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An Overview on Cryptococcal Meningitis

Marcia S. C. Melhem and Mara Cristina S. M. Pappalardo
Adolfo Lutz Institute, Laboratory Reference Center and Emilio Ribas, Research Institute of the Secretary of Health of São Paulo State, Brazil

1. Introduction

Cryptococcosis is a systemic disease caused by the yeast *Cryptococcus* spp. *Cryptococcus neoformans* and *C. gattii* are the etiological agents of fungal meningoencephalitis. Chronic meningitis is the most common clinical presentation of cryptococcosis. In contrast with the acute meningitis, patients with chronic meningitis develop an indolent course of symptoms for at least four weeks like headache, nausea, decreased memory and comprehension. Cerebral cryptococcomas can also cause significant neurological morbidity, and these mass lesions require relief of increased intracranial pressure and prolonged antifungal therapy. Although cryptococcosis is considered one opportunistic infection of the central nervous system and lungs, extra neural and non-pulmonary forms may be found. The disease is almost always associated with impaired immunity, and occurs in patients with lymph proliferative disorders, steroid therapy and organ transplantation. Before the acquired immune deficiency syndrome (AIDS) the cases with cryptococcosis were sporadic. Despite of the highly active antiretroviral therapy-HAART, acute mortality due to HIV-associated cryptococcal meningitis remains unacceptably high (Lortholary et al., 2006), and consequently, this disease remains a leading cause of death in Africa, Asia, and Brazil (French et al., 2002; Vidal et al., 2008; Pappalardo et al., 2009).

Cryptococcosis has been documented in few (~3%) of solid-organ transplant recipients with 68% of the cases occurring one year after transplantation., and almost half cases have pulmonary cryptococcal infection. The disease is limited to the lungs only in 6% to 33% of cases, although cryptococcal meningitis and disseminated infections have been documented in up to 60% of patients (Husain et al., 2001; Vilchez et al., 2002; Singh et al., 2007; Shaariah et al., 1992). Data on non-transplant patients or presumably immunocompetent hosts presenting cryptococcal meningitis are scarse, because the majority of patients prior to the HIV epidemic were significantly immunosuppressed, receiving steroids or having cancer or other degenerative diseases (Perfect et al., 2010).

2. Cryptococcosis and AIDS

Cryptococcus neoformans is yeast with a tropism for the central nervous system, and 70-90% of infections caused by this species manifested as meningitis, after spores inhalation and hematologic dissemination. Meningitis is frequently associated to the pulmonary form. In immunosuppressed patients with pulmonary cryptococcosis, meningitis should be always

ruled out by lumbar puncture (Mitchell & Perfect, 1995). Cryptococcal meningitis is a common and often fatal opportunistic infection in HIV-infected patients, especially in developing countries and in patients with CD4 cells < 100/μL. Incidence of cryptococcosis decreased in the era HAART, but the incidence and mortality of the disease are still high in some areas of the world. Recent review suggests that there are ~1 million new cases and at least 500.000 annual deaths world-wide due to HIV-associated cryptococcosis (Park et al., 2009).

Computed tomography or magnetic resonance imaging head scans should be done in all patients prior to any diagnostic or therapeutic lumbar puncture, with focal neurological signs or impaired mental functions. Patients with HIV disease generally do not have hydrocephalus or cryptococcal mass lesions and these exams commonly are normal or show cerebral atrophy without obstruction or other abnormality (Graybill et al., 2000).

The most common signs and symptoms are headaches, fever, nausea, vomiting, lethargy, coma, memory loss over 2 to 4 weeks; however, sometimes patients only refer general bodily discomfort. Patients can also present with pulmonary or cutaneous manifestations with or without apparent neurologic disease (Perfect et al., 2010).

The diagnosis of the meningeal cryptococcosis through mycological procedures is easy and based on the visualization of encapsulated yeast cells in the cerebral spinal fluid specimen, and immunological assays. If cryptococal meningitis is confirmed, extra neural sites should be discharged by means of screening of cutaneous lesions, procedures for blood cultures, examination of urine, pleural fluid, sputum, prostatic fluid, and others clinical specimens for detect the etiological agent..

Antifungal drugs more commonly used for treat cryptococcal meningitis are amphotericin B deoxycholate, amphotericin B lipid complex or liposomal formulation, flucytosine, and fluconazole (Perfect et al., 2010). Ideally, antifungal therapy should rapidly sterilize the central nervous system and this should be the primary focus of any induction strategy (Bicanic et al., 2007). The antifungal therapy in cryptococcal meningitis in AIDS patients is divided into 3 phases: induction (for at least 2 weeks), consolidation (for a minimum of eight weeks) and maintenance or suppression phase.

