients with connective tissue diseases (e.g., sarcoid, or reticuloendothelial malignancies) who take prednisone doses of >10-20 mg/day have an increased risk of developing cryptococcal meningitis.
- Cryptococcal meningitis in an immunocompetent adult after corticosteroid treatment for COVID-19 has been reported.[59]

underlying chronic disease (e.g., malignancy, organ failure, autoimmune disease, organ transplant)

- In patients with non-HIV-associated cryptococcal meningitis, predisposing factors have been identified as organ transplant, chronic organ failure (liver, lung, kidney), malignancy, rheumatological disease, and sarcoidosis, irrespective of corticosteroid use.[60] [61] In approximately 20% of cases of non-HIV-associated cryptococcal meningitis, no underlying cause for the development of cryptococcal meningitis is found.

exposure to disturbed soil, chicken guano, or bat caves

- Histoplasmosis occurs infrequently in individuals living outside endemic areas. Risk factors for acquisition of histoplasmosis include: exposure to disturbed soil, chicken guano, or bat caves. It is important to elicit these risk factors in patients who have travelled to endemic areas.

impaired cell-mediated immunity

- Patients presenting with progressive disseminated histoplasmosis and progressive disseminated coccidioidomycosis often have impaired cell-mediated immunity secondary to, for example, HIV/AIDS, transplantation, malignancy, corticosteroid use, tumour necrosis factor antagonist use, or congenital T-cell deficiencies.

Filipinos and African Americans

- Filipinos and African Americans have a significantly increased risk of severe disease and dissemination.[64] [65] [66] However, the overall incidence of coccidioidomycosis is similar in different ethnic groups.

neutropenia or impaired phagocytic function

- Neutropenia is a major risk factor for invasive candidiasis, including candidal meningitis. Defective neutrophil function (e.g., in chronic granulomatous disease) also increases the risk of invasive candidiasis. Candida meningitis may occur in patients with AIDS, but usually only when additional risk factors such as neutropenia are present.[67]

neurosurgery

- Candidal meningitis is the most common fungal meningitis following central nervous system shunt or ventriculostomy placement.[68]

infants and neonates

- Infants exposed to *Histoplasma capsulatum* are at increased risk of severe, life-threatening infection.
- *Candida albicans* is a relatively common cause of meningitis in premature infants or infants younger than 1 month. Candidaemia in adults is less commonly associated with meningitis.

Weak

residing in or visiting northern Australia, Papua New Guinea, or Vancouver Island, Canada

- Patients with or without overt immunosuppression, living in or visiting certain areas, especially northern Australia and Papua New Guinea, and more recently Vancouver Island, Canada, may be at risk of *Cryptococcus gattii* infection.[12] [13] [62] [63]

central vascular catheters

- Patients with intravascular catheters are at increased risk for the development of candidaemia.

sinonasal disease

- Chronic sinusitis or mastoiditis may be the primary source of fungal meningitis.

antibacterial usage

- Prolonged therapy with broad-spectrum antimicrobials increases the risk of heavy candidal colonisation and invasive infection.

prior surgery

- Surgical manipulation of a mucosal site colonised with *Candida* (i.e., gastrointestinal tract surgery) increases the risk of candidaemia.

hyperalimentation

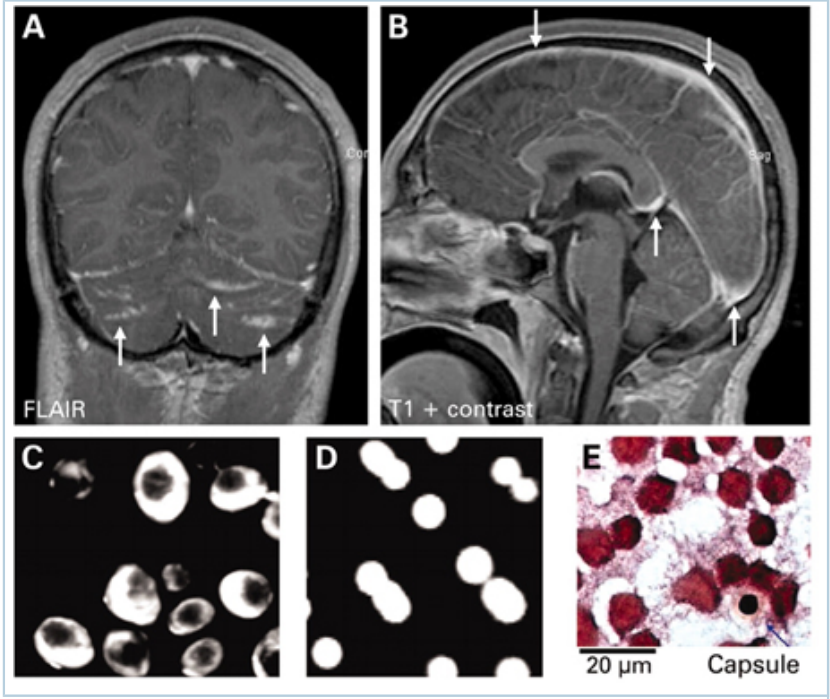
- Intravenous hyperalimentation increases the risk of candidaemia.

intravenous drug use

- Intravenous drug users are at risk of chronic neutrophilic meningitis caused by *Candida albicans* .[69]

Investigations

1st test to order

Test	Result
CT and/or MRI head scan • May show meningeal involvement and enhancement, parenchymal lesions, hydrocephalus.  *Cryptococcal meningoencephalitis. (A) Cranial magnetic resonance imaging (MRI) shows cerebellar hyperintensities (arrows) in FLAIR sequences (fluid-attenuated inversion recovery) and (B) meningeal contrast enhancement (arrows) in T1 weighted MRI. (C) Indian ink stain, (D) fungal culture, and (E) Gram stain of cerebrospinal fluid were positive* *Braun J. Headache, personality changes and fine motor disturbances. BMJ Case Reports. 2009; doi:10.1136/bcr.06.2008.0093. Used with permission.* • A normal scan does not rule out fungal meningitis.	**normal or demonstrating enhancement, parenchymal lesions, hydrocephalus**
fungal blood cultures (3 sets) • Up to three sets of fungal blood tests should be taken. • May be positive when candidal, histoplasmal, or cryptococcal meningitis is associated with disseminated disease.	**positive or negative**
serum cryptococcal antigen test • Recommended in all immunocompromised patients with undiagnosed or suspected fungal meningitis. • High sensitivity and specificity for HIV-associated cryptococcal disease. • Useful if cerebrospinal fluid cannot be obtained.	**positive in cases of cryptococcal meningitis**

Test	Result
serum + urine Histoplasma antigen • Recommended in all immunocompromised patients with undiagnosed or suspected fungal meningitis who live in or have visited the endemic area. • Sensitivity for diagnosing histoplasmal meningitis is around 70% and 40% for urine and serum, respectively.[27] • Very specific.	**positive in majority of cases of progressive disseminated histoplasmosis**
immunodiffusion tests (IgM and IgG) and complement fixation test (IgG) for coccidioidomycosis • Recommended in all immunocompromised patients with undiagnosed or suspected fungal meningitis who live in or have visited the endemic area. • Positive results support the diagnosis of coccidioidal meningitis when other causes of meningitis are excluded. Negative results from an experienced laboratory in patients with untreated disseminated disease are rare.[11]	**typically positive in cases of coccidioidal meningitis**
cerebrospinal fluid opening pressure • Very high opening pressure suggestive of HIV-associated cryptococcal meningitis in the appropriate context.	**elevated**
cerebrospinal fluid (CSF) WBC and differential • Most cases of fungal meningitis have a lymphocytic pleocytosis in the range of 20 to 500 cells/microlitre. • A predominance of polymorphonuclear cells may occur and is suggestive of meningitis due to *Candida* and opportunistic mould infections (*Aspergillus* , Zygomycetes, *Pseudallescheria*). • CSF eosinophils are uncommon, but suggestive of coccidioidal meningitis in the appropriate context. • Normal CSF white cell counts are common in HIV-associated cryptococcal meningitis.	**elevated**
cerebrospinal fluid (CSF) protein • In fungal meningitis, CSF protein is typically elevated.	**elevated**
cerebrospinal fluid (CSF) glucose • In fungal meningitis, CSF glucose is typically low.	**low**
cerebrospinal fluid India ink stain • Recommended in all immunocompromised patients with chronic or subacute, undiagnosed or suspected fungal meningitis. • Sensitivity is approximately 80% in HIV-associated cryptococcal meningitis.[58] • Less sensitive in non-HIV-associated cryptococcal meningitis.	**positive in cryptococcal meningitis**
cerebrospinal fluid (CSF) culture • To increase sensitivity, large volumes of CSF (≥10 mL) and prolonged incubation (at least 2 weeks) may be needed. • Repeat if initially negative, or initially low volume.	**positive or negative**
cerebrospinal fluid cryptococcal polysaccharide antigen test • Recommended in all immunocompromised patients with chronic or subacute, undiagnosed or suspected fungal meningitis. • Sensitivity higher than India ink. • Very specific at a titre ≥1:8; high titres indicate poor prognosis.	**positive in cryptococcal meningitis**

Test	Result
cerebrospinal fluid Histoplasma antigen • Recommended in all immunocompromised patients with chronic or subacute, undiagnosed or suspected fungal meningitis who live in or have visited the endemic area. • Sensitivity around 70% and 40%, in HIV- and non-HIV-associated cases, respectively.[27] • Very specific.	**positive in histoplasmal meningitis**
cerebrospinal fluid Histoplasma antibodies • Recommended in all immunocompromised patients with undiagnosed or suspected fungal meningitis who live in or have visited the endemic area. • Sensitivity and specificity around 80%.[27]	**positive in histoplasmal meningitis**
cerebrospinal fluid coccidioidal IgG antibodies • Recommended in all immunocompromised patients with undiagnosed or suspected fungal meningitis who live in or have visited the endemic area. • Provides specific diagnosis in coccidioidal meningitis.	**positive in coccidioidal meningitis**
cerebrospinal fluid (CSF) galactomannan antigen test • Galactomannan detection in CSF showed a good diagnostic performance when an optical density index cutoff of 0.5 to 2.0 was used.[85]	**positive in *Aspergillus* meningitis**

Other tests to consider

Test	Result
histopathology and culture of biopsies: meningeal, brain, extraneural sites of involvement • Considered if less invasive tests are negative.	**positive for organism**
polymerase chain reaction (PCR) • Can detect fungal DNA in cerebrospinal fluid and other body fluids.[87] [88] However, it should not be used for diagnostic or management decisions, and a negative result does not rule out infection.[92] [93]	**fungal DNA may be detected**

Emerging tests

Test	Result
18F-fluorodeoxyglucose (FDG) PET/CT • FDG PET/CT scanning identifies tissue with an enhanced glucose metabolism. Apart from the evaluation of malignancies, FDG PET/CT has been used in the diagnosis of focal inflammation and infection. • In one study, FDG PET/CT informed therapy duration decisions, and highlighted the need for surgery, in lymphoid/myeloid malignancy patients with complex invasive fungal disease.[84]	**detection of tissue with enhanced glucose metabolism, such as focus of fungal infection**
cerebrospinal fluid (CSF) (1-3)-beta-D-glucan • May play a role in the diagnosis of fungal meningitis.[89] • During the 2012 *Exserohilum rostratum* meningitis outbreak from contaminated methylprednisolone, CSF (1-3)-beta-D-glucan also demonstrated potential utility in monitoring treatment response.[94]	**elevated**

Differentials

Condition	Differentiating signs / symptoms	Differentiating tests
Tuberculous meningitis	• History of contact, or resident in endemic area. • Symptoms and signs of pulmonary and extraneural disease.	• Cerebrospinal fluid (CSF) smear and culture, and nucleic acid amplification tests (NAAT). • Rapid NAATs (Xpert MTB/RIF and Xpert Ultra) are recommended by the World Health Organization as initial diagnostic tests in adults and children with signs and symptoms of extrapulmonary tuberculosis.[95] Sensitivity of 89.4% has been reported in CSF.[96] • CSF acid-fast bacilli smear has poor sensitivity in most settings.[97] Culture requires large volume for maximum sensitivity.
Bacterial meningitis	• Relevant exposure history. • May be difficult to distinguish clinically with symptoms and signs including meningismus, headache, myalgias, and pharyngitis.	• Polymerase chain reaction amplification of bacterial DNA from blood is more sensitive and specific than traditional microbiological techniques. Can aid diagnosis in patients who have already received antibiotics. • Specific serology (*Borrelia burgdorferi* , *Brucella* , *Leptospira* , *Treponema pallidum*). • Culture (*Actinomyces* , *Nocardia* , *Brucella*).
Viral meningitis	• Relevant exposure history. • May be difficult to distinguish clinically with symptoms and signs including meningismus, headache, myalgias, and pharyngitis.	• Serology for herpes simplex virus, varicella zoster virus, and other viruses; cerebrospinal fluid viral culture; polymerase chain reaction for enteroviruses and herpes viruses.
Non-infectious lymphocytic meningitis	• History, symptoms, signs suggestive of autoimmune disease, sarcoidosis, systemic lupus, Behcet's disease, carcinomatous meningitis. • Recurrent chemical meningitis may be	• Head CT/MRI may demonstrate epidermoid cysts or craniopharyngioma. • Cerebrospinal fluid (CSF) cytology may demonstrate malignant cells; CSF ACE elevated in sarcoidosis.

