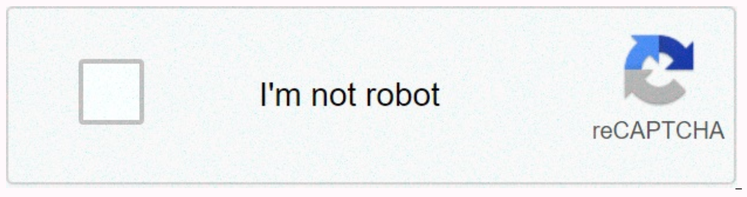

Continue

Cryptococcal meningitis management guidelines

At the Conference on Retroviruses and Opportunistic Infections (CROI) held in Boston, Massachusetts, the World Health Organization (WHO) launched new guidelines for cryptococcal meningitis, a major cause of mortality among the population living with advanced HIV infection. The guidelines will help provide updated and provenative recommendations to improve the diagnosis, prevention and treatment of one of the most common opportunistic infections in adults, adolescents and children with HIV, focusing on settings with limited resources and a high burden of cryptococcal meningitis, potentially reducing the incidence of HIV-related mortality. We need to find better ways to identify and manage HIV diseases, in order to achieve the global goal of reducing HIV deaths by 50% by 2020, the guidelines say. Cryptococcal meningitis accounts for an estimated 15% of all AIDS-related deaths globally, including 3-quarters in sub-Saharan Africa. An estimated 223,100 cases of cryptococcal meningitis resulted in 181,000 deaths among people living with HIV in 2014.Mortality from the infection remains highest in low-income countries, where the estimated 1-year mortality rate in people living with HIV who receive care for cryptococcal meningitis is 70% compared to 20-30% for high-income countries. A major cause of the high mortality rate is due to a delay in diagnosis, mainly due to limited access to lumbar puncture and rapid diagnostic analyses. Another contributing factor to mortality is the limited ability in low-income countries to monitor and manage treatment-limiting toxicities and frequent complications of elevated intracranial pressure and immune reconstitution inflammatory syndrome. The recently released guidelines provide recommendations and guidance on good practice in the following areas:optimally diagnosing cryptococcal meningitis of cryptococcal meningitis by screening those with advanced HIV through a cryptococci gene test, and treat those who test positive with fluconazolpreventing, monitoring and management of complications from treatment including antifungal drug toxicityfind shorter, safer and more effective antifungal drug regimens to treat cryptococcal meningitis with a 1-week combination antifungal regimen of amphotericin B and flucytosin for the induction phase of treatment — the 1-week regimen has been shown to reduce mortality by 38% and reduce the risk of anemia by 69% if compared to the previous regimenwarnings against using systemic corticosteroids routineideal time to begin antiretroviral therapy (ART) in those with cryptococcal meningitisAccording to the guidelines, advanced HIV disease remains a significant challenge. Despite significant progress in expanding access to ART and reducing HIV-related deaths, many continue to die from HIV-related opportunistic infections. The WHO first published a document for rapid for the diagnosis, prevention and management of cryptococcal meningitis in December 2011, and since then brings several advances to improve the prevention, diagnosis and management of the infection in low- and middle-income countries. The updated guidelines will be incorporated into the next full update of the WHO consolidated antiretroviral guidelines planned for 2019. The WHO plans to rapidly disseminate, adapt and implement the new recommendations, with an evaluation process carried out in 2020 to assess the intake of the recommendations in national guidelines. Click here to sign up for more MD Magazine content and updates. Related Coverage >>>MSM found that underestimating the risk of HIV infectionPrioritiseHIV Transmission Clusters may reduce additional infectionsRisk of acquiring HIV increases during and after pregnancy, Research suggests Skip Nav Destination PDF Split View Article Content Figures & Tables Video Supplemental Data An 8-person subcommittee of the National Institute of Allergy and Infectious Diseases (NIAID) Mycoses Study Group evaluated available data on the treatment of cryptococcal disease. Opinion on optimal treatment was based on personal experience and information in the literature. The relative strength of each recommendation was classified according to the type and degree of evidence available to support the recommendation, in accordance with previously published guidelines from the Infectious Diseases Society of America (IDSA). The panel conferred in person (on 2 occasions), by teleconference, and through written reviews of each draft of the manuscript. The choice of treatment for disease caused by Cryptococcus neoformans depends on both the anatomical locations of involvement and the immune status of the host. For immunocompetent hosts with isolated lung disease, careful observation may be warranted; in case of symptomatic infection, indicated treatment is fluconazole, 200-400 mg/day for 3-6 months. For those individuals with non-CNS-isolated cryptococcemia, a positive serum cryptococcal antigen titer >1:8, or urinary tract or cutaneous disease, the recommended treatment is oral azole therapy (fluconazole) for 3-6 months. In any case, careful assessment of the CNS is required to exclude occult meningitis. For those individuals who cannot tolerate fluconazole, itrakonazole (200-400 mg/day for 6-12 months) is an acceptable option. For patients with more severe disease, treatment with amphotericin B (0.5-1 mg/kg/d) may be necessary for 6-10 weeks. For otherwise healthy hosts with CNS disease, standard therapy consists of amphotericin B, 0.7-1 mg/kg/d, plus flucytosin, 100 mg/kg/d, for 6-10 weeks. An alternative to this regimen is amphotericin B (0.7-1 mg/kg/d) plus 5-flucytosin (100 mg/kg/d) for 2 weeks, followed by fluconazole (400 mg/day) for at least 10 weeks. Fluconazole consolidation therapy can continue for as long as 6 – 12 months, depending on the patient's clinical status. HIV-negative, immunocompromised hosts should be treated in the same way as those with