The induction phase aims the achievement of sterilization of cerebral spinal fluid, or reduction of fungal burden. The consolidation phase warrants maintenance of negative cultures and normalization of clinical parameters. Some experts and guidelines suggest a routine lumbar puncture at the second week, with prolongation of the induction phase if the cerebrospinal fluid culture is not yet sterile. The drug of choice for induction is amphotericin B (0,7-1,0 mg/kg per day intravenously), and fluconazole is the choice for consolidation [400 mg (6 mg/kg) per day orally]. Fluconazole should be introduced for consolidation regimen whenever the mental status recovered, fever, headache and meningeal symptoms disappear, and/or yeast culture results are negative at the second week. Despite the theoretic antagonism between amphotericin B and fluconazole, most animal model data suggests that both drugs together are a very effective combination against *C. neoformans* (Menichetti et al., 1996; Larsen et al., 2004; Larsen et al., 2005; Pappas et al., 2009; Perfect et al., 2010).

Maintenance therapy should be initiated after completion of primary therapy with an induction and consolidation regimen, and continued until there is evidence of persistent

immune reconstitution with successful HAART. Since a cure doesn't exist in AIDS patients, maintenance should be done for at least one year with 200 mg/daily of fluconazole (standard for consolidation and maintenance), with CD4 cell count > 100 cells/μL and undetectable or very low HIV RNA level sustained for ≥3 months (minimum of 12 months of antifungal therapy). Itraconazole is an alternative, albeit less effective, choice for maintenance therapy. Oral itraconazole if patient is intolerant of fluconazole, may be administered (200 mg per day or a higher dosage 200 mg twice per day orally) (Denning et al, 1989).

The management of cryptococcosis is difficult, particularly in some developing countries where flucytosine is no more commercialized and liposomal or lipid complex amphotericin B formulations are not affordable. The nephrotoxicity of amphotericin B deoxycholate represents a big challenge for the physicians in such regions (Sharkey et al., 1996). Furthermore the treatment of increased intracranial pressure represents another serious issue since approximately one-half of HIV-infected patients have elevated baseline opening intracranial pressures requiring drainage of cerebral spinal fluid daily (Bicanic et al., 2009). Medications other than antifungal drugs are not useful in the management of increased intracranial pressure in cryptococcal meningoencephalitis (Perfect et al. 2010).

The rapid clearance of infection by sterilization of cerebrospinal fluid associated with clinical improvement on day 14 of treatment is predictive of a good evaluation in the 10th week (Robinson et al., 1999). The rate of clearance of cryptococcal colony-forming units is a clinically meaningful endpoint. Maybe deaths within two weeks are nearly all related to cryptococcal infection, whereas, after this time, deaths are increasingly related to other complications of late-stage HIV infections or extended hospitalization (Bicanic et al., 2009). The good control of elevated CSF pressure and symptoms are very important, and they are some of the most critical determinants in the outcome of cryptococcal meningitis (Perfect et al., 2010). This elevated CSF pressure level is generally linked to a high burden of yeast in the cerebrospinal fluid (Bicanic et al., 2009). Factors that indicate a bad outcome in cryptococcal meningitis include abnormal mental status, poor host inflammatory response (cerebrospinal fluid white cells <20/mL), raised CSF opening pressure (> 25 cm H_2O), high organism burden, extra neural sites and the lack of effective antifungal treatment. Some studies confirm the greater fungicidal activity of amphotericin B plus flucytosine to improve prognosis (Brouwer et al., 2004).

Potential complications in management of cryptococcal infection, includes increased intracranial pressure, immune reconstitution inflammatory syndrome, drug resistance, and cryptococcomas. Opportunistic infections such bacteremia, toxoplasmosis, histoplasmosis, or oropharingeal candidosis, tumors, drug-related complications may occur in heavily immunocompromised patients. Moreover, the long-time of hospitalization, never less than two weeks, increased the risk for hospital infections Development of classic hydrocephalus later during treatment and follow-up can occur. Furthermore, impaired vision, mental deficit and cranial nerve palsies are described sequels of cryptocccosis.

After discontinuation of maintenance therapy, relapses with positive culture result may occur and so careful follow-up of patients is necessary. Patients will need follow-up lumbar punctures and intracranial pressure should be measured. Reinstitution of fluconazole maintenance therapy should be considered if the CD4 cell count decreases to <100 cells/mL and/or the serum cryptococcal antigen titer increases [Zolopa et al., 2009)

2.1 Cryptococcosis and IRIS

Immune reconstitution inflammatory syndrome (IRIS) consists of clinical manifestations compatible with enormous tissue inflammation in patients with rapid improvement in cellular immunity and worsening in central nervous system signs and/ or symptoms of the disease. About 30% of patients with cryptococcal meningitis will develop IRIS when HAART is initiated (Bicanic et al., 2006; Antinori et al., 2009). Perfect et al. (2010) suggest a wide range of two to ten weeks after initiation of cryptococcosis therapy to introduce HAART. The exact moment to start HAART in patients with cryptococcal meningitis to avoid immune reconstitution inflammatory syndrome, is still uncertain.