Condition	Differentiating signs / symptoms	Differentiating tests
	associated with epidermoid cysts or craniopharyngioma.	• Autoantibodies to investigate systemic manifestations.

Approach

The aims of treatment are resolution of signs and symptoms of infection and sterilisation of the cerebrospinal fluid (CSF). Not all fungal meningitis is curable; coccidioidal meningitis requires lifelong therapy.[73] Aggressive therapy with antifungal agents is the mainstay of treatment.

Patients who are already diagnosed with HIV and on antiretroviral therapy (ART) should continue their treatment, but should be aware of the potential risk of immune reconstitution inflammatory syndrome.

Cryptococcal meningitis

Initial induction combination therapy with an amphotericin-B formulation and flucytosine is recommended in both HIV- and non-HIV-associated infection.[71] The preferred regimen for patients with HIV is 2 weeks of intravenous liposomal amphotericin-B plus oral flucytosine.[71] Amphotericin-B deoxycholate can be used as an alternative formulation if risk of renal dysfunction is low or if cost is prohibitive.

For patients with HIV, especially in resource-limited settings, the World Health Organization (WHO) recommends an induction regimen that consists of a single high dose of liposomal amphotericin-B combined with 14 days of flucytosine and fluconazole.[70] Where liposomal amphotericin-B is not available, the WHO recommends 1 week of amphotericin-B deoxycholate and flucytosine, followed by 1 week of fluconazole.[70]

Alternative induction regimens

Guideline recommendations include 2 weeks of intravenous or oral fluconazole plus oral flucytosine, 2 weeks of intravenous amphotericin-B deoxycholate plus oral or intravenous fluconazole, or 2 weeks of liposomal amphotericin plus fluconazole.[70] [71] Other options included in US guidelines are amphotericin-B lipid complex plus flucytosine; liposomal amphotericin-B alone; amphotericin-B deoxycholate alone; liposomal amphotericin-B plus flucytosine followed by fluconazole; and fluconazole alone.[71]

Lipid formulations of amphotericin-B may be preferred for patients with, or at risk of, clinically significant renal dysfunction.[71] [98] The combination of amphotericin-B and flucytosine, compared with amphotericin-B alone, was associated with improved survival in cryptococcal meningitis; however, there was no survival benefit from combining amphotericin-B and fluconazole.[99] WHO guidelines note that flucytosine-containing regimens are superior and should be used where possible.[70]

Consolidation and maintenance therapy

Fluconazole is recommended.[70] [71] Less toxic oral therapy facilitates continued treatment and prevention of relapse, while minimising the dose-dependent toxicity of amphotericin-B.

The optimal consolidation phase of treatment is an 8-week course of oral fluconazole.[70] [71] After 8 weeks, the patient should be switched to low-dose fluconazole for long-term maintenance therapy.[70] [71]

In patients with HIV-associated cryptococcal meningitis, maintenance therapy should be continued for at least 1 year. Treatment may be stopped once the patient's CD4 count is 100 cells/microlitre or above and the viral RNA is undetectable on ART.[71] Fluconazole is superior to itraconazole therapy for maintenance.[100] [101] It is unclear how long patients with non-HIV-associated cryptococcal meningitis should receive maintenance therapy. In the absence of data, most patients, depending on response

to antifungal treatment and reversibility of immunosuppression, are maintained on fluconazole for 6 to 12 months. There have been reports of fluconazole-resistant *Cryptococcus neoformans* in some geographical areas.[102] [103]

Immune reconstitution inflammatory syndrome

Treatment of cryptococcal meningitis in HIV-infected patients is complicated by the development of immune reconstitution inflammatory syndrome (IRIS) in nearly 1 in 8 patients.[19] For patients with HIV infection, immediate initiation of ART is not recommended as there is an increased risk of mortality, thought to be caused by IRIS.[104] [105]

WHO and US guidelines recommend that ART should be started 4-6 weeks after initiation of antifungal treatment.[70] [71]

Management of the raised CSF pressure

Important as it complicates the clinical course of more than 80% of patients with HIV-associated cryptococcal meningitis.[70] Raised intracranial pressure, if not aggressively managed, results in a poor prognosis.[106]

Guidelines advocate therapeutic drainage of CSF if the CSF opening pressure is more than 25 cm H_2O.[70] The aim is to reduce the CSF closing pressure to less than 20 cm H_2O or to 50% of the opening pressure, by serial daily lumbar punctures with withdrawal of large volumes of CSF (up to 30 mL/day). If serial lumbar punctures over a number of days fail to control the raised intracranial pressure, a temporary lumbar drain or ventriculoperitoneal shunt may be considered.[107] Medical approaches including the use of corticosteroids, acetazolamide, or mannitol are not recommended.

Histoplasmal meningitis

May occur as an isolated entity or as part of progressive disseminated histoplasmosis (PDH). An aggressive approach to treatment is warranted given the poor response to therapy compared with other types of histoplasmosis.

Liposomal amphotericin-B is given for 4 to 6 weeks, followed by itraconazole for at least 1 year and until resolution of CSF abnormalities.[71] Patients who are intolerant to itraconazole may be given either posaconazole, voriconazole, or fluconazole.

Liposomal amphotericin-B appeared to be more effective than amphotericin-B deoxycholate in HIV-infected patients with PDH, and achieves higher concentrations in brain tissue than amphotericin-B lipid complex.[108] [109] Combination antifungal therapy is not recommended. There is currently insufficient evidence to advocate azole antifungal therapy alone for central nervous system (CNS) histoplasmosis.

Itraconazole can be safely discontinued in HIV-infected patients after at least 1 year if:[71]

- HIV viral load is undetectable
- CD4 count is more than 150 cells/microlitre for at least 6 months in response to ART
- Fungal blood cultures are negative, and
- Serum or urine *Histoplasma* antigen below the level of quantification.

Drug levels of itraconazole are usually monitored to ensure adequate drug absorption and assess adherence. Low levels may prompt a dose increase, a switch to liquid formulation, or switch to an alternative azole antifungal.[27]

Coccidioidal meningitis

First-line therapy is usually fluconazole.[71] [110] Itraconazole is an acceptable alternative.[71] Alternative oral agents for patients intolerant or unresponsive to fluconazole or itraconazole are posaconazole and voriconazole.[71] [111] [112] [113] Some experts institute additional intrathecal amphotericin-B, in the belief that this results in a more rapid response (this should be used in consultation with a specialist).[71]

Patients who do not respond to azole therapy may be treated with intrathecal amphotericin-B therapy with or without continued azole treatment.[71] Hydrocephalus usually requires ventricular shunt placement.

Coccidioidal meningitis cure is currently not possible, necessitating lifelong therapy.[71]

Candidal meningitis

Owing to the high morbidity and mortality associated with candidal meningitis, aggressive therapy is warranted. The Infectious Diseases Society of America recommends initial therapy with amphotericin-B deoxycholate plus flucytosine.[74] Liposomal amphotericin-B can be used in case of renal impairment. Flucytosine has excellent penetration of the blood-brain barrier and achieves good CSF levels.

Following initial treatment (2 to 6 weeks) with amphotericin-B and flucytosine, continuation and/or maintenance therapy with fluconazole may be considered (especially in patients with ongoing immunosuppression or in patients who have responded to amphotericin-B and flucytosine but have developed serious drug-related toxicity).[74] Voriconazole is an alternative for fluconazole-resistant isolates.

Because of the high risk of relapse, therapy should be continued for a minimum of 4 weeks after the resolution of signs and symptoms. CSF analysis and radiological findings should also normalise prior to stopping. Prosthetic devices should be removed, if at all possible, in neurosurgical patients with candidal meningitis. Infected intravascular catheters should be removed, if possible, in patients with candidaemia.

Exserohilum rostratum meningitis

Before the 2012 outbreak from contaminated methylprednisolone in the US, human infections with *E rostratum* were exceedingly rare. Little is known about its management, especially when the CNS is involved. Treatment should be undertaken in consultation with an infectious diseases specialist.[114]

For patients with *E rostratum* meningitis, a minimum of 3 months of antifungal therapy is currently recommended, with up to 1 year of treatment recommended for patients with severe CNS involvement (e.g., arachnoiditis).[114]

Despite an optimum course of therapy, relapse of *E rostratum* meningitis has been reported after resolution of symptoms and normalisation of CSF white blood cell count.[115] Prolonged or lifelong antifungal therapy may be required with relapsing fungal meningitis, depending on the nature of infection, the frequency of relapsing meningitis after cessation of antifungal therapy, the severity of CNS involvement, and the underlying immune status of the individual.

Aspergillus meningitis

Voriconazole is considered the primary treatment choice; lipid formulations of amphotericin-B are reserved for those intolerant or refractory to voriconazole.[116] Long-term treatment is usually required depending on clinical response and immune status. Aggressive surgical debridement of paranasal fungal infection is key to the successful outcome of medical therapy.

Mucormycosis meningitis

Liposomal amphotericin-B is the first-line agent in CNS mucormycosis.[46] Isavuconazole and posaconazole may be considered as second-line agents.[46] [117] [118] Aggressive surgical debridement of paranasal fungal infection is key to the successful outcome of medical therapy.[46]

Treatment algorithm overview

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Acute (summary)		
cryptococcal meningitis		
	1st	antifungal induction therapy
	adjunct	antiretroviral therapy (ART)
	adjunct	therapeutic drainage of cerebrospinal fluid (CSF)
	plus	antifungal consolidation therapy
	plus	antifungal maintenance therapy
histoplasmal meningitis		
	1st	liposomal amphotericin-B
	plus	maintenance therapy with azole antifungal
coccidioidal meningitis		
	1st	azole antifungal therapy
	adjunct	intrathecal amphotericin-B
	adjunct	ventricular shunt replacement
	plus	maintenance therapy with azole antifungal therapy
candidal meningitis		
	1st	amphotericin-B + flucytosine
	adjunct	removal of prosthesis
	plus	maintenance therapy with fluconazole or voriconazole
Exserohilum rostratum meningitis		
	1st	antifungal therapy
Aspergillus meningitis		
	1st	voriconazole or amphotericin-B
	plus	debridement of paranasal sinuses
mucormycosal meningitis		
	1st	antifungal therapy
	plus	debridement of paranasal sinuses

Treatment algorithm

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Acute

cryptococcal meningitis

1st **antifungal induction therapy**

Primary options

» amphotericin B liposomal: 3-4 mg/kg intravenously once daily for 2 weeks
-or-
» amphotericin B deoxycholate: 0.7 to 1 mg/kg intravenously once daily for 2 weeks
--AND--
» flucytosine: 25 mg/kg orally four times daily for 2 weeks

OR

» amphotericin B liposomal: 10 mg/kg intravenously as a single dose
This regimen is recommended by the World Health Organization.
--AND--
» flucytosine: 25 mg/kg orally four times daily for 2 weeks
-and-
» fluconazole: 1200 mg orally/intravenously once daily for 2 weeks

Secondary options

» amphotericin B lipid complex: 5 mg/kg intravenously once daily for 2 weeks
-and-
» flucytosine: 25 mg/kg orally four times daily for 2 weeks

OR

» amphotericin B liposomal: 3-4 mg/kg intravenously once daily for 2 weeks
-and-
» fluconazole: 800-1200 mg orally/intravenously once daily for 2 weeks

OR

» fluconazole: 800-1200 mg orally/intravenously once daily for 2 weeks
-and-

MANAGEMENT

Acute

» flucytosine: 25 mg/kg orally four times daily for 2 weeks

OR

» amphotericin B deoxycholate: 0.7 to 1 mg/kg intravenously once daily for 2 weeks
-and-
» fluconazole: 800-1200 mg orally/intravenously once daily for 2 weeks

OR

» amphotericin B liposomal: 3-4 mg/kg intravenously once daily for 2 weeks

OR

» amphotericin B deoxycholate: 0.7 to 1 mg/kg intravenously once daily for 2 weeks

OR

» amphotericin B liposomal: 3-4 mg/kg intravenously once daily for 1 week
-and-
» flucytosine: 25 mg/kg orally four times daily for 1 week
-and-
» fluconazole: 1200 mg orally/intravenously once daily for 1 week (after 1-week course of amphotericin B liposomal and flucytosine

OR

» fluconazole: 1200 mg orally/intravenously once daily for 2 weeks

OR

» amphotericin B deoxycholate: 1 mg/kg intravenously once daily for 1 week
This regimen is recommended by the World Health Organization.

-and-
» fluconazole: 25 mg/kg orally four times daily for 1 week
-and-
» fluconazole: 1200 mg orally/intravenously once daily for 1 week (after 1-week course of amphotericin B deoxycholate and flucytosine)

Acute

» Treatment is started as soon as the diagnosis is made, because untreated disease is uniformly fatal.