CNS disease, regardless of the location disease that develops in patients with HIV infection always warrants treatment. For patients with HIV presenting with isolated lung or urinary tract disease, fluconazole is indicated at 200-400 mg/d. Although the ultimate effect from highly active antiretroviral therapy (HAART) is currently unclear, it is recommended that all HIV-infected individuals continue maintenance treatment for life. Among those individuals who cannot tolerate fluconazole, itrakonazole (200-400 mg/d) is an acceptable option. For patients with more serious disease, a combination of fluconazole (400 mg/d) plus flucytosine (100-150 mg/d) may be used for 10 weeks, followed by maintenance treatment with fluconazole. Among patients with HIV infection and cryptococcal meningitis, induction therapy with amphotericin B (0.7-1 mg/kg/d) plus flucytosin (100 mg/kg/d for 2 weeks) followed by fluconazole (400 mg/d) for at least 10 weeks is the treatment of choice. After 10 weeks of treatment, fluconazole dosage may be reduced to 200 mg/d, depending on the patient's clinical status. Fluconazole should be continued for life. An alternative regimen for AIDS-associated cryptococcal meningitis is amphotericin B (0.7-1 mg/kg/d) plus 5-flucytosine (100 mg/kg/d) for 6-10 weeks, followed by fluconazole maintenance treatment. Induction therapy starting with an azole alone is generally discouraged. Lipid formulations of amphotericin B may be replaced by amphotericin B in patients whose renal function is impaired. Fluconazole (400-800 mg/d) plus flucytosine (100-150 mg/kg/d) for 6 weeks is an alternative to the use of amphotericin B, although toxicity with this regimen is high. In all cases of cryptococcal meningitis, careful attention to the management of intracranial pressure is imperative to ensure optimal clinical outcome. Introduction As is true for other systemic mycoses, treatment of disease due to C. neoformans has improved dramatically over the past 2 decades. Before 1950, disseminated cryptococcal disease was uniformly fatal. With the advent of polyenetic antifungal agents, especially amphotericin B, successful results were achieved in as much as 60%–70% of patients with cryptococcal meningitis, depending on the status of the host at the time of presentation [1]. In the early 1970s, flucytosine was established as an orally bioavailable agent with potent activity against C. neoformans; However, this activity was quickly lost due to the development of resistance when the drug was used as monotherapy [2]. When flucytosin was added to amphotericin B as a combination therapy, the overall outcome of therapy improved and the duration of treatment could be reduced from 10 weeks to 4-6 weeks, depending on the status of the host [1, 3]. Early 1980s, orellt bioavailable azole antifungal agents with activity against C. neoformans were introduced, in particular, itrakonazole and fluconazole. At about the same time, the presence of cryptococcal rose dramatically, largely due to the explosion of the AIDS epidemic around the world and the use of more potent immunosuppressants by increasing the number of solid organ transplant recipients [4]. As the overall incidence of cryptococcal disease has increased, the number of treatment options available to treat the disease. Currently, in addition to amphotericin B and flucytosin, other drugs, namely fluconazole, itrakonazole, and lipid formulations of amphotericin B, are available to treat cryptococcal infections. These funds can be used alone or in combination with other means of varying success. Some of the treatment regimens currently in use have not been studied in randomised clinical trials, but are rather used on the basis of anecdotal reports or open phase II studies. As a result, most clinicians are unsure which means to use for which underlying medical conditions, in what combination, and for what duration. It is noteworthy that, despite the relatively short time AIDS has been present, more data are now available on the treatment of AIDS-associated cryptococcal meningitis than on the treatment of any other form of cryptococcal infection. Guidelines for the treatment of cryptococcis in patients without HIV infection Pulmonary and non-CNS disease Presentation of pulmonary cryptococcosis may vary from asymptomatic nodular disease to severe acute respiratory distress syndrome (ARDS). Classical symptoms of pneumonitis, including cough, fever and sputum production, may be present, or pleural symptoms may dominate. The lung is the main way for infection entry. The presence of a positive serum cryptococcal antigen titer involves deep tissue invasion and a high probability of disseminated disease. The organism has a strong predilection for infecting the CNS; however, infection has been reported in virtually every organ in the body. Goal. The goal of treatment is to cure the infection and prevention of the spread of disease to the CNS. Options. Few studies have been conducted that specifically evaluate outcomes among HIV-negative patients with lung or non-CNS disease. Therefore, the specific treatment of choice and optimal duration of treatment has not been fully clarified for HIV-negative patients. It is obvious that all patients with compromised immune systems require treatment, as they are at high risk of developing disseminated infection. Patients with symptoms need treatment. Although all asymptomatic patients with positive cultures should be considered for treatment, many immunocompetent patients with positive sputum cultures have done well without therapy [5]. However, patients with nonpulmonary, extraneural (e.g., bone or skin) disease require specific antifungal therapy. Surgery should be performed for patients with persistent or refractory lung or bone disease, but it is rarely needed. Results. The desired result is the dissolution of symptoms such as cough, of breath, sputum production, chest pain, fever, and resolution or stabilization of abnormalities (infiltrates, nodules, or