3. Etiologic agents

Cryptococcus neoformans and *Cryptococcus gattii* cause nearly all human and animal cryptococcal infections. In addition to these common species, there are nearby 15 other members of this genus which have appeared as human clinical isolates, such as *C. laurentii, C. luteolus* (80% of non-*neoformans* and non-*gattii* cases), *C. albidus, C. diffluens,* and *C. uniguttulatus* (Heitman et al. 2011). *Cryptococcus gattii* can be discerned from *C. neoformans* using a wide range of microbiological and molecular techniques. A simple and classical method is the use of canavanine-glycine-bromothymol blue (CGB) medium, which allows *C. gattii* but not *C. neoformans* to grow changing the color medium from green-yellowish to blue. Molecular approaches yield determine distinct genotypes among the species. Polymerase chain reaction (PCR) fingerprinting, restriction fragment length polymorphism (RFLP), analysis of specific loci, and amplified fragment length polymorphism (AFLP) fingerprint analysis, and multi-locus sequence typing scheme (Meyer et al., 2009) are molecular tools (Meyer et al., 2009). Furthermore, interspecies hybrid forms have been isolated from clinical samples, and they seem to present a higher virulence potential than regular *C. gattii* or *C. neoformans* isolates (Boekhout et al., 2001).

The species differs in many aspects and improved surveillance should enable better assessment of the local incidence of these two species and also clinical manifestation and course associated to each species. Whereas *C. neoformans* primarily affects persons infected with human immunodeficiency virus worldwide, *C. gattii* primarily affects HIV-uninfected persons in tropical and subtropical regions (Pappalardo and Melhem, 2003; Chaturvedi et al, 2005; Martins et al., 2007; Heitman et al. 2011).

It noteworthy the emergence of *C. gattii* in temperate climate regions that suggests the pathogen might have adapted to a new climatic niche or that climatic warming might have created an environment for spore survival and propagation of this species. *Cryptococcus gattii* is more likely to cause cryptococcomas, and seems to be less responsive to antifungal drugs (Gomez-Lopes et al., 2008).

The profile of antifungal susceptibility can be assessed through *in vitro* antifungal susceptibility testing. Performance of these tests may help not only to monitor the development of resistance in *Cryptococcus* isolates, but could also determine the best antifungal therapy, predicting possible failures due to a resistant strain. Antifungal susceptibility testing is indeed a recognized useful tool to aid the treatment of *Candida* infections. References broth microdilution methods for this genus are described in document M27-A3 of the Clinical and Laboratory Standards Institute – CLSI, and in the doc.

E.Def 7.1 of the European Committee on Antimicrobial Susceptibility Testing (EUCAST) (CLSI, 2008, Subcommittee on Antifungal Susceptibility Testing of the ESCMID, 2008). Although the reference methodologies of CLSI and EUCAST are different, the results are very similar and results are comparable.

Determination of resistance in isolates of *Cryptococcus,* quite distinct yeast in which fermentation is absent, the micro dilution methods present some technical problems. The most relevant one is the low growth of *Cryptococcus* strains due to the oxygen limited environment found in the microdilution plates. So, the standard methods developed for *Candida* are not still completely reliable for test *Cryptococcus* isolates and efforts have been made toward standardization of antifungal susceptibility testing of *Cryptococcus* and other non-fermentative yeasts (Zaragoza et al., 2011).

The minimum inhibition concentration (MIC) of antifungal drugs against clinical and environmental *Cryptococcus* strains has been extensively studied. *Cryptococcus neoformans* has been more frequently assessed for its *in vitro* susceptibility to a wide variety of antifungal compounds, including the new triazoles posaconazole, voriconazole, ravuconazole, and isavuconazole. Otherwise, few studies using relatively small sets of *C. gattii* isolates have been performed to investigate their *in vitro* susceptibilities to these drugs. Since fluconazole may last for a very long period of time, development of resistance to this agent has been reported both *in vivo* and *in vitro.* Many studies pointed out a significant emergence of clinical isolates of *C. neoformans* which present high fluconazole-MICs (MIC >4 mg/L) in different geographical regions (Aller et al., 2000; Dias et al., 2006; Pfaller et al, 2004). Resistance to fluconazole or to other azole compounds is not a cause of concern in the continent of America, where 3% to 10% of strains present high MIC. On opposite, the data from African, Cambodian and Spanish *C. neoformans* isolates showed high fluconazole-MICs (Bicanic et al., 2006; Perkins at al., 2005; Pfaller et al, 2004; Sar et al., 2004). It should be also pointed out that some authors did not find any correlation with clinical failure and the *in vitro* MIC data (Dannaoui et al., 2006). Therefore, the interpretation of the data is quite difficult since there are not interpretative clinical breakpoints for distinguish between resistant or susceptible *Cryptococcus* isolates that could predict failure or clinical success. However, breakpoints have not been defined yet, it is worth performing antifungal susceptibility testing against sequential isolates obtained from patients under antifungal therapy. An increased in MICs values during the monitoring could predict development of resistance of the original strain resulting in therapeutic concerning. Moreover, heteroresistance to fluconazole in *C. neoformans* or *C. gattii* is a phenomen that could play a role in clinical failure (Mondon et al., 1999; Varma, and Kwon-Chung, 2010).