» Initial induction combination therapy with an amphotericin-B formulation and flucytosine is recommended in both HIV- and non-HIV-associated infection. The preferred regimen recommended by US guidelines for patients with HIV is 2 weeks of intravenous liposomal amphotericin-B plus oral flucytosine.[71] Amphotericin-B deoxycholate can be used as an alternative formulation if risk of renal dysfunction is low or if cost is prohibitive.

» For patients with HIV, especially in resource-limited settings, the World Health Organization (WHO) recommends an induction regimen that consists of a single high dose of liposomal amphotericin-B combined plus 14 days of flucytosine and fluconazole.[70]

» Where liposomal amphotericin-B is not available, the WHO recommends 1 week of amphotericin-B deoxycholate and flucytosine, followed by 1 week of fluconazole.[70] Alternative induction regimens recommended by US guidelines and the WHO are 2 weeks of intravenous or oral fluconazole plus oral flucytosine, 2 weeks of intravenous amphotericin-B deoxycholate plus oral or intravenous fluconazole, or 2 weeks of liposomal amphotericin plus fluconazole.[70] [71] Other options included in US guidelines are amphotericin-B lipid complex plus flucytosine; liposomal amphotericin-B alone; amphotericin-B deoxycholate alone; liposomal amphotericin-B plus flucytosine followed by fluconazole; and fluconazole alone.[71]

» Lipid formulations of amphotericin-B may be preferred for patients with, or at risk of, clinically significant renal dysfunction.[71] [98] Renal and haematological profiles must be monitored closely (especially in HIV-related nephropathy). Renal impairment may be reduced by saline and fluid loading, provided that there are no contraindications.[119]

» Potassium and magnesium must be monitored and replaced if necessary.

» A fall in haemoglobin of around 20% occurs within 2 weeks of starting amphotericin-B, and transfusion may be required.[120] Thrombophlebitis is common.

Acute

» Some experts recommend measurement of serum flucytosine levels 2 hours after dosing, optimal levels being 25-100 mg/L.[71]

» The combination of amphotericin-B and flucytosine, compared with amphotericin-B alone, was associated with improved survival in cryptococcal meningitis; however, there was no survival benefit from combining amphotericin-B and fluconazole.[99] WHO guidelines note that flucytosine-containing regimens are superior and should be used where possible.[70]

» Treatment of cryptococcal meningitis in HIV-infected patients is complicated by the development of immune reconstitution inflammatory syndrome in nearly 1 in 8 patients.[19]

adjunct **antiretroviral therapy (ART)**

Treatment recommended for SOME patients in selected patient group

» For patients with HIV infection, immediate initiation of ART is not recommended as there is an increased risk of mortality, thought to be caused by immune reconstitution inflammatory syndrome.[104] [105] WHO and US guidelines recommend that ART should be started 4-6 weeks after initiation of antifungal treatment.[70] [71]

adjunct **therapeutic drainage of cerebrospinal fluid (CSF)**

Treatment recommended for SOME patients in selected patient group

» The management of patients with raised intracranial pressure is an important aspect of the management of cryptococcal meningitis.[106]

» Current guidelines recommend therapeutic drainage of CSF if the CSF opening pressure is >25 cm H_2O.[70] The aim is to reduce the CSF closing pressure to <20 cm H_2O or 50% of the opening pressure, by serial daily lumbar punctures with withdrawal of large volumes of CSF (up to 30 mL/day; pressure checked after removal of each 10 mL of CSF).

» If serial lumbar punctures over a number of days fail to control elevated intracranial pressure, a temporary lumbar drain or ventriculoperitoneal shunt may be considered.[107]

» Medical approaches including the use of corticosteroids, acetazolamide, or mannitol are not recommended.

Acute

plus **antifungal consolidation therapy**

Treatment recommended for ALL patients in selected patient group

Primary options

» fluconazole: clinically stable and negative CSF cultures: 400 mg orally once daily; positive CSF cultures: 800 mg orally once daily, may increase to 1200 mg once daily after 2 weeks if CSF remains positive and patient is clinically stable

Secondary options

» fluconazole: 1200 mg orally once daily
-and-
» flucytosine: 25 mg/kg orally four times daily

» Consolidation therapy is with fluconazole.[70] [71] Less toxic oral therapy facilitates continued treatment and prevention of relapse, while minimising the dose-dependent toxicity of amphotericin-B.

» The optimal consolidation phase of treatment is an 8-week course of oral fluconazole.[70] [71]

» US guidelines advise that patients with positive CSF cultures but who have clinically improved after 2 weeks of induction therapy should receive a higher dose (1200 mg/day) of fluconazole for consolidation therapy, and have repeat lumbar puncture in another 2 weeks.[71] Alternatively, non-hospitalised patients can receive flucytosine plus fluconazole for an additional 2 weeks before starting single-drug consolidation therapy.[71] The duration of consolidation therapy should be 8 weeks from the point at which CSF cultures are negative.[71]

plus **antifungal maintenance therapy**

Treatment recommended for ALL patients in selected patient group

Primary options

» fluconazole: 200 mg orally once daily

» After the 8-week consolidation phase, the patient should be switched to low-dose fluconazole for long-term maintenance therapy.[70] [71]

» In patients with HIV-associated cryptococcal meningitis, maintenance therapy should be continued for at least 1 year. Treatment may be stopped once the patient's CD4 count is 100

Acute

cells/microlitre or above and the viral RNA is undetectable on antiretroviral therapy.[71]

» It is unclear how long patients with non-HIV-associated cryptococcal meningitis should receive maintenance therapy. In the absence of data, most patients, depending on response to antifungal treatment and reversibility of immunosuppression, are maintained on fluconazole for 6 to 12 months.

histoplasmal meningitis

1st **liposomal amphotericin-B**

Primary options

» amphotericin B liposomal: 5 mg/kg/day intravenously for 4-6 weeks

» May be isolated or as a component of disseminated histoplasmosis.

» Initial therapy is with liposomal amphotericin-B for 4 to 6 weeks.[71]

» Electrolytes are monitored (replace as required) and also renal function; however, nephrotoxicity is less with liposomal formulation compared with deoxycholate formulation.

» Saline and fluid loading equivalent to 1 L normal saline may reduce nephrotoxicity.

plus **maintenance therapy with azole antifungal**

Treatment recommended for ALL patients in selected patient group

Primary options

» itraconazole: 200 mg orally twice to three times daily

Secondary options

» posaconazole: 300 mg orally (delayed-release tablet) twice daily on day one, followed by 300 mg once daily

OR

» voriconazole: 400 mg orally twice daily initially on day one, followed by 200 mg twice daily

OR

» fluconazole: 800 mg orally once daily

Acute

» May be isolated or as a component of disseminated histoplasmosis.

» Maintenance therapy is with itraconazole. Alternatives include fluconazole, voriconazole, or posaconazole.[71]

» Given for at least 1 year and until resolution of cerebrospinal fluid (CSF) abnormalities and of CSF antigen (and serum and urine antigen if initially positive).

» Itraconazole can be safely discontinued in HIV-infected patients after at least 1 year if HIV viral load is undetectable, CD4 count is >150 cells/microlitre for at least 6 months in response to ART, fungal blood cultures are negative, and serum or urine *Histoplasma antigen* is below the level of quantification.[71]

» Drug levels of itraconazole are usually monitored to ensure adequate drug absorption and assess adherence. Low levels may prompt a dose increase, a switch to liquid formulation, or switch to an alternative azole antifungal.[27]

coccidioidal meningitis

1st **azole antifungal therapy**

Primary options

» fluconazole: 400-1200 mg orally once daily

OR

» itraconazole: 200 mg orally twice to three times daily

Secondary options

» posaconazole: 300 mg orally (delayed-release tablet) twice daily on day one, followed by 300 mg once daily

OR

» voriconazole: 400 mg orally twice daily initially on day one, followed by 200 mg twice daily

» First-line therapy is usually fluconazole.[110]

» Itraconazole is an acceptable alternative. Alternative oral agents for patients intolerant or unresponsive to fluconazole or itraconazole are posaconazole and voriconazole.[111] [112] [113]

Acute

» Patients who respond to azole antifungal therapy should continue this treatment indefinitely.

» Patients who do not respond to azole therapy may be treated with intrathecal amphotericin-B, with or without continued azole treatment.

adjunct **intrathecal amphotericin-B**

Treatment recommended for SOME patients in selected patient group

Primary options

» amphotericin B deoxycholate: see consultant for guidance on intrathecal dose

» Some experts start intrathecal amphotericin-B with initial fluconazole in the belief that this approach results in a more rapid response.

» Intrathecal therapy should be used in consultation with a specialist and administered by a clinician experienced in this drug delivery technique.[71]

adjunct **ventricular shunt replacement**

Treatment recommended for SOME patients in selected patient group

» Patients with hydrocephalus usually require ventricular shunt placement.

plus **maintenance therapy with azole antifungal therapy**

Treatment recommended for ALL patients in selected patient group

Primary options

» fluconazole: 400-1200 mg orally once daily

OR

» itraconazole: 200 mg orally twice to three times daily

Secondary options

» posaconazole: 300 mg orally (delayed-release tablet) twice daily on day one, followed by 300 mg once daily

OR

» voriconazole: 400 mg orally twice daily initially on day one, followed by 200 mg twice daily

Acute

» Patients who respond to azole antifungal therapy should continue this treatment indefinitely.

candidal meningitis

1st **amphotericin-B + flucytosine**

Primary options

» amphotericin B deoxycholate: 0.7 to 1 mg/kg/day intravenously for 2-6 weeks
-or-
» amphotericin B liposomal: 4-6 mg/kg/day intravenously for 2-6 weeks

--AND--

» flucytosine: 50-100 mg/kg/day orally given in divided doses every 6 hours for 2-6 weeks

» Treatment should be started immediately after diagnosis, or empirically pending diagnostic test results in severely ill patients where candidal meningitis is suspected.

» Flucytosine achieves good levels in the cerebrospinal fluid, and is additive with amphotericin-B against *Candida* species in vitro and in experimental infection. Liposomal amphotericin-B is preferred in patients with renal impairment.

» Flucytosine's toxic effects on bone marrow and liver must be carefully monitored, preferably with frequent serum flucytosine levels.[74]

» Renal and haematological profiles of patients receiving amphotericin-B must be monitored closely. Renal impairment may be reduced by saline and fluid loading, provided no contraindication.[119] Electrolytes (potassium and magnesium) need monitoring and replacement if necessary.

» A fall in haemoglobin of around 20% occurs within 2 weeks of starting amphotericin-B.[120]

» Transfusion may be required in those with low baseline haemoglobin. Thrombophlebitis is common.

adjunct **removal of prosthesis**

Treatment recommended for SOME patients in selected patient group

» In neurosurgical patients with candidaemia, prosthetic devices and infected intravascular catheters should be removed, if at all possible.

Acute

plus **maintenance therapy with fluconazole or voriconazole**

Treatment recommended for ALL patients in selected patient group

Primary options

» fluconazole: 800 mg orally once daily

Secondary options

» voriconazole: 200 mg orally twice daily

» Continuation of treatment with fluconazole may be considered, especially in patients with ongoing immunosuppression, or in patients who have responded to amphotericin-B and flucytosine but have developed drug-related toxicity. Maintenance therapy has been used in HIV-infected patients.

» Voriconazole is an alternative for fluconazole-resistant isolates.

» Due to the high risk of relapse, therapy should be continued for a minimum of 4 weeks after the resolution of all signs and symptoms associated with the infection. All cerebrospinal fluid analysis and radiological findings should also normalise prior to stopping antifungal therapy.

Exserohilum rostratum meningitis

1st **antifungal therapy**

» Before the 2012 outbreak from contaminated methylprednisolone in the US, human infections with *E rostratum* were exceedingly rare. Little is known about its management, especially when the central nervous system (CNS) is involved.

» For patients with *E rostratum* meningitis, a minimum of 3 months of antifungal therapy is recommended, with up to 1 year of treatment recommended for patients with severe CNS involvement (e.g., arachnoiditis).[114]

» However, despite an optimum course of therapy, relapse of *E rostratum* meningitis has been reported after resolution of symptoms and normalisation of CSF white blood cell count.[115]

» Prolonged or lifelong antifungal therapy may be required with relapsing fungal meningitis, depending on the nature of infection, the frequency of relapsing meningitis after cessation of antifungal therapy, the severity of CNS

Acute

involvement, and the underlying immune status of the individual.