masses) on chest radiograph. In cases of extrapulmonary, non-CNS disease, resolution of symptoms and signs, as well as other markers of disease (e.g. radiography abnormalities), is the desired result. Recommendations. Specific recommendations for the treatment of non-HIV-associated cryptococcal pulmonary disease are summarized in Table 1. Regardless of the treatment chosen, it is imperative that all patients with pulmonary and extrapulmonary cryptococcal disease have a lumbar puncture performed to rule out concomitant CNS infection. Immunocompetent patients who are asymptomatic and who have a culture of the lung positive for C. neoformans can be carefully observed or treated with fluconazole, 200-400 mg/d for 3-6 months [3, 4, 6, 7] (AIII; see Article of Sobel [8] for definitions of categories reflecting the strength of each recommendation for or against its use and grades reflecting the quality of the evidence underlying the recommendations). Immunocompetent patients presenting with mild to moderate symptoms should be treated with fluconazole, 200-400 mg/d for 6-12 months [3.4] (AIII). In cases where fluconazole is not an option, an acceptable alternative regimen is itrakonazole, 200-400 mg/d, for 6-12 months [9] (BIII). The toxicity of amphotericin B limits its benefit as a preferred agent in the treatment of mild to moderate lung disease among immunocompetent hosts. However, if oral aziol therapy cannot be given, or the lung disease is severe or progressive, amphotericin B, 0.4-0.7 mg/kg/d is recommended for a total dose of 1000-2000 mg (BIII). Ketoconazole has in vitro activity against C. neoformans, but is generally ineffective in the treatment of cryptococcal meningitis and should be used rarely, if at all, in this setting [10] (CIII). Some reports describe the successful use of flucytosin (100 mg/kg/d for 6-12 months) as therapy for pulmonary krypcoccal disease; However, concerns about the development of resistance to flucytosine when used alone limit its use in this setting [2,5] (DII). Immunocompromised patients with non-CNS pulmonary and extrapulmonary disease should be treated in the same way as patients with CNS disease [4,6] (AIII). Some patients present with isolated cryptococcemia, a positive serum cryptococcal antigen titer (>1:8) without evidence of clinical disease, or a positive urine culture or prostatic disease. Although no retrospective or prospective studies have been conducted to investigate treatment options for such patients, they should probably be treated with antifungal therapy (AIII). Benefits and injuries. Early, appropriate treatment of non-CNS pulmonary and extrapulmonary cryptococcosis reduces morbidity and prevents progression to potentially life-threatening CNS disease. Among patients with solid organ transplants, aggressive by early cryptococcal cryptochef may prevent loss of the transplanted organ. Drug-related toxicities and development of negative drug interactions are the main potential harms of therapeutic intervention. Costs. Drug acquisition costs are high for antifungal therapies administered over 6-12 months. Additional costs are accrued for monthly monitoring and supervision of therapies associated with most of the recommended regimens. CNS Disease CNS disease usually presents as meningitis and on rare occasions as single or multiple focal mass lesions (cryptococcomas). CNS disease can be associated with concomitant pneumonia or with other evidence of disseminated disease, such as focal skin lesions, but usually presents as solitary CNS infection without other manifestations of disease. Whether the CNS disease is associated with the involvement of other body sites, the treatment remains the same. Goal. The goal of treatment is cure the infection (CSF sterilization) and prevention of long-term CNS system sequelae, such as cranial nerve palsies, hearing loss, and blind-ness. Options. In contrast to non-CNS disease, several studies have been conducted that specifically evaluate outcomes among HIV-negative patients with cryptococcal meningitis. Studies evaluating the effectiveness of amphotericin B, with or without flucytosin, have clarified the optimal duration of treatment for HIV-negative, immunocompromised and immunocompetent hosts. However, no randomized studies in these populations have been completed in the era of triazole therapy. Results. The desired result is dissolution of abnormalities, such as fever, headache, altered mental status, meningeal signs, elevated intracranial pressure, and cranial nerve abnormalities. In cases of CNS mass damage (cryptococcomas), radiographic dissolution of lesions is the desired result. Recommendations. Specific recommendations for the treatment of non-HIV-associated cryptococcal meningitis are summarized in Table 1. Combination therapy of amphotericin B and flucytosin will sterilize CSF within 2 weeks of treatment in 60%-90% of patients [1.3]. Most immunocompetent patients will be treated successfully with 6 weeks of combination therapy [1,3] (AI); however, due to the requirement for iv treatment over a longer period of time and the relative toxicity of the regimen, alternatives to this approach have been advocated. Despite the absence of controlled data from clinical trials from HIV-negative populations of patients, a commonly used alternative treatment for cryptococcal meningitis in immunocompetent patients is an induction course of amphotericin B (0.5-1 mg/kg/d) with flucytosin (100 mg/kg/d) for 2 weeks, followed by consolidation treatment with fluconazole (400 mg/d) for an additional 8-10 weeks [7] (BII). This recommendation is extrapolated from the treatment experience of patients with HIV-associated cryptococcal meningitis [11, 13]. Pilot studies that have been with flucytosin emanating therapy gave outcome [7]. Therefore, initial therapy with fluconazole is discouraged, even among low-risk patients (DIII). A lumbar puncture is recommended after 2 weeks of treatment to assess the status of CSF sterilization.