The identification of amphotericin B resistant organisms seems to be more difficult however, as reference methods fail to detect it and trustworthy comparisons have not been done. Consistent detection of AMB resistance *in vitro* in *Cryptococcus neoformans* has proven difficult, and few studies demonstrated that majority of the initials isolates are susceptible to the polyene (Lozano-Chiu et al., 1998; Rodero et al., 2000a). Time-kill curves, a methodology to measure the fungicidal activity of amphotericin B, have been evaluated to identify resistance or tolerance to this antifungal agent in *Cryptococcus* isolates (Rodero et al., 2000b). Yeast isolates with amphotericin B MICs 2 mg/L are extremely uncommon, and therefore any strain with a MIC > 2 mg/L should be considered as potentially resistant to this polyene (CLSI, 2008).

4. Laboratory identification of *cryptococcus* in a routine clinical laboratory

The distinguishing feature of *Cryptococcus* genus is a polysaccharide capsule, and techniques that detect this cryptococcal structure and its components are the most useful tools as diagnostic tests. Evaluation of spinal fluid is essential in diagnosing central nervous system disease. The yeast cells of *Cryptococcus* are spherical in shape and approximately 5 to 7 μm in diameter while the capsules vary enormously in their thickness and are of a few micrometers of average. A rapid, simple and inexpensive procedure employs India ink staining to detect the encapsulated cells of *Cryptococcus* in pellets from centrifuged cerebrospinal fluid and other specimens. The lower limit of detection of India ink is ~10^3 to 10^4 yeast cell/ml. Disadvantages include the poor sensitivity of the technique in diagnosing cryptococcal meningitis in non-HIV-infected patients (30 to 72%) compared with culture. The sensitivity of India ink in high (~80%) for patients with overwhelming infection such HIV-infected patients (Kwon-Chung and Bennett, 1992; Heitman et al. 2011).

False-positive results can occur if inexperienced readers interpret lymphocytes or fat droplets as fungal cells. The capsular polysaccharide antigen that can be detect using commercial systems and represents the most valuable rapid test for the laboratory diagnosis of cryptococcosis. During infection, the capsular antigen is solubilized in cerebrospinal fluid, serum, urine and fluid recovered from the lungs. Almost all high fungal burden patients will have a positive serum and cerebrospinal fluid. Commercial kits typically demonstrate 90 to 100% sensitivity and 97 to 100% specificity for cerebrospinal fluid compared with culture and clinical diagnosis. However, in patients without AIDS the sensitivity of serum cryptococcal antigen in diagnosing cryptococcal meningitis is ~60%. The level of detection of most kits is at least 10 ng of antigen/ml. The most common testing format to detect antigen is latex agglutination assay. Moreover, antigen detection can be quantitative as the greatest dilution of the fluid that gives a positive result. Uncommon false-positive results can be encountered, particularly in serum contaminated with syneresis fluid, in presence of rheumatoid factor. In addition, false-positive results can occurs in patients with collagen vascular disease, chronic meningitis, malignancy (<0.3%), or even presenting a yeast infection caused by *Trichosporon.* Many kits include an enzymatic or heat pre-treatment in order to minimize the false-positive results, and incorporate a control reagent. In cases in which physicians doubt a positive results, they may ask the laboratory personal to treat the specimen with 2,β-mercaptoethanol, as it eliminates non-specific reactions. False-negative results were described in low organism burden infections and for capsule-deficient *Cryptococcus.* The latex assay also yields false-negative reactions due to a prozone effect that can be improved by specimen serial dilutions. An enzyme immunoassay is also available to detect glucuronoxylomannan, the principal polysaccharide component. The enzymatic assay it is slightly more sensitive than latex assay; similar to latex test, false-positive and false-negative results can occur (Kwon-Chun et al, 1981).

Measuring capsular antigen titers in serial clinical specimens for monitoring cerebrospinal fluid or serum cryptococcal antigen levels is useful in the management of cryptococcosis in non-AIDS patients. Decrease in antigen titers has limited value in the management of meningitis in such cases. Although it is