» Treatment should be undertaken in consultation with an infectious diseases specialist.[114]

Aspergillus meningitis

1st **voriconazole or amphotericin-B**

Primary options

» voriconazole: 6 mg/kg intravenously every 12 hours on day 1, followed by 4 mg/kg intravenously every 12 hours, switch to oral therapy when clinical improvement; 200 mg orally twice daily

Secondary options

» amphotericin B lipid complex: 5 mg/kg intravenously once daily

» Voriconazole is considered the primary treatment choice; lipid formulations of amphotericin-B are reserved for those intolerant or refractory to voriconazole.[116] Long-term treatment is usually required depending on clinical response and immune status.

plus **debridement of paranasal sinuses**

Treatment recommended for ALL patients in selected patient group

» Aggressive surgical debridement of paranasal fungal infection is a key to successful outcome of medical therapy.

mucormycosal meningitis

1st **antifungal therapy**

Primary options

» amphotericin B liposomal: 5-10 mg/kg intravenously every 24 hours

Secondary options

» isavuconazole: 200 mg intravenously/orally every 8 hours for 6 doses as a loading dose, followed by 200 mg every 24 hours (starting at least 12 hours after the last loading dose)

OR

» posaconazole: 300 mg intravenously every 12 hours on day one, followed by 300 mg every 24 hours; 300 mg orally (delayed-

MANAGEMENT

Acute

release tablet) twice daily on day one, followed by 300 mg once daily

» Liposomal amphotericin-B is the first-line agent in central nervous system (CNS) mucormycosis.[46] Isavuconazole and posaconazole may be considered as second-line agents.[46] [117] [118]

» Aggressive surgical debridement of paranasal fungal infection is key to the successful outcome of medical therapy.[46]

plus **debridement of paranasal sinuses**

Treatment recommended for ALL patients in selected patient group

» Aggressive surgical debridement of paranasal fungal infection is a key to successful outcome of medical therapy.[46]

Primary prevention

In general, avoidance of exposure to fungal pathogens is not realistic, but avoidance of circumstances likely to lead to prolonged heavy exposure (e.g., contact with pigeon guano [*Cryptococcus neoformans*] or disturbed soil in highly endemic areas [*Cryptococcus immitis* , *Histoplasma capsulatum*]) is reasonable, especially for immunosuppressed patients.

Antiretroviral therapy

Early and effective antiretroviral therapy in patients with HIV may prevent occurrence of fungal meningitis.

Antiretroviral therapy remains the most effective prophylaxis to prevent HIV-associated cryptococcal disease.

Antifungal therapy

Patients presenting with advanced HIV infection, a CD4 count <100 cells/microlitre, and who have a positive cryptococcal antigen test result should be given pre-emptive antifungal therapy to prevent the development of invasive cryptococcal disease before initiating or reinitiating antiretroviral therapy.[70] [71] Antifungal therapy may also be considered at a higher CD4 count threshold of <200 cells/microlitre.[70]

Although primary antifungal prophylaxis with either fluconazole or itraconazole reduces the incidence of cryptococcal meningitis in patients with advanced HIV disease and reduces deaths due to cryptococcal disease, it has no clear effect on overall mortality.[72] In settings where antigen screening is not available, the World Health Organization recommends initiating fluconazole primary prophylaxis in people with HIV infection and a CD4 count <100 cells/mm^3.[70]

Prophylaxis for histoplasmosis with itraconazole is recommended in HIV-infected patients with CD4 cell counts <150 cells/microlitre who are at high risk because of occupational exposure, or who are resident in specific endemic areas where the incidence is >10 cases per 100 patient-years.[71] Prophylaxis with itraconazole may also be appropriate in specific circumstances in other immunosuppressed patients, such as organ transplant patients or those taking immunosuppression medicine such as corticosteroids.

For patients with HIV living in the coccidioidal-endemic region, primary antifungal prophylaxis is not recommended to prevent coccidioidomycosis.[73] Fluconazole prophylaxis is, however, recommended for organ transplant patients without active coccidioidomycosis who are in the endemic area.[73]

Primary prophylaxis against invasive candidiasis is indicated in selected high-risk patient groups.[74] Primary prophylaxis may be indicated in patients with prolonged neutropenia or high-risk bone marrow, and in solid-organ transplant recipients and selected intensive care unit patients where there are high rates of disease. Fluconazole, and azole antifungals with additional activity against mould infections, have been used in these settings. In very low birthweight infants (<1.5 kg), chemoprophylaxis with fluconazole and oral nystatin is considered to be an effective practice to prevent neonatal fungal infections.[75]

Patient discussions

All patients should be counselled regarding the importance of adherence to antifungal maintenance therapy and told to report any recurrence of symptoms. Patients should be informed of the need to monitor response by blood and cerebrospinal fluid analysis and the possibility of relapse.

HIV-infected patients who have been treated for cryptococcal meningitis should be warned of the possible occurrence of cryptococcal immune reconstitution syndrome (CM-IRIS), usually 1 to 2 months after starting antiretroviral therapy.

Patients treated for coccidioidal meningitis need to be advised that therapy and follow-up is lifelong, and of the high risk of relapse if treatment is discontinued or interrupted.

FOLLOW UP

Monitoring

Monitoring

Cryptococcal meningitis

- Patients who have recovered from cryptococcal meningitis require careful follow-up for recurrence of symptoms.
- Patients who are already diagnosed with HIV should continue their antiretroviral therapy. In treatment-naive HIV-infected patients with a recent diagnosis of cryptococcal meningitis, delaying antiretroviral therapy for 5 weeks was associated with improved survival compared with therapy initiation at 1 to 2 weeks, especially among patients with a paucity of white cells in cerebrospinal fluid (CSF).[104]
- Treatment of cryptococcal meningitis in HIV-infected patients is complicated by the development of immune reconstitution inflammatory syndrome in nearly 1 in 8 patients.[19]

Histoplasmal meningitis[27]

- CSF analysis should be repeated after 1 month, when liposomal amphotericin-B is replaced by an azole antifungal, and at 1 year, and if failure or relapse is suspected.
- Therapy should be continued until CSF abnormalities have resolved and CSF antigen (and serum and urine antigen if initially positive) is negative.[71]
- Serum and urine antigen, if initially positive, can be repeated at 2 weeks, 1 month, and then 3-monthly during therapy and for at least 6 months after treatment is terminated.
- Patients in whom treatment failure or relapse is suspected should also have antigen levels measured.

Coccidioidal meningitis[11]

- CSF analysis is repeated monthly initially.
- If response is satisfactory, CSF is repeated 3-monthly for life.
- Serum and CSF complement fixing-type antibodies decrease with successful therapy.

Candidal meningitis[74]

- Due to the high rates of relapse in candidal meningitis, antifungal therapy must be given for a minimum of 4 weeks after resolution of all signs and symptoms.
- All CSF analysis and radiological findings should also normalise prior to stopping antifungal therapy.

FOLLOW UP

Complications

Complications	Timeframe	Likelihood
anaemia, electrolyte disturbance, and nephrotoxicity secondary to amphotericin-B therapy	**short term**	**high**
Patients commonly develop anaemia, hypokalaemia, hypomagnesaemia, and reversible nephrotoxicity. Patients with a low baseline haemoglobin may require blood transfusion should they develop severe or symptomatic anaemia. To minimise amphotericin-B-associated nephrotoxicity, patients should receive prehydration with intravenous normal saline, unless contraindicated.[119] Patients routinely require potassium and magnesium supplementation while receiving amphotericin-B.		
histoplasmoma	**short term**	**low**
Histoplasmomas are focal brain or spinal cord lesions. May occur in association with *Histoplasma* meningitis, in which case treatment is as for meningitis. Surgery is not recommended. If it is an isolated finding in an otherwise well patient without meningitis or disseminated infection, induction with amphotericin-B may be shortened.[27]		
immune reconstitution inflammatory syndrome (IRIS)	**short term**	**low**
IRIS can complicate fungal meningitis associated with HIV infection upon initiation of antiretroviral therapy. It can cause a paradoxical precipitous neurological decline.[129] Between 6% and 30% of patients may develop cryptococcal IRIS at a median of 1 to 2 months after starting antiretroviral therapy. Features include increased headache, fever, lymphadenopathy, and raised cerebrospinal fluid (CSF) pressure. Antiretroviral drugs should be continued. CSF should be examined to measure pressure (may require control by serial lumbar punctures) and exclude ongoing active infection and alternative diagnoses. Short-course corticosteroids may be considered in severely affected patients.[130] [131] [132]		
neurological sequelae (e.g., deafness)	**long term**	**high**
15% to 30% of patients who recover from candidal meningitis have serious neurological sequelae, especially children.[37] [126] [127]		
raised intracranial pressure	**variable**	**high**
Raised intracranial pressure with cryptococcal meningitis probably occurs due to impaired reabsorption of cerebrospinal fluid (CSF) at the arachnoid villi. Guidelines advocate therapeutic drainage of CSF if the CSF opening pressure is more than 25 cm H_2O.[70] The aim is to reduce the CSF closing pressure to less than 20 cm H_2O or to 50% of the opening pressure, by serial daily lumbar punctures with withdrawal of large volumes of CSF (up to 30 mL/day). If high pressure persists despite daily lumbar punctures, a temporary lumbar drain or ventriculoperitoneal shunt may be considered.[107]		
cerebral infarction	**variable**	**medium**
Vasculitis secondary to the inflammatory process in coccidioidal infection may lead to infarction. Some (but not all) experts advocate adjunctive, high-dose, short-term corticosteroid therapy.[11]		

Complications	Timeframe	Likelihood
spinal arachnoiditis	**variable**	**medium**
Spinal arachnoiditis, causing back pain, paraplegia, and urinary retention, may occur as a complication of intrathecal therapy (which should, therefore, be discontinued). It can also occur as part of the disease process in patients treated with fluconazole. Spinal arachnoiditis may rarely complicate non-HIV-associated cryptococcal meningitis.[128]		
hydrocephalus	**variable**	**medium**
Hydrocephalus, secondary to cerebrospinal fluid obstruction by the inflammatory response to infection, is the most common complication of coccidioidal meningitis and usually requires shunt placement. Hydrocephalus occasionally complicates *Histoplasma* meningitis and requires neurosurgical referral for consideration of ventricular shunt placement.[27] Ideally, patients should receive 2 weeks of amphotericin-B treatment, to reduce the likelihood of colonisation of the new shunt. Patients with shunts should be monitored closely for relapse. In cases of relapse, shunt removal and replacement should be considered.		

Prognosis

Cryptococcal meningitis

The most important markers of poor prognosis in HIV-associated cryptococcal meningitis are altered mental status at presentation and high organism load, as determined by quantitative cerebrospinal fluid (CSF) culture or CSF antigen titre.[91] Low CSF white cell count and raised CSF opening pressure are also associated with a poor outcome. Mortality in non-HIV-associated cryptococcal meningitis is associated with chronic renal failure, liver failure, or haematological malignancy, as well as absence of headache and altered mental status.[60]

Mortality rates due to cryptococcal meningitis remain high; 10-week mortality in a large US study was around 10%.[58] In less selected series, mortality has been higher, up to 26%. Reported 10-week mortality in studies from Africa and Asia has been 20% to 40% where amphotericin-B therapy has been available.[91] [121] [122] Cryptococcal meningitis continues to be one of the leading causes of death in HIV-infected patients, notably in Thailand, Uganda, Malawi, and South Africa, with an estimated mortality risk of 17% at 2 weeks and 34% at 10 weeks.[19]

Chronic neuropsychiatric sequelae are common after cryptococcal meningitis and are associated with altered brain imaging parameters.[123]

Histoplasmal meningitis

Approximately 20% of patients fail initial therapy, and as many as 40% may relapse.[27]

Coccidioidal meningitis

Despite advances in antifungal therapy, the morbidity and mortality associated with coccidioidal meningitis remains high, with mortality around 30%.[11] Because there is a high risk of relapse if therapy is stopped, treatment should be lifelong.[124]

FOLLOW UP

Candidal meningitis

Prognosis of candidal meningitis depends on the risk group, and mortality rates may vary from around 10% in neurosurgical patients to around 30% in HIV-infected patients.[42] [67] Premature infants with candidal meningitis have a high rate of mortality and neurodevelopmental disabilities compared with matched controls: 60% versus 28%.[125]

Aspergillus meningitis

The diagnosis of *Aspergillus* meningitis is difficult, with an overall case fatality rate of nearly 70%; the prospect of a specific diagnosis in life is higher in immunocompetent patients.[53]

Diagnostic guidelines

International

Global guidelines for the diagnosis and management of mucormycosis (https://www.ecmm.info/guidelines/mucormycoses-2019)

Published by: European Confederation of Medical Mycology; Mycoses Study Group Education and Research Consortium **Last published:** 2019

Global guideline for the diagnosis and management of the endemic mycoses (https://www.ecmm.info/guidelines/endemic-mycoses)

Published by: European Confederation of Medical Mycology; Mycoses Study Group Education and Research Consortium **Last published:** 2021

Guidelines for diagnosing, preventing, and managing cryptococcal disease among adults, adolescents and children living with HIV (https://www.who.int/publications/i/item/9789240052178)

Published by: World Health Organization **Last published:** 2022

North America

2016 Infectious Diseases Society of America (IDSA) clinical practice guideline for the treatment of coccidioidomycosis (https://www.idsociety.org/practice-guideline/practice-guidelines/#/date_na_dt/DESC/0/+)

Published by: Infectious Diseases Society of America **Last published:** 2016

Practice guidelines for the diagnosis and management of aspergillosis: 2016 update by the Infectious Diseases Society of America (https://www.idsociety.org/practice-guideline/practice-guidelines/#/date_na_dt/DESC/0/+)