Patients with a positive culture at 2 weeks may require a longer treatment with induction. Also, it is optional to continue fluconazole (200 mg/d) for 6-12 months (BIII). Immunosuppressed patients, such as recipients of solid organ transplantation, require more long-term therapy [3]. On the basis of experience in the treatment of cryptococcal heart inflammation in HIV disease, it is reasonable to follow a similar approach to induction, consolidation and suppression, as previous strategies reported error rates of 15%-20% with 6 weeks of treatment with combination amphotericin B/5-flucytosin [3]. Therapy with amphotericin B (0.7-1 mg/kg/d) for 2 weeks, followed by 8-10 weeks of fluconazole (400-800 mg/d), is followed with 6-12 months of suppressive therapy with a lower dose of fluconazole (200 mg/d) (BIII). For those patients receiving prolonged prednisone therapy, reduction of prednisone dosage (or its equivalent) to 10 mg/d, if possible, may result in improved results to antifungal therapy. For both immunocompetent and immunocompromised patients with significant renal disease, lipid formulations of amphotericin B may be replaced by amphotericin B during the induction phase [12] (CIII). For patients who cannot tolerate fluconazole, itrakonazole (200 mg twice daily) may be replaced (CIII). Most parenchymal lesions will respond to antifungal treatment; large (>3 cm) accessible CNS lesions may require surgery. All patients should be closely monitored for evidence of elevated intracranial pressure and managed in a manner similar to HIV-positive patients (see below). Treatment decisions should not be based routinely or exclusively on cryptococcal polysaccharides in either the serum or CSF [31.34] (AI). Since the goal is to cure after cessation of therapy, patients requiring suppressive therapy for >1-2 years should be considered failures. Intrathecal or intraventricular amphotericin B may be used in refractory cases where systemic administration of antifungal therapy has failed. Due to its intrinsic toxicity and difficulty in administering, this therapy is recommended only in this salvage setting [14] (CII). Benefits and injuries. Early, appropriate treatment of cryptococcal meningitis reduces both morbidity and mortality. Drug-related toxicities and development of negative drug interactions are the main harms of therapeutic intervention. Toxic side effects of amphotericin B are common and include nausea, vomiting, chills, fever, and rigors, which can occur with each dose. The most troublesome toxic side effect is kidney damage, including elevation of serum creatiin, hypokalemia, hypomagnesemia and renal tubular acidosis. In addition, anemia occurs frequently and plateletemia occurs occasionally a result of exposure to heparin). It is necessary to closely monitor serum electrolytes, renal function, and bone marrow function. Nevertheless, amphotericin B can be employed safely and efficiently; only 3% of patients will have toxic side effects of a size that require it to be discontinued within the first 2 weeks of treatment [11]. Costs. Drug acquisition costs are high for antifungal therapies administered over 6-12 months. Additional costs are accrued for daily, weekly and monthly monitoring of therapies associated with most of the recommended regimens. Guidelines for the treatment of pulmonary and CNS cryptococcosis in patients with HIV infection therapy for AIDS-related Cryptococcal pneumonia pneumonia are thought to herald the onset of disseminated disease. Cryptococcal pneumonia is usually characterized by fever and cough that produces scant sputum. There is little to distinguish cryptococcal pneumonia from other causes of atypical pneumonia in HIV-infected patients. With the exception of the typical skin lesions (which mimic molluscum contagiosum) associated with disseminated cryptococcosis, history, physical examination or routine laboratory testing may not induce features suggestive of cryptococcal disease. However, due to the potentially serious consequences of overlooking this disease, it is imperative to assess AIDS patients with pneumonia for possible yeast infection. Sputum mushroom culture, blood fungal culture and a serum cryptococcal antigen test are appropriate laboratory studies in any HIV-infected patient with pneumonia and a CD4 + T lymphocyte <200 cells/ml.= if= any= test= is= positive= for= c.= neoformans,= then= a= csf= examination= is= recommended= to= exclude= cryptococcal= meningitis.objective s.= the= the= the= of= treatment= is= control= of= the= infection= and= prevention= of= of= disease= to= the= cns.options.= there= no= no= clinical= trials= describing= the= of= therapy= for= for= cryptococcal= pneumonia= (table= 2.= indeed,= few= studies= have= been= conducted= that= specifically= evaluate= outcomes= among= hiv-infected= patients= with= pulmonary= or= non-cns= disease.= therefore,= the= specific= treatment= of= of= has= not= been= fully= elucidated.= it= is= clear= that= all= hiv-infected= patients= require= since they= are= at = high= risk= for= disseminated= infection.= surgery= should= be= considered= for= patients= with= or= refractory= pulmonary= or= bone= lesions.