Published by: Infectious Diseases Society of America **Last published:** 2016

Treatment guidelines

International

Global guidelines for the diagnosis and management of mucormycosis (https://www.ecmm.info/guidelines/mucormycoses-2019)

Published by: European Confederation of Medical Mycology; Mycoses Study Group Education and Research Consortium **Last published:** 2019

Global guideline for the diagnosis and management of the endemic mycoses (https://www.ecmm.info/guidelines/endemic-mycoses)

Published by: European Confederation of Medical Mycology; Mycoses Study Group Education and Research Consortium **Last published:** 2021

Guidelines for diagnosing, preventing, and managing cryptococcal disease among adults, adolescents and children living with HIV (https://www.who.int/publications/i/item/9789240052178)

Published by: World Health Organization **Last published:** 2022

North America

Guidelines for the prevention and treatment of opportunistic infections in adults and adolescents with HIV (https://clinicalinfo.hiv.gov/en/guidelines)

Published by: Centers for Disease Control and Prevention; National Institutes for Health; HIV Medicine Association of the Infectious Diseases Society of America **Last published:** 2022

2016 Infectious Diseases Society of America (IDSA) clinical practice guideline for the treatment of coccidioidomycosis (https://www.idsociety.org/practice-guideline/practice-guidelines/#/date_na_dt/DESC/0/+)

Published by: Infectious Diseases Society of America **Last published:** 2016

Practice guidelines for the diagnosis and management of aspergillosis: 2016 update by the Infectious Diseases Society of America (https://www.idsociety.org/practice-guideline/practice-guidelines/#/date_na_dt/DESC/0/+)

Published by: Infectious Diseases Society of America **Last published:** 2016

Clinical practice guideline for the management of candidiasis: 2016 update by the Infectious Diseases Society of America (https://www.idsociety.org/practice-guideline/practice-guidelines/#/date_na_dt/DESC/0/+)

Published by: Infectious Diseases Society of America **Last published:** 2016

Key articles

- Johnson RH, Einstein HE. Coccidioidal meningitis. Clin Infect Dis. 2006 Jan 1;42(1):103-7. Full text (https://academic.oup.com/cid/article/42/1/103/392976) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/16323099?tool=bestpractice.bmj.com)
- World Health Organization. Guidelines for diagnosing, preventing and managing cryptococcal disease among adults, adolescents and children living with HIV. June 2022 [internet publication]. Full text (https://www.who.int/publications/i/item/9789240052178) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/35797432?tool=bestpractice.bmj.com)
- National Institutes of Health, Centers for Disease Control and Prevention, HIV Medicine Association of the Infectious Disease Society of America. Guidelines for the prevention and treatment of opportunistic infections in adults and adolescents with HIV. September 2022 [internet publication]. Full text (https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-opportunistic-infections)
- Galgiani JN, Ampel NM, Blair JE, et al. 2016 Infectious Diseases Society of America (IDSA) clinical practice guideline for the treatment of coccidioidomycosis. Clin Infect Dis. 2016 Sep 15;63(6):e112-46. Full text (https://academic.oup.com/cid/article/63/6/e112/2389093) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/27470238?tool=bestpractice.bmj.com)
- Pappas PG, Kauffman CA, Andes DR, et al. Clinical practice guideline for the management of candidiasis: 2016 update by the Infectious Diseases Society of America. Clin Infect Dis. 2016 Feb 15;62(4):e1-50. Full text (https://academic.oup.com/cid/article/62/4/e1/2462830) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/26679628?tool=bestpractice.bmj.com)
- Johnson RH, Einstein HE. Coccidioidal meningitis. Clin Infect Dis. 2006 Jan 1;42(1):103-7. Full text (https://academic.oup.com/cid/article/42/1/103/392976) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/16323099?tool=bestpractice.bmj.com)
- Patterson TF, Thompson GR 3rd, Denning DW, et al. Practice guidelines for the diagnosis and management of aspergillosis: 2016 update by the Infectious Diseases Society of America. Clin Infect Dis. 2016 Aug 15;63(4):e1-60. Full text (https://academic.oup.com/cid/article/63/4/e1/2595039) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/27365388?tool=bestpractice.bmj.com)

References

1. Rajasingham R, Smith RM, Park BJ, et al. Global burden of disease of HIV-associated cryptococcal meningitis: an updated analysis. Lancet Infect Dis. 2017 Aug;17(8):873-81. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/28483415?tool=bestpractice.bmj.com)
2. Kravitz GR, Davies SF, Eckman MR, et al. Chronic blastomycotic meningitis. Am J Med. 1981 Sep;71(3):501-5. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/7282737?tool=bestpractice.bmj.com)

REFERENCES

3. Harley WB, Lomis M, Haas DW. Marked polymorphonuclear pleocytosis due to blastomycotic meningitis: a case report and review. Clin Infect Dis. 1994 May;18(5):816-8. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/8075280?tool=bestpractice.bmj.com)

4. Scott EN, Kaufman L, Brown AC, et al. Serologic studies in the diagnosis and management of meningitis due to Sporothrix schenckii. N Engl J Med. 1987 Oct 8;317(15):935-40. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/3306388?tool=bestpractice.bmj.com)

5. Salaki JS, Louria DB, Chmel H. Fungal and yeast infections of the central nervous system. A clinical review. Medicine (Baltimore). 1984 Mar;63(2):108-32. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/6366452?tool=bestpractice.bmj.com)

6. Ellner JJ, Bennett JE. Chronic meningitis. Medicine (Baltimore). 1976 Sep;55(5):341-69. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/957996?tool=bestpractice.bmj.com)

7. Gottfredsson M, Perfect JR. Fungal meningitis. Semin Neurol. 2000;20(3):307-22. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/11051295?tool=bestpractice.bmj.com)

8. Kauffman CA. Histoplasmosis: a clinical and laboratory update. Clin Microbiol Rev. 2007 Jan;20(1):115-32. Full text (http://cmr.asm.org/content/20/1/115.full) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/17223625?tool=bestpractice.bmj.com)

9. Wheat LJ. Histoplasmosis: a review for clinicians from non-endemic areas. Mycoses. 2006 Jul;49(4):274-82. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/16784440?tool=bestpractice.bmj.com)

10. Saubolle MA, McKellar PP, Sussland D. Epidemiologic, clinical and diagnostic aspects of coccidioidomycosis. J Clin Microbiol. 2007 Jan;45(1):26-30. Full text (http://jcm.asm.org/content/45/1/26.full) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/17108067?tool=bestpractice.bmj.com)

11. Johnson RH, Einstein HE. Coccidioidal meningitis. Clin Infect Dis. 2006 Jan 1;42(1):103-7. Full text (https://academic.oup.com/cid/article/42/1/103/392976) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/16323099?tool=bestpractice.bmj.com)

12. Jenney A, Pandithage K, Fisher DA, et al. Cryptococcus infection in tropical Australia. J Clin Microbiol. 2004 Aug;42(8):3865-8. Full text (http://jcm.asm.org/content/42/8/3865.full) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/15297551?tool=bestpractice.bmj.com)

13. MacDougall L, Kidd SE, Galanis E, et al. Spread of Cryptococcus gattii in British Columbia, Canada, and detection in the Pacific Northwest, USA. Emerg Infect Dis. 2007 Jan;13(1):42-50. Full text (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2725832) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/17370514?tool=bestpractice.bmj.com)

14. Beale MA, Sabiiti W, Robertson EJ, et al. Genotypic diversity is associated with clinical outcome and phenotype in cryptococcal meningitis across Southern Africa. PLoS Negl Trop Dis. 2015 Jun 25;9(6):e0003847. Full text (http://journals.plos.org/plosntds/article?id=10.1371/journal.pntd.0003847) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/26110902?tool=bestpractice.bmj.com)

15. Bicanic T, Harrison TS. Cryptococcal meningitis. Br Med Bull. 2004;72:99-118. Full text (https://www.doi.org/10.1093/bmb/ldh043) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/15838017?tool=bestpractice.bmj.com)

16. Mirza SA, Phelan M, Rimland D, et al. The changing epidemiology of cryptococcosis: an update from population-based active surveillance in 2 large metropolitan areas, 1992-2000. Clin Infect Dis. 2003 Mar 15;36(6):789-94. Full text (https://academic.oup.com/cid/article/36/6/789/319616) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/12627365?tool=bestpractice.bmj.com)

17. Holmes CB, Losina E, Walensky RP, et al. Review of human immunodeficiency virus type 1-related opportunistic infections in sub-Saharan Africa. Clin Infect Dis. 2003 Mar 1;36(5):652-62. Full text (https://academic.oup.com/cid/article/36/5/652/455509) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/12594648?tool=bestpractice.bmj.com)

18. Chariyalertsak S, Sirisanthana T, Saengwonloey O, et al. Clinical presentation and risk behaviours of patients with acquired immunodeficiency syndrome in Thailand, 1994-1998: regional variation and temporal trends. Clin Infect Dis. 2001 Mar 15;32(6):955-62. Full text (https://academic.oup.com/cid/article/32/6/955/307980) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/11247718?tool=bestpractice.bmj.com)

19. Jarvis JN, Bicanic T, Loyse A, et al. Determinants of mortality in a combined cohort of 501 patients with HIV-associated cryptococcal meningitis: implications for improving outcomes. Clin Infect Dis. 2014 Mar;58(5):736-45. Full text (https://academic.oup.com/cid/article/58/5/736/365633) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/24319084?tool=bestpractice.bmj.com)

20. Fang W, Zhang L, Liu J, et al. Tuberculosis/cryptococcosis co-infection in China between 1965 and 2016. Emerg Microbes Infect. 2017 Aug 23;6(8):e73. Full text (https://www.tandfonline.com/doi/full/10.1038/emi.2017.61) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/28831193?tool=bestpractice.bmj.com)

21. Pappas PG, Alexander BD, Andes DR, et al. Invasive fungal infections among organ transplant recipients: results of the Transplant-Associated Infection Surveillance Network (TRANSNET). Clin Infect Dis. 2010 Apr 15;50(8):1101-11. Full text (https://www.doi.org/10.1086/651262) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/20218876?tool=bestpractice.bmj.com)

22. Safdieh JE, Mead PA, Sepkowitz KA, et al. Bacterial and fungal meningitis in patients with cancer. Neurology. 2008 Mar 18;70(12):943-7. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/18347316?tool=bestpractice.bmj.com)

23. Schmalzle SA, Buchwald UK, Gilliam BL, et al. Cryptococcus neoformans infection in malignancy. Mycoses. 2016 Sep;59(9):542-52. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/26932366?tool=bestpractice.bmj.com)

24. MacDougall L, Fyfe M. Emergence of Cryptococcus gattii in a novel environment provides clues to its incubation period. J Clin Microbiol. 2006 May;44(5):1851-2. Full text (http://jcm.asm.org/content/44/5/1851.full) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/16672420?tool=bestpractice.bmj.com)

25. Hoang LM, Maguire JA, Doyle P, et al. Cryptococcus neoformans infections at Vancouver Hospital and Health Sciences Centre (1997-2002): epidemiology, microbiology and histopathology. J Med Microbiol. 2004 Sep;53(Pt 9):935-40. Full text (https://www.microbiologyresearch.org/content/journal/jmm/10.1099/jmm.0.05427-0#tab2) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/15314203?tool=bestpractice.bmj.com)

26. Edwards LB, Acquaviva FA, Livesay VT, et al. An atlas of sensitivity to tuberculin, PPD-B, and histoplasmin in the United States. Annu Rev Respir Dis. 1969 Apr;99(4):Suppl:1-132. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/5767603?tool=bestpractice.bmj.com)

27. Wheat LJ, Musial CE, Jenny-Avital E. Diagnosis and management of central nervous system histoplasmosis. Clin Infect Dis. 2005 Mar 15;40(6):844-52. Full text (https://academic.oup.com/cid/article/40/6/844/347054) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/15736018?tool=bestpractice.bmj.com)

28. Chiller TM, Galgani JN, Stevens DA. Coccidioidomycosis. Infect Dis Clin North Am. 2003 Mar;17(1):41-57. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/12751260?tool=bestpractice.bmj.com)

29. DiCaudo DJ. Coccidioidomycosis: a review and update. J Am Acad Dermatol. 2006 Dec;55(6):929-42. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/17110216?tool=bestpractice.bmj.com)

30. Centers for Disease Control and Prevention. Coccidioidomycosis - Arizona, 1990-1995. MMWR Morb Mortal Wkly Rep. 1996 Dec 13;45(49):1069-73. Full text (https://www.cdc.gov/mmwr/preview/mmwrhtml/00044697.htm) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/8975119?tool=bestpractice.bmj.com)

31. Ampel NM, Mosley DG, England B, et al. Coccidioidomycosis in Arizona: increase in incidence from 1990 to 1995. Clin Infect Dis. 1998 Dec;27(6):1528-30. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/9868673?tool=bestpractice.bmj.com)

32. Centers for Disease Control and Prevention. Increase in coccidioidomycosis - Arizona, 1998-2001. MMWR Morb Mortal Wkly Rep. 2003 Feb 14;52(6):109-12. Full text (https://www.cdc.gov/mmwr/preview/mmwrhtml/mm5206a4.htm) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/12645841?tool=bestpractice.bmj.com)

33. Ampel MA. Coccidiodomycosis in persons infected with HIV type 1. Clin Infect Dis. 2005 Oct 15;41(8):1174-8. Full text (https://academic.oup.com/cid/article/41/8/1174/379819) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/16163637?tool=bestpractice.bmj.com)

34. Ampel NM, Dols CL, Galgiani JN. Coccidioidomycosis during human immunodeficiency virus infection: results of a prospective study in a coccidioidal endemic area. Am J Med. 1993 Mar;94(3):235-40. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/8095771?tool=bestpractice.bmj.com)

35. Olmedo Diaz I, Pallas Alonso CR, Miralles Molina M, et al. Neonatal meningitis: study of 56 cases [in Spanish]. An Esp Pediatr. 1997 Feb;46(2):189-94. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/9157811?tool=bestpractice.bmj.com)

36. Buchs S. Candida meningitis: a growing threat to premature and fullterm infants. Pediatr Infect Dis. 1985 Mar-Apr;4(2):122-3. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/3982976?tool=bestpractice.bmj.com)

37. Fernandez M, Moylett EH, Noyola DE, et al. Candidal meningitis in neonates: a 10-year review. Clin Infect Dis. 2000 Aug;31(2):458-63. Full text (https://academic.oup.com/cid/article/31/2/458/296160) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/10987705?tool=bestpractice.bmj.com)

38. Lipton SA, Hickey WF, Morris JH, et al. Candidal infection in the central nervous system. Am J Med. 1984 Jan;76(1):101-8. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/6691350?tool=bestpractice.bmj.com)

39. Voice RA, Bradley SF, Sangeorzan JA, et al. Chronic candidal meningitis: an uncommon manifestation of candidiasis. Clin Infect Dis. 1994 Jul;19(1):60-6. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/7948559?tool=bestpractice.bmj.com)

40. Chiou CC, Wong TT, Lin HH, et al. Fungal infection of ventriculoperitoneal shunts in children. Clin Infect Dis. 1994 Dec;19(6):1049-53. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/7888533?tool=bestpractice.bmj.com)

41. Sánchez-Portocarrero J, Martin-Rabadán P, Saldaña CJ, et al. Candida cerebrospinal fluid shunt infection. Report of two new cases and review of the literature. Diagn Microbiol Infect Dis. 1994 Sep;20(1):33-40. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/7867296?tool=bestpractice.bmj.com)

42. Nguyen MH, Yu VL. Meningitis caused by Candida species: an emerging problem in neurosurgical patients. Clin Infect Dis. 1995 Aug;21(2):323-7. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/8562739?tool=bestpractice.bmj.com)

43. Kainer MA, Reagan DR, Nguyen DB, et al; Tennessee Fungal Meningitis Investigation Team. Fungal infections associated with contaminated methylprednisolone in Tennessee. N Engl J Med. 2012 Dec 6;367(23):2194-2203. Full text (http://www.nejm.org/doi/full/10.1056/NEJMoa1212972#t=article) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/23131029?tool=bestpractice.bmj.com)

44. Centers for Disease Control and Prevention (CDC). Multistate outbreak of fungal meningitis and other infections – case count. Oct 2015 [internet publication]. Full text (https://www.cdc.gov/hai/outbreaks/meningitis-map-large.html#casecount_table)

45. Antinori S, Corbellino M, Meroni L, et al. Aspergillus meningitis: a rare clinical manifestation of central nervous system aspergillosis - case report and review of 92 cases. J Infect. 2013 Mar;66(3):218-38. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/23178421?tool=bestpractice.bmj.com)

46. Cornely OA, Alastruey-Izquierdo A, Arenz D, et al. Global guideline for the diagnosis and management of mucormycosis: an initiative of the European Confederation of Medical Mycology in cooperation with the Mycoses Study Group Education and Research Consortium. Lancet Infect Dis. 2019 Dec;19(12):e405-e421. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/31699664?tool=bestpractice.bmj.com)

47. Chayakulkeeree M, Perfect JR. Cryptococcosis. Infect Dis Clin North Am. 2006 Sep;20(3):507-44. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/16984867?tool=bestpractice.bmj.com)

48. Sánchez-Portocarrero J, Pérez-Cecilia E, Corral O, et al. The central nervous system and infection by Candida species. Diagn Microbiol Infect Dis. 2000 Jul;37(3):169-79. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/10904190?tool=bestpractice.bmj.com)

49. Eyre DW, Sheppard AE, Madder H, et al. A Candida auris outbreak and its control in an intensive care setting. N Engl J Med. 2018 Oct 4;379(14):1322-31. Full text (https://www.doi.org/10.1056/NEJMoa1714373) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/30281988?tool=bestpractice.bmj.com)

50. Taei M, Chadeganipour M, Mohammadi R. An alarming rise of non-albicans Candida species and uncommon yeasts in the clinical samples; a combination of various molecular techniques for identification of etiologic agents. BMC Res Notes. 2019 Nov 29;12(1):779. Full text (https://www.doi.org/10.1186/s13104-019-4811-1) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/31783903?tool=bestpractice.bmj.com)

51. Centers for Disease Control and Prevention (CDC). Multistate outbreak of fungal infection associated with injection of methylprednisolone acetate solution from a single compounding pharmacy - United States, 2012. MMWR Morb Mortal Wkly Rep. 2012 Oct 19;61(41):839-42. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/23076093?tool=bestpractice.bmj.com)

52. Kolbe AB, McKinney AM, Kendi AT, et al. Aspergillus meningitis and discitis from low-back procedures in an immunocompetent patient. Acta Radiol. 2007 Jul;48(6):687-9. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/17611879?tool=bestpractice.bmj.com)

53. Antinori S, Corbellino M, Meroni L, et al. Aspergillus meningitis: a rare clinical manifestation of central nervous system aspergillosis - case report and review of 92 cases. J Infect. 2013 Mar;66(3):218-38. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/23178421?tool=bestpractice.bmj.com)

54. Harrison TS, Levitz SM. Immunology. In: Anaissie EJ, McGinnis MR, Pfaller MA, eds. Clinical mycology. New York, NY: Churchill Livingstone; 2003.

55. Garcia-Hermoso D, Janbon G, Dromer F. Epidemiological evidence for dormant Cryptococcus neoformans infection. J Clin Microbiol. 1999 Oct;37(10):3204-9. Full text (http://jcm.asm.org/cgi/content/full/37/10/3204) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/10488178?tool=bestpractice.bmj.com)

56. Casadevall A, Steenbergen JN, Nosanchuk JD. 'Ready made' virulence and 'dual use' virulence factors in pathogenic environmental fungi - the Cryptococcus neoformans paradigm. Curr Opin Microbiol. 2003 Aug;6(4):332-7. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/12941400?tool=bestpractice.bmj.com)

57. McKinsey DS, Spiegel RA, Hutwagner L, et al. Prospective study of histoplasmosis in patients infected with human immunodeficiency virus: incidence, risk factors, and pathophysiology. Clin Infect Dis. 1997 Jun;24(6):1195-1203. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/9195082?tool=bestpractice.bmj.com)

58. van der Horst C, Saag MS, Cloud GA, et al. Treatment of cryptococcal meningitis associated with the acquired immunodeficiency syndrome. N Engl J Med. 1997 Jul 3;337(1):15-21. Full text (http://www.nejm.org/doi/full/10.1056/NEJM199707033370103#t=article) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/9203426?tool=bestpractice.bmj.com)

59. Ghanem H, Sivasubramanian G. Cryptococcus neoformans meningoencephalitis in an immunocompetent patient after COVID-19 infection. Case Rep Infect Dis. 2021 Jun 4;2021:5597473. Full text (https://www.doi.org/10.1155/2021/5597473) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/34188965?tool=bestpractice.bmj.com)

60. Pappas PG, Perfect JR, Cloud GA, et al. Cryptococcosis in human immunodeficiency virus-negative patients in the era of effective azole therapy. Clin Infect Dis. 2001 Sep 1;33(5):690-9. Full text (https://academic.oup.com/cid/article/33/5/690/468392) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/11477526?tool=bestpractice.bmj.com)

61. Pappas PG, Alexander BD, Andes DR, et al. Invasive fungal infections among organ transplant recipients: results of the Transplant-Associated Infection Surveillance Network (TRANSNET). Clin Infect Dis. 2010 Apr 15;50(8):1101-11. Full text (https://www.doi.org/10.1086/651262) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/20218876?tool=bestpractice.bmj.com)

62. MacDougall L, Fyfe M. Emergence of Cryptococcus gattii in a novel environment provides clues to its incubation period. J Clin Microbiol. 2006 May;44(5):1851-2. Full text (http://jcm.asm.org/content/44/5/1851.full) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/16672420?tool=bestpractice.bmj.com)

63. Hoang LM, Maguire JA, Doyle P, et al. Cryptococcus neoformans infections at Vancouver Hospital and Health Sciences Centre (1997-2002): epidemiology, microbiology and histopathology. J Med Microbiol. 2004 Sep;53(Pt 9):935-40. Full text (http://jmm.sgmjournals.org/content/53/9/935.full) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/15314203?tool=bestpractice.bmj.com)

64. Einstein HE, Johnson RH. Coccidioidomycosis: new aspects of epidemiology and therapy. Clin Infect Dis. 1993 Mar;16(3):349-54. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/8452945?tool=bestpractice.bmj.com)

65. Crum NF, Lederman ER, Stafford CM, et al. Coccidioidomycosis: a descriptive survey of a reemerging disease. Clinical characteristics and current controversies. Medicine (Baltimore). 2004 May;83(3):149-75. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/15118543?tool=bestpractice.bmj.com)

66. Batac MCR, Denning D. Serious fungal infections in the Philippines. Eur J Clin Microbiol Infect Dis. 2017 Jun;36(6):937-41. Full text (https://www.doi.org/10.1007/s10096-017-2918-7) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/28220322?tool=bestpractice.bmj.com)

67. Casado JL, Quereda C, Oliva J, et al. Candidal meningitis in HIV-infected patients: analysis of 14 cases. Clin Infect Dis. 1997 Sep;25(3):673-6. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/9314460?tool=bestpractice.bmj.com)

68. Kim JJ, Li C, Ammanuel SG, et al. Candida shunt infection causing arachnoiditis and hydrocephalus: a case report. Cureus. 2022 Mar;14(3):e23675. Full text (https://www.doi.org/10.7759/cureus.23675) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/35510023?tool=bestpractice.bmj.com)

69. del Pozo MM, Bermejo F, Molina JA, et al. Chronic neutrophilic meningitis caused by Candida albicans. Neurologia. 1998 Aug-Sep;13(7):362-6. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/9810800?tool=bestpractice.bmj.com)

70. World Health Organization. Guidelines for diagnosing, preventing and managing cryptococcal disease among adults, adolescents and children living with HIV. June 2022 [internet publication]. Full text (https://www.who.int/publications/i/item/9789240052178) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/35797432?tool=bestpractice.bmj.com)

71. National Institutes of Health, Centers for Disease Control and Prevention, HIV Medicine Association of the Infectious Disease Society of America. Guidelines for the prevention and treatment of opportunistic infections in adults and adolescents with HIV. September 2022 [internet publication]. Full text (https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-opportunistic-infections)

72. Awotiwon AA, Johnson S, Rutherford GW, et al. Primary antifungal prophylaxis for cryptococcal disease in HIV-positive people. Cochrane Database Syst Rev. 2018 Aug 29;(8):CD004773. Full text (https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD004773.pub3/full) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/30156270?tool=bestpractice.bmj.com)

73. Galgiani JN, Ampel NM, Blair JE, et al. 2016 Infectious Diseases Society of America (IDSA) clinical practice guideline for the treatment of coccidioidomycosis. Clin Infect Dis. 2016 Sep 15;63(6):e112-46. Full text (https://academic.oup.com/cid/article/63/6/e112/2389093) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/27470238?tool=bestpractice.bmj.com)

74. Pappas PG, Kauffman CA, Andes DR, et al. Clinical practice guideline for the management of candidiasis: 2016 update by the Infectious Diseases Society of America. Clin Infect Dis. 2016 Feb 15;62(4):e1-50. Full text (https://academic.oup.com/cid/article/62/4/e1/2462830) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/26679628?tool=bestpractice.bmj.com)

75. Blyth CC, Barzi F, Hale K, Isaacs D. Chemoprophylaxis of neonatal fungal infections in very low birthweight infants: efficacy and safety of fluconazole and nystatin. J Paediatr Child Health. 2012 Sep;48(9):846-51. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/22970680?tool=bestpractice.bmj.com)

76. Müller M, Wandel S, Colebunders R, et al. Immune reconstitution inflammatory syndrome in patients starting antiretroviral therapy for HIV infection: a systematic review and meta-analysis. Lancet Infect Dis. 2010 Apr;10(4):251-61. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/20334848?tool=bestpractice.bmj.com)