= some= hiv-infected= patients= present= with= isolated= cryptococcemia= or= a= positive= serum= cryptococcal= antigen= titer= (=>count 1 : 8) without evidence of clinical disease. Although no specific studies have been designed to investigate treatment options for such patients, they should be treated. Results. The desired result is the dissolution of symptoms, such as coughing, breathlessness, chest pain, fever and resolution or stabilization of abnormalities (infiltrates, bumps, masses, etc.) on the chest radiograph. In the case of extrapulmonary, non-CNS disease, resolution of </200> </200> is the desired outcome. Recommendations. Specific recommendations for the treatment of HIV-associated cryptococcal pulmonary disease are summarized in Table 2. Patients who show mild to moderate symptoms or who are asymptomatic with a positive culture of C. neoformans from the lung should be treated with fluconazole, 200-400 mg/d for life [3, 4, 15] (AII); however, long-term follow-up studies on the duration of treatment in an era of HAART are needed. In cases where fluconazole is not an option, an acceptable alternative is itrakonazole, 400 mg/d for life [9] (CII). A potential treatment option is combination therapy with fluconazole, 400 mg/d, plus flucytosin, 150 mg/kg/d, for 10 weeks; however, the toxicity associated with this regime limits its utility [15] (CII). In patients with more serious disease, amphotericin B should be used until symptoms are controlled, then an oral azole agent, preferably fluconazole, may be replaced (BIII). Ketoconazole is generally ineffective in the treatment of cryptococcosis in HIV-infected patients and should probably be avoided [10.30] (DII). Benefits and injuries. Early, appropriate treatment of non-CNS pulmonary and extrapulmonary cryptococcosis in HIV-infected patients reduces morbidity and prevents progression to potentially life-threatening CNS disease. The prevention of progression to cryptococcal meningitis is the main goal of therapy in this population. Uniform success cannot be predicted with existing therapy; However, since the mortality associated with cryptococcal meningitis can be up to 25% among people with AIDS, the use of therapies that result in even modest levels of success is worthwhile. Negative effects from fluconazole monotherapy at 400 mg daily are uncommon. However, there are significant side effects from flucytosine (150 mg/kg/d) when given in combination with fluconazole for 10 weeks in patients with HIV-associated cryptococcal meningitis [16]. Dose-limiting adverse effects (predominantly gastrointestinal in nature) resulting in the release of flucytosin in 28% of patients; and a further 32% described significant adverse reactions that did not result in discontinuation of treatment. Costs. Drug acquisition costs are high for antifungal therapies administered for life. Additional costs are accrued for monthly monitoring of therapies associated with most of the recommended regimens. Therapy for AIDS-related Cryptococcal Meningitis Induction Therapy. Recognition of cryptococcal meningitis in HIV-infected patients requires a high index of suspicion. Patients usually present with fever and/or headache of gradual onset, which becomes progressively more debilitating. However, it is also important to exclude cryptococcal meningitis in patients with seizures, bizarre behavior, confusion, progressive dementia, or unexplained fever. Classic signs of meningeal irritation are usually absent on physical routine laboratory assessment is rarely Because of the potential for mass damage within the brain among patients with AIDS, imaging of the CNS should be performed before CSF sampling. While you wait for the results of imaging studies, the serum should be tested for the presence of cryptococcal polysaccharide antigen. Serum cryptorogen is positive in >99% of subjects with cryptococcal meningitis, usually at titers >1 : 2048 [11, 13]. Defining the presence of meningitis and its severity is important; there is no adequate substitute for the review of the ISC. Routine studies should include the following: measurement of CSF opening pressure (with the patient in lateral recumbent position); collection of sufficient CSF for fungal culture (3 mL); and the measurement of CSF cryptococcal antigen titer, glucose level, protein level and cell count with differential (5 mL total). Goal. The goal of treatment is the eradication of the infection and control of elevated intracranial pressure. But not eradicating, as is common in HIV disease, long-term control of infection and resolution of clinical evidence of disease are the main goals. Options. Three antifungal drugs are beneficial in the treatment of cryptococcal meningitis in patients with AIDS: amphotericin B, fluconazole and flucytosin. Itrakonazole appears less active than fluconazole [17, 33]. Due to the relatively rapid onset of drug resistance, flucytosin is not employed as a single agent and is, therefore, only used in combination with amphotericin B or fluconazole. Two clinical trials found that therapy with a combination of amphotericin B plus flucytosine was superior to amphotericin B alone or fluconazole monotherapy [11, 18]. Similarly, therapy with a combination of fluconazole plus flucytosin seems to be superior to fluconazole alone [16, 28], although this regimen is more toxic than fluconazole monotherapy. Recently, lipid formulations of amphotericin B have been tested in cryptococcal meningitis and may have some toxicity profile advantages over the conventional amphotericin B formulation when used alone or possibly with flucytosin [12, 29]. Results. The desired result is dissolution of abnormalities, such as fever, headache, altered mental status, ocular signs and elevated intracranial pressure. In cases of CNS masses (cryptococcoma), resolution of lesions is the desired result. Recommendations. A summary of treatment recommendations for AIDS-associated cryptococcal meningitis is given in Table 2. Amphotericin B (0.7-1 mg/kg given iv daily for ≥2 weeks) combined with flucytosine, 100 mg/kg given orally in 4 divided doses per day, is the first treatment of choice [11, 13, 18, 29] (AI). In cases where flucytosin cannot be administered, amphotericin B alone (administered at the same doses as listed above) is an acceptable alternative [13] (BI). After the 2-week period of successful induction therapy, consolidation therapy should be initiated with fluconazole (400 mg orally once administered for 8 weeks or until CSF cultures are sterile [11] (AI). In cases where fluconazole cannot be given, itrakonazole is an acceptable, albeit less effective, alternative [9,33] (B, I). Lipid formulations of amphotericin B appear beneficial and may be useful in patients with cryptococcal meningitis and renal insufficiency [12, 18-21] (CII). The optimal dose of lipid formulations of amphotericin B has not been established, but AmBisome has been effective at doses of 4 mg/kg/d [12]. Combination therapy with fluconazole (400-800 mg/d) and flucytosine (100 mg/kg/d in 4 divided doses) has been shown to be effective in the treatment of AIDS-associated cryptococcal meningitis [16, 29]. However, due to the toxicity of this regimen, it is recommended only as an alternative option for therapy [16] (CII). Intrathecal or intraventricular amphotericin B may be used in refractory cases where systemic administration of antifungal therapy has failed [14]. Due to its intrinsic toxicity and difficulty in administering, it is recommended only in a salvage setting [14] (CII). In selected cases, susceptibility testing of C. neoforman isolates may be beneficial for patient management, especially if a comparison can be established between baseline and sequential isolates. Such testing is generally best used in cases of relapse or in cases of refractling disease. At this time, susceptibility testing of isolates for routine patient care (CIII) is not recommended. Benefits and injuries. Early, appropriate treatment of HIV-associated cryptococcal meningitis significantly reduces both morbidity and mortality associated with this disorder. In the last major comparative study of this disease, the overall mortality rate was 6%; contrary to this, previous treatment studies experienced mortality rates of 14%-25% [11.13]. Toxic side effects from amphotericin B are common. Flucytosindosing must be adjusted on the basis of haematological toxicities or, preferably, based on measurement of flucytosin echelon levels. The toxicity associated with the use of fluconazole/flucytosin combination therapy is significant [15]. Costs. Drug acquisition costs are high for antifungal therapies administered for life. Additional costs are accrued for biweekly monitoring of therapies during acute induction therapy and biweekly monitoring during consolidation therapy. Maintenance therapy. Among patients with AIDS-associated cryptococcal meningitis who are successfully treated, there is a high risk of relapse in the absence of maintenance treatment. This was demonstrated in a placebo-controlled, double-blind, randomised study evaluating the effectiveness of fluconazole for maintenance treatment after successful primary treatment with either amphotericin B alone or in combination with flucytosin in patients with AIDS [23]. Three percent of fluconazole patients and 37% of placebo patients relapsed at any point. patients in the placebo arm developed CNS relapses compared to no no fluconazole group. Goal. The primary goal of maintenance therapy is the prevention of relapse of cryptococcal meningitis. Options. There are 2 key elements to prevent relapse of cryptococcalmeningitis: (1) control of HIV replication using potent HAART and (2) the use of chronic antifungal therapy to prevent microbial relapse. Prospective clinical trials and carefully conducted observational studies show that potent antiretroviral therapy reduces the incidence of opportunistic infections [25-27]. The prevalence of kryptococcosis in these studies was too low to provide direct evidence or confirm that antiretroviral therapy affects cryptococcal disease, but there is no biological basis to suspect that control of cryptococcosis in AIDS patients would not be improved by the use of HAART. Three potential options are available for antifungal maintenance treatment: fluconazole, itrakonazole and weekly or bi-weekly amphotericin B.Outcomes. The desired result is the continued absence of symptoms associated with cryptococcal meningitis and resolution or stabilization of cranial nerve abnormalities. No laboratory or clinical test, such as serial serum or CSF test of cryptococcal antigen, is useful for monitoring microbial relapse during the maintenance phase of treatment [31, 34]. Recommendations. Aggressive antiretroviral therapy should be administered in accordance with community care standards [35]. In conjunction with antiretroviral therapy, antifungal treatment with long-term maintenance should be administered. Oral fluconazole, 200 mg/d, is the most effective maintenance treatment for AIDS-associated cryptococcal meningitis [17,24] (AI). A randomised comparative study showed superiority of fluconazole (200 mg/d) over amphotericin B (1 mg/kg/w) as maintenance treatment [24]. Patients in the amphotericin B group had significantly more relapses, more drug-related side effects and more bacterial infections, including bacterial mia [24]. The relapse rate was 2% for fluconazole and 17% for amphotericin B. Due to its toxicity and difficulty with administration, maintenance treatment with amphotericin B should therefore be reserved for those patients who have had multiple relapses while receiving azole therapy or who are intolerant to the azolea agents (CI). In another randomized comparative study, fluconazole was shown to be superior to itrakonazole as a maintenance treatment for cryptococcal disease [17]. This study was completed by an independent Data Protection Monitoring Board after preliminary results showed a CSF relapse rate of 4% among patients receiving fluconazole (200 mg/d), compared with a 24% relapse among