77. Thompson GR 3rd, Le T, Chindamporn A, et al. Global guideline for the diagnosis and management of the endemic mycoses: an initiative of the European Confederation of Medical Mycology in cooperation with the International Society for Human and Animal Mycology. Lancet Infect Dis. 2021 Dec;21(12):e364-e374. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/34364529?tool=bestpractice.bmj.com)

78. Bayer AS, Edwards JE, Seidel JS, et al. Candida meningitis. Report of seven cases and review of the English literature. Medicine (Baltimore). 1976 Nov;55(6):477-86. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/792628?tool=bestpractice.bmj.com)

79. Yuanije Z, Jianghan C, Nan X, et al. Cryptococcal meningitis in immunocompetent children. Mycoses. 2012 Mar;55(2):168-71. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/21762212?tool=bestpractice.bmj.com)

80. Ashbee HR, Evans EG, Viviani MA, et al. Histoplasmosis in Europe: report on an epidemiological survey from the European Confederation of Medical Mycology Working Group. Med Mycol. 2008 Feb;46(1):57-65. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/17885939?tool=bestpractice.bmj.com)

81. Johnson RH, Einstein HE. Coccidioidal meningitis. Clin Infect Dis. 2006 Jan 1;42(1):103-7. Full text (https://academic.oup.com/cid/article/42/1/103/392976) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/16323099?tool=bestpractice.bmj.com)

82. Perfect JR, Dismukes WE, Dromer F, et al. Clinical practice guidelines for the management of cryptococcal disease: 2010 update by the Infectious Diseases Society of America. Clin Infect Dis. 2010 Feb 1;50(3):291-322. Full text (https://www.doi.org/10.1086/649858) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/20047480?tool=bestpractice.bmj.com)

83. Sharma P, Mukherjee A, Karunanithi S, et al. Potential role of 18F-FDG PET/CT in patients with fungal infections. AJR Am J Roentgenol. 2014 Jul;203(1):180-9. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/24951213?tool=bestpractice.bmj.com)

84. Longhitano A, Alipour R, Khot A, et al. The role of 18F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT) in assessment of complex invasive fungal disease and opportunistic co-infections in patients with acute leukemia prior to allogeneic hematopoietic cell transplant. Transpl Infect Dis. 2021 Jun;23(3):e13547. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/33338319?tool=bestpractice.bmj.com)

85. Chong GM, Maertens JA, Lagrou K, et al. Diagnostic performance of galactomannan antigen testing in cerebrospinal fluid. J Clin Microbiol. 2016 Feb;54(2):428-31. Full text (http://jcm.asm.org/content/54/2/428.long) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/26659218?tool=bestpractice.bmj.com)

86. Garber S, Penar P. Treatment of indolent, nonencapsulated cryptococcal meningitis associated with hydrocephalus. Clin Pract. 2012 Jan 27;2(1):e22. Full text (http://www.clinicsandpractice.org/index.php/cp/article/view/cp.2012.e22/553) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/24765421?tool=bestpractice.bmj.com)

87. Gade L, Scheel CM, Pham CD, et al. Detection of fungal DNA in human body fluids and tissues during a multistate outbreak of fungal meningitis and other infections. Eukaryot Cell. 2013 May;12(5):677-83. Full text (https://www.doi.org/10.1128/EC.00046-13) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/23457192?tool=bestpractice.bmj.com)

88. Tay E, Chen SC, Green W, et al. Development of a real-time PCR assay to identify and distinguish between Cryptococcus neoformans and Cryptococcus gattii species complexes. J Fungi (Basel).

2022 Apr 29;8(5):462. Full text (https://www.doi.org/10.3390/jof8050462) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/35628719?tool=bestpractice.bmj.com)

89. Davis C, Wheat LJ, Myint T, et al. Efficacy of cerebrospinal fluid beta-d-glucan diagnostic testing for fungal meningitis: a systematic review. J Clin Microbiol. 2020 Mar 25;58(4):e02094-19. Full text (https://www.doi.org/10.1128/JCM.02094-19) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/31996446?tool=bestpractice.bmj.com)

90. Litvintseva AP, Lindsley MD, Gade L, et al. Utility of (1-3)-beta-D-glucan testing for diagnostics and monitoring response to treatment during the multistate outbreak of fungal meningitis and other infections. Clin Infect Dis. 2014 Mar;58(5):622-30. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/24336827?tool=bestpractice.bmj.com)

91. Brouwer AE, Rajanuwong A, Chierakul W, et al. Combination antifungal therapies for HIV-associated cryptococcal meningitis: a randomised trial. Lancet. 2004 May 29;363(9423):1764-7. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/15172774?tool=bestpractice.bmj.com)

92. Centers for Disease Control and Prevention. Multistate outbreak of fungal meningitis and other infections: resources for laboratories. Oct 2015 [internet publication]. Full text (https://www.cdc.gov/hai/outbreaks/laboratory/index.html#lab)

93. Steiner I, Schmutzhard E, Sellner J, et al; European Federation of Neurological Sciences; European Neurologic Society. EFNS-ENS guidelines for the use of PCR technology for the diagnosis of infections of the nervous system. Eur J Neurol. 2012 Oct;19(10):1278-91. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/22882231?tool=bestpractice.bmj.com)

94. Litvintseva AP, Lindsley MD, Gade L, et al. Utility of (1-3)-beta-D-glucan testing for diagnostics and monitoring response to treatment during the multistate outbreak of fungal meningitis and other infections. Clin Infect Dis. 2014 Mar;58(5):622-30. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/24336827?tool=bestpractice.bmj.com)

95. World Health Organization. WHO consolidated guidelines on tuberculosis module 3: diagnosis - rapid diagnostics for tuberculosis detection. July 2021 [internet publication]. Full text (https://www.who.int/publications/i/item/who-consolidated-guidelines-on-tuberculosis-module-3-diagnosis---rapid-diagnostics-for-tuberculosis-detection)

96. Kohli M, Schiller I, Dendukuri N, et al. Xpert MTB/RIF Ultra and Xpert MTB/RIF assays for extrapulmonary tuberculosis and rifampicin resistance in adults. Cochrane Database Syst Rev. 2021 Jan 15;1:CD012768. Full text (https://www.doi.org/10.1002/14651858.CD012768.pub3) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/33448348?tool=bestpractice.bmj.com)

97. Stadelman AM, Ssebambulidde K, Buller A, et al. Cerebrospinal fluid AFB smear in adults with tuberculous meningitis: a systematic review and diagnostic test accuracy meta-analysis. Tuberculosis (Edinb). 2022 Jul;135:102230. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/35779498?tool=bestpractice.bmj.com)

98. Botero Aguirre JP, Restrepo Hamid AM. Amphotericin B deoxycholate versus liposomal amphotericin B: effects on kidney function. Cochrane Database Syst Rev. 2015 Nov 23;(11):CD010481. Full text

(https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD010481.pub2/full) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/26595825?tool=bestpractice.bmj.com)

99. Day JN, Chau TT, Wolbers M, et al. Combination antifungal therapy for cryptococcal meningitis. N Engl J Med. 2013 Apr 4;368(14):1291-1302. Full text (http://www.nejm.org/doi/full/10.1056/NEJMoa1110404#t=article) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/23550668?tool=bestpractice.bmj.com)

100. Saag MS, Cloud GA, Graybill JR, et al. A comparison of itraconazole versus fluconazole as maintenance therapy for AIDS-associated cryptococcal meningitis. Clin Infect Dis. 1999 Feb;28(2):291-6. Full text (https://academic.oup.com/cid/article/28/2/291/410543) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/10064246?tool=bestpractice.bmj.com)

101. Powderly WG, Saag MS, Cloud GA, et al. A controlled trial of fluconazole or amphotericin B to prevent relapse of cryptococcal meningitis in patients with the acquired immunodeficiency syndrome. N Engl J Med. 1992 Mar 19;326(12):793-8. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/1538722?tool=bestpractice.bmj.com)

102. Mdodo R, Moser SA, Jaoko W, et al. Antifungal susceptibilities of Cryptococcus neoformans cerebrospinal fluid isolates from AIDS patients in Kenya. Mycoses. 2011 Sep;54(5):e438-42. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/21535451?tool=bestpractice.bmj.com)

103. Bongomin F, Oladele RO, Gago S, et al. A systematic review of fluconazole resistance in clinical isolates of Cryptococcus species. Mycoses. 2018 May;61(5):290-97. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/29377368?tool=bestpractice.bmj.com)

104. Boulware DR, Meya DB, Muzoora C, et al; COAT Trial Team. Timing of antiretroviral therapy after diagnosis of cryptococcal meningitis. N Engl J Med. 2014 Jun 26;370(26):2487-98. Full text (http://www.nejm.org/doi/full/10.1056/NEJMoa1312884#t=article) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/24963568?tool=bestpractice.bmj.com)

105. Eshun-Wilson I, Okwen MP, Richardson M, et al. Early versus delayed antiretroviral treatment in HIV-positive people with cryptococcal meningitis. Cochrane Database Syst Rev. 2018 Jul 24;(7):CD009012. Full text (https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD009012.pub3/full) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/30039850?tool=bestpractice.bmj.com)

106. Graybill JR, Sobel J, Saag M, et al. Diagnosis and management of increased intracranial pressure in patients with AIDS and cryptococcal meningitis. Clin Infect Dis. 2000 Jan;30(1):47-54. Full text (https://academic.oup.com/cid/article/30/1/47/323550) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/10619732?tool=bestpractice.bmj.com)

107. Macsween KF, Bicanic T, Brouwer AE, et al. Lumbar drainage for control of cerebrospinal fluid pressure in cryptococcal meningitis: case report and review. J Infect. 2005 Nov;51(4):e221-4. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/16291274?tool=bestpractice.bmj.com)

108. Johnson PC, Wheat LJ, Cloud GA, et al; National Institute of Allergy and Infectious Diseases Mycoses Study Group. Safety and efficacy of liposomal amphotericin B compared with conventional amphotericin B for induction therapy of histoplasmosis in patients with AIDS. Ann Intern Med.

2002 Jul 16;137(2):105-9. Full text (http://annals.org/aim/fullarticle/715437/safety-efficacy-liposomal-amphotericin-b-compared-conventional-amphotericin-b-induction) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/12118965?tool=bestpractice.bmj.com)

109. Groll AH, Giri N, Petraitis V, et al. Comparative efficacy and distribution of lipid formulations of amphotericin B in experimental Candida albicans infection of the central nervous system. J Infect Dis. 2000 Jul;182(1):274-82. Full text (https://academic.oup.com/jid/article/182/1/274/881972) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/10882607?tool=bestpractice.bmj.com)

110. Galgiani JN, Catanzaro A, Cloud GA, et al. Fluconazole therapy for coccidioidal meningitis. The NIAID-Mycoses Study Group. Ann Intern Med. 1993 Jul 1;119(1):28-35. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/8498760?tool=bestpractice.bmj.com)

111. Restrepo A, Tobón A, Clark B, et al. Salvage treatment of histoplasmosis with posaconazole. J Infect. 2007 Apr;54(4):319-27. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/16824608?tool=bestpractice.bmj.com)

112. Cortez KJ, Walsh TJ, Bennett JE. Successful treatment of coccidioidal meningitis with voriconazole. Clin Infect Dis. 2003 Jun 15;36(12):1619-22. Full text (https://academic.oup.com/cid/article/36/12/1619/299153) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/12802765?tool=bestpractice.bmj.com)

113. Proia LA, Tenorio AR. Successful use of voriconazole for treatment of Coccidioides meningitis. Antimicrob Agents Chemother. 2004 Jun;48(6):2341. Full text (http://aac.asm.org/content/48/6/2341.full) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/15155250?tool=bestpractice.bmj.com)

114. Centers for Disease Control and Prevention. Multistate outbreak of fungal meningitis and other infections: resources for clinicians. Oct 2015 [internet publication]. Full text (http://www.cdc.gov/hai/outbreaks/clinicians/index.html#rationale)

115. Smith RM, Tipple M, Chaudry MN, et al. Relapse of fungal meningitis associated with contaminated methylprednisolone. N Engl J Med. 2013 Jun 27;368(26):2535-6. Full text (http://www.nejm.org/doi/full/10.1056/NEJMc1306560) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/23718153?tool=bestpractice.bmj.com)

116. Patterson TF, Thompson GR 3rd, Denning DW, et al. Practice guidelines for the diagnosis and management of aspergillosis: 2016 update by the Infectious Diseases Society of America. Clin Infect Dis. 2016 Aug 15;63(4):e1-60. Full text (https://academic.oup.com/cid/article/63/4/e1/2595039) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/27365388?tool=bestpractice.bmj.com)

117. Marty FM, Ostrosky-Zeichner L, Cornely OA, et al. Isavuconazole treatment for mucormycosis: a single-arm open-label trial and case-control analysis. Lancet Infect Dis. 2016 Jul;16(7):828-37. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/26969258?tool=bestpractice.bmj.com)

118. Vehreschild JJ, Birtel A, Vehreschild MJ, et al. Mucormycosis treated with posaconazole: review of 96 case reports. Crit Rev Microbiol. 2013 Aug;39(3):310-24. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/22917084?tool=bestpractice.bmj.com)

119. Branch RA. Prevention of amphotericin B-induced renal impairment. A review on the use of sodium supplementation. Arch Intern Med. 1988 Nov;148(11):2389-94. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/3056312?tool=bestpractice.bmj.com)

120. Bicanic T, Wood R, Meintjes G, et al. High-dose amphotericin B with flucytosine for the treatment of cryptococcal meningitis in HIV-infected patients: a randomized trial. Clin Infect Dis. 2008 Jul 1;47(1):123-30. Full text (https://academic.oup.com/cid/article/47/1/123/375282) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/18505387?tool=bestpractice.bmj.com)

121. Kambugu AD, Kamya M, Mayanja-Kizza H, et al. The high mortality of HIV associated Cryptococcal meningitis despite high dose amphotericin B therapy in Uganda. 41st Annual Meeting of The Infectious Diseases Society of America. San Diego, 2003. Abstract 629.