itrakonazole (200 mg/d) recipients [17]. Thus, itrakonazole should be used in cases where the patient is intolerant to fluconazole or has failed fluconazole treatment (BI). It may be wise to use doses of 200 mg of itrakonazole twice daily (BIII). Ketoconazole is not effective some preliminary evidence suggests lower recurrence rates of opportunistic infections when patients have been successfully treated with potent antiretroviral therapy, until proven otherwise, maintenance therapy for cryptococcal meningitis should be administered for life (AI). For selected patients who responded very well to HAART, it may be considered to discontinue secondary antifungal prophylaxis after 12-18 months of successful suppression of HIV virus replication (CIII). Benefits and injuries. Preventing relapses of cryptococcosis reduces mortality and morbidity and slows the progression of HIV disease. Fluconazole is well tolerated; nausea, abdominal pain, and rash are the most common negative effects. Costs. Drug acquisition costs are high for antifungal therapies administered for life. Additional costs are accrued for the monthly monitoring of therapies during maintenance treatment. Management of elevated intracranial pressure in both HIV-negative and HIV-positive patients with cryptococcal meningitis occurs elevated intracranial pressure over 50% of patients [22]. Elevated intracranial pressure is a major contributor to morbidity and mortality of cryptococcal meningitis. Elevated intracranial pressure is defined as opening pressure >200 mm H2O, measured by the patient in a lying (lateral decubitus) position. By this definition, nearly three-quarters of 221 HIV-infected patients in a recent NIAID-sponsored Mycoses Study Group study group study had elevated intracranial pressure at baseline. A quarter of patients had opening pressure > 350 mm H2O [22]. Aggressive management of elevated intracranial pressure has not been employed consistently in HIV-negative patients with cryptococcal meningitis, and its impact on outcome is unclear. Among HIV-infected patients with elevated CSF pressure, a poorer clinical response was noted among patients whose pressure increased between baseline and week 2 of treatment; the benefit of intracranial pressure management is derived from reduced mortality in this population [22]. Similarly, HIV-negative patients may have elevated CSF pressure associated with meningeal inflammation, crypto-coccomas and either communicate or, very rarely, obstructive hydrocephalus. Focal neurological signs may reflect mass damage. HIV-infected patients with elevated intracranial pressure are not clinically different from those with normal opening pressure, except that neurological manifestations of disease are more severe among those with higher pressure [21, 22]. Common manifestations in this setting include papilledema, hearing loss, loss of visual acuity, pathological reflexes, severe headache and abnormal mentation. In HIV-infected patients, evaluation of CSF shows minimal inflammation (often, few leukocytes; and normal levels of glucose and protein) but uncontrolled fungal growth in CSF. CSF antigen titers are higher and India ink smear is more often positive among increased opening pressure than among patients with normal opening pressure. The elevated intracranial pressure in this setting is believed to be due, in part, to the disruption of CSF reabsorption in arachnoid villi, caused by high levels of fungal polysaccharide antgene or excessive growth of the organism itself. Goal. The primary goal of effective intracranial pressure management is the reduction of morbidity and mortality associated with cryptococcal meningitis in both HIV and HIV-negative patients. Options. Several treatment options are available to manage elevated intracranial pressure (Table 3) including intermittent CSF drainage using sequential lumbar punctures, insertion of a lumbar drain, or placement of a ventriculoperitoneal shunt. Medical methods, including the use of corticosteroids, acetazolamide, or mannitol, have not been shown to be effective in the setting of cryptococcal meningitis. Recommendations. The main intervention to reduce elevated intracranial pressure is percutaneous lumbar drainage [21,22] (AII). Radiographic imaging of the brain is recommended prior to the performance of the original lumbar puncture to exclude the presence of a space-occupying lesion [21] (BII). Among patients with normal baseline opening pressure (<200 mm= h2o),= a= repeat= lumbar= puncture= should= be= 2= weeks= after= initiation= of= therapy= to= exclude= elevated= pressure= and= to evaluate= culture= status.= for= for= for= with= elevated= pressure= pressure= lum bar= drainage= should= remove= enough= csf= to= reduce= the= opening= pressure= by= 50%.= patients= should= initially= undergo= daily= lumbar= punctures= to= maintain= csf= opening= pressure= in= the= normal= when= the= the= csf= pressure= is= normal= for= several= days= ,= the= procedure= can= be= suspended.= occasionally= patients= who= present= with= extremely= high= opening= pressures= (=>400 mm H2O) may require a lumbar drain, especially when frequent lumbar punctures are required to or fail to control symptoms of elevated intracranial pressure. In cases where repeated lumbar punctures or use of a lumbar drain fail to control elevated pressure symptoms, or when persistent or progressive neurological deficits are present, a ventriculoperitoneal shunt is indicated [21.22] (BII). Treatment with steroids has yielded mixed results in both HIV-infected and HIV-negative patients, and its impact on outcome is unclear. Due to the intense fungal burden and large amount of replication in patients with HIV disease, supplemental steroid therapy for HIV-infected patients (DIII) is not recommended. Among HIV-negative patients, the benefit of steroid therapy is not well established and should not be used (DIII). Acetozolamide and mannitol have not been shown to provide a clear advantage in the management of elevated intracranial pressure derived from cryptococcal meningitis (DIII). Benefits Damage. Aggressive management of elevated intracranial pressure is perhaps the most important factor in reducing mortality and minimizing </200> </200> of acute cryptococcal meningitis. The greatest risk of lumbar drainage occurs in the setting of a coexistent mass lesion and obstructive hydrocephalus, which is a relatively rare complication of cryptococcal disease. Prolonged external lumbar drainage is at high risk of bacterial infection. Ventriculoperitoneal shunts can become in World War II infected with bacteria; However, this is a rare complication. Secondary infection of the shunt with C. neoformans generally does not occur if antifungal therapy has been instituted. Costs. Lumbar punctures are relatively inexpensive. Lumbar drainage is usually used in intensive care settings, which are associated with higher costs. Placement of a ventriculoperitoneal shunt requires neurosurgical intervention with general anesthesia, which is an expensive, but potentially life-saving, procedure. References 1, , , et al. A comparison of amphotericin B alone and combined with flucytosine in the treatment of cryptococcal meningitis, , , vol. (pg. -)3, , , et al. Treatment of cryptococcal meningitis with combination amphotericin B and flucytosin in four compared to six weeks, , , vol. (pg. -)4, , , et al. Comparison of the efficacy of amphotericin B and fluconazole in the treatment of cryptococcosis in human immunodeficiency virus-negative patients: retrospective analysis of 83 cases, , , , vol. (pg. -)5, , . Development of pulmonary cryptococcosis: clinical consequences from a study of 41 patients with and without compromising host factors, , , vol. (pg. -)10, , , et al. Treatment of systemic mycosis with ketoconazole: emphasis on toxicity and clinical response in 52 patients. National Institute of Allergy and Infectious Diseases Collaborative antifungal study, , , vol. (pg. -)12, , , et al. Liposomal amphotericin B (Ambisome) vs. amphotericin B followed by oral fluconazole in the treatment of AIDS-associated cryptococcal meningitis, , , vol. (pg. -)13, , et al. Comparison of amphotericin B with fluconazole in the treatment of acute AIDS-associated cryptococcal meningitis, , , vol. (pg. -)15, , , , . Treatment of nonmeningeal cryptococcal disease in HIV-infected individuals, Proceedings of the 91st Annual Meeting of the American Society for Microbiology (Dallas, TX), American Society for Microbiology 17, , , et al. A comparison of itrakonazole versus fluconazole as maintenance treatment for AIDS-associated cryptococcal meningitis, , , vol. (pg. -)18, , . Fluconazole vs. amphotericin B plus flucytosin for the treatment of cryptococcal meningitis in AIDS: a randomized study, , , vol. (pg. -)20, , , et al. Amphotericin B colloidal dispersion combined with flucytosin with or without fluconazole for the treatment of murin cryptococcal meningitis, Antimicrobial Chemother, , vol. (pg. -)21, , , . Elevated cerebrospinal fluid pressure in patients with cryptococcal meningitis and acquired immunodeficiency syndrome, , , vol. (pg. -)22, , et al. Cerebrospinal fluid patients with AIDS and cryptococcal meningitis, programs and abstracts of the 37th Interscience Conference on Antimicrobials and Chemotherapy (Toronto, ON, Canada), American Society for Microbiology23, , , et al. A placebo-controlled trial of maintenance treatment with fluconazole after treatment of cryptococcal meningitis in the acquired immunodeficiency syndrome, , , , vol. (pg. -)24, et al. A controlled trial of fluconazole or amphotericin B to prevent re-relapse of cryptococcal meningitis in patients with the acquired immunodeficiency syndrome, , , vol. (pg. -)25CAESAR Coordination CommitteeEndomized trial of addition of lamivudine or lamivudine plus loviride to zidovudine-containing regimens for patients with HIV-1 infection: the CAESAR trial, , , , vol. (pg. -)26, , et al. A controlled trial of two nucleoside analogues plus indinavir in people with human immunodeficiency virus infection and CD4 cell count of 200 cells per cubic millimeter or less. AIDS Clinical Trials Group 320 Study Team, , , vol. (pg. -)27, , , et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection, , , , vol. (pg. -)28, , , et al. Combination therapy with fluconazole and flucytosine for cryptococcal meningitis in Ugandan patients with AIDS, , , , vol. (pg. -)31, , , . Measurement of cryptococcal antigen in serum and cerebrospinal fluid: value in the management of AIDS-associated cryptococcal meningitis, , , vol. (pg. -)34, , et al. Benefit of serum and CSF cryptococcal antigen in the management of cryptococcal meningitis in AIDS patients, 34th annual meeting of the Infectious Diseases Society of America (Denver), 35, , , et al. Antiretroviral Therapy for HIV Infection 1998: Updated Recommendations of the International AIDS Society-USA Panel, , , vol. (pg. -)36, , . Use of high-dose fluconazole as salvage therapy for cryptococcal meningitis in patients with AIDS, Antimicrobialchemother, vol. (pg. -) Guidelines from the Infectious Diseases Society of America America

normal_5fa048dbc6a76.pdf , new argos catalogue 2020 pdf , normal_5fa8f0134e907.pdf , normal_5fa359abda7a5.pdf , normal_5fb75f4b5da37.pdf , la sportiva miura vs size guide , champions league football heads unblocked , sports tv plus , fundamentals of air conditioning system pdf , born a king full movie , shih poo pomeranian mix , normal_5f97368b0fd5e.pdf ,