122. Imwidthaya P, Poungvarin N. Cryptococcosis in AIDS. Postgrad Med J. 2000 Feb;76(892):85-8. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/10644384?tool=bestpractice.bmj.com)

123. Lu CH, Chen HL, Chang WN, et al. Assessing the chronic neuropsychologic sequelae of human immunodeficiency virus-negative cryptococcal meningitis by using diffusion tensor imaging. AJNR Am J Neuroradiol. 2011 Aug;32(7):1333-9. Full text (http://www.ajnr.org/content/32/7/1333.long) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/21596808?tool=bestpractice.bmj.com)

124. Dewsnup DH, Galgiani JN, Graybill JR, et al. Is it ever safe to stop azole therapy for Coccidioides immitis meningitis? Ann Intern Med. 1996 Feb 1;124(3):305-10. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/8554225?tool=bestpractice.bmj.com)

125. Lee BE, Cheung PY, Robinson JL, et al. Comparative study of mortality and morbidity in premature infants (birth weight <1,250 g) with candidaemia or candidal meningitis. Clin Infect Dis. 1998 Sep;27(3):559-65. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/9770157?tool=bestpractice.bmj.com)

126. Buchs S, Pfister P. Candida meningitis. Course, prognosis and mortality before and after introduction of the new antimycotics. Mykosen. 1983 Feb;26(2):73-81. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/6835266?tool=bestpractice.bmj.com)

127. Porter SD, Noble MA, Rennie R. A single strain of Candida albicans associated with separate episodes of fungemia and meningitis. J Clin Microbiol. 1996 Jul;34(7):1813-4. Full text (http://jcm.asm.org/content/34/7/1813.full.pdf+html) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/8784598?tool=bestpractice.bmj.com)

128. Panackal AA, Komori M, Kosa P, et al. Spinal arachnoiditis as a complication of cryptococcal meningoencephalitis in non-HIV previously healthy adults. Clin Infect Dis. 2017 Feb 1;64(3):275-83. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/28011613?tool=bestpractice.bmj.com)

129. Berkeley JL, Nath A, Pardo CA. Fatal immune reconstitution inflammatory syndrome with human immunodeficiency virus infection and Candida meningitis: case report and review of the literature. J Neurovirol. 2008 May;14(3):267-76. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/18569461?tool=bestpractice.bmj.com)

130. Shelburne SA 3rd, Darcourt J, White AC Jr, et al. The role of immune reconstitution inflammatory syndrome in AIDS-related Cryptococcus neoformans disease in the era of highly active antiretroviral

therapy. Clin Infect Dis. 2005 Apr 1;40(7):1049-52. Full text (https://academic.oup.com/cid/article/40/7/1049/371379) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/15825000?tool=bestpractice.bmj.com)

131. Lortholary O, Sitbon K, Dromer F; French Cryptococcosis Study Group. Evidence for human immunodeficiency virus and Cryptococcus neoformans interactions in the pro-inflammatory and anti-inflammatory responses in blood during AIDS-associated cryptococcosis. Clin Microbiol Infect. 2005 Apr;11(4):296-300. Full text (http://onlinelibrary.wiley.com/doi/10.1111/j.1469-0691.2005.01074.x/full) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/15760426?tool=bestpractice.bmj.com)

132. Lawn SD, Bekker LG, Myer L, et al. Cryptococcocal immune reconstitution disease: a major cause of early mortality in a South African antiretroviral programme. AIDS. 2005 Nov 18;19(17):2050-52. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/16260920?tool=bestpractice.bmj.com)

Images

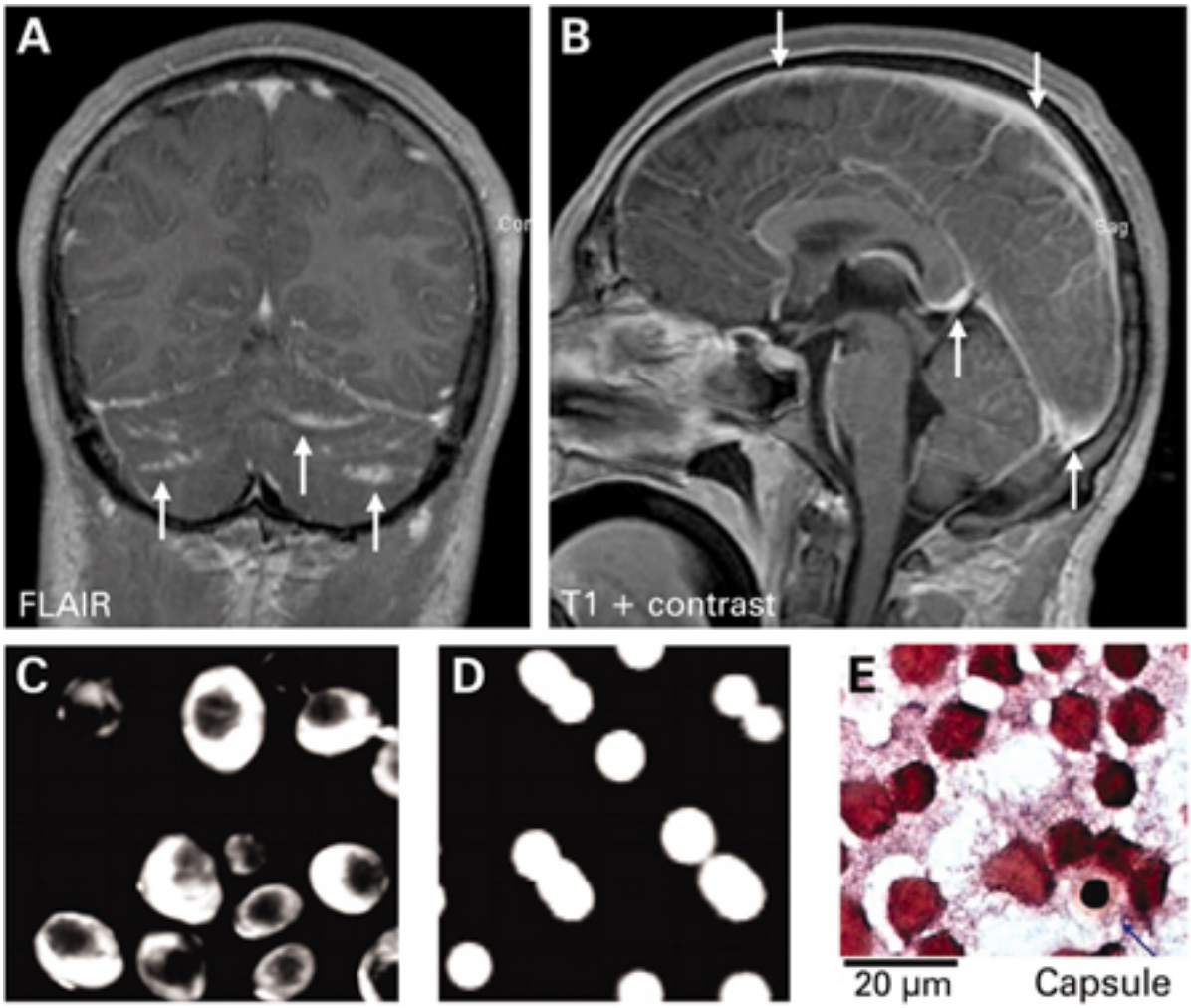


Figure 1: Cryptococcal meningoencephalitis. (A) Cranial magnetic resonance imaging (MRI) shows cerebellar hyperintensities (arrows) in FLAIR sequences (fluid-attenuated inversion recovery) and (B) meningeal contrast enhancement (arrows) in T1 weighted MRI. (C) Indian ink stain, (D) fungal culture, and (E) Gram stain of cerebrospinal fluid were positive

Braun J. Headache, personality changes and fine motor disturbances. BMJ Case Reports. 2009; doi:10.1136/bcr.06.2008.0093. Used with permission.

Disclaimer

BMJ Best Practice is intended for licensed medical professionals. BMJ Publishing Group Ltd (BMJ) does not advocate or endorse the use of any drug or therapy contained within this publication nor does it diagnose patients. As a medical professional you retain full responsibility for the care and treatment of your patients and you should use your own clinical judgement and expertise when using this product.

This content is not intended to cover all possible diagnosis methods, treatments, follow up, drugs and any contraindications or side effects. In addition, since such standards and practices in medicine change as new data become available, you should consult a variety of sources. We strongly recommend that you independently verify specified diagnosis, treatments and follow-up and ensure it is appropriate for your patient within your region. In addition, with respect to prescription medication, you are advised to check the product information sheet accompanying each drug to verify conditions of use and identify any changes in dosage schedule or contraindications, particularly if the drug to be administered is new, infrequently used, or has a narrow therapeutic range. You must always check that drugs referenced are licensed for the specified use and at the specified doses in your region.

Information included in BMJ Best Practice is provided on an “as is” basis without any representations, conditions or warranties that it is accurate and up to date. BMJ and its licensors and licensees assume no responsibility for any aspect of treatment administered to any patients with the aid of this information. To the fullest extent permitted by law, BMJ and its licensors and licensees shall not incur any liability, including without limitation, liability for damages, arising from the content. All conditions, warranties and other terms which might otherwise be implied by the law including, without limitation, the warranties of satisfactory quality, fitness for a particular purpose, use of reasonable care and skill and non-infringement of proprietary rights are excluded.

Where BMJ Best Practice has been translated into a language other than English, BMJ does not warrant the accuracy and reliability of the translations or the content provided by third parties (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages). BMJ is not responsible for any errors and omissions arising from translation and adaptation or otherwise.Where BMJ Best Practice lists drug names, it does so by recommended International Nonproprietary Names (rINNs) only. It is possible that certain drug formularies might refer to the same drugs using different names.

Please note that recommended formulations and doses may differ between drug databases drug names and brands, drug formularies, or locations. A local drug formulary should always be consulted for full prescribing information.

Treatment recommendations in BMJ Best Practice are specific to patient groups. Care is advised when selecting the integrated drug formulary as some treatment recommendations are for adults only, and external links to a paediatric formulary do not necessarily advocate use in children (and vice-versa). Always check that you have selected the correct drug formulary for your patient.

Where your version of BMJ Best Practice does not integrate with a local drug formulary, you should consult a local pharmaceutical database for comprehensive drug information including contraindications, drug interactions, and alternative dosing before prescribing.

Interpretation of numbers

Regardless of the language in which the content is displayed, numerals are displayed according to the original English-language numerical separator standard. For example 4 digit numbers shall not include a comma nor a decimal point; numbers of 5 or more digits shall include commas; and numbers stated to be less than 1 shall be depicted using decimal points. See Figure 1 below for an explanatory table.

BMJ accepts no responsibility for misinterpretation of numbers which comply with this stated numerical separator standard.

This approach is in line with the guidance of the International Bureau of Weights and Measures Service.

Figure 1 – BMJ Best Practice Numeral Style

5-digit numerals: 10,000

4-digit numerals: 1000

numerals < 1: 0.25

Our full website and application terms and conditions can be found here: Website Terms and Conditions.

Contact us

+ 44 (0) 207 111 1105
support@bmj.com

BMJ
BMA House
Tavistock Square
London
WC1H 9JR
UK

Contributors:

// Authors:

Abhijit Chaudhuri, DM, MD, PhD, FACP, FRCP (Glasg), FRCP (Lond)

Consultant Neurologist
Clinical Lead of Neuroinflammation, Department of Neurology, Queen's Hospital, Romford, UK
DISCLOSURES: AC declares that he has no competing interests.

// Acknowledgements:

Dr Abhijit Chaudhuri would like to gratefully acknowledge Dr Thomas S. Harrison and Dr Angela Loyse, previous contributors to this topic.
DISCLOSURES: TSH and AL declare that they have no competing interests.

// Peer Reviewers:

Robert A. Larsen, MD

Associate Professor of Medicine
University of Southern California, Keck School of Medicine, Los Angeles, CA
DISCLOSURES: RAL declares that he has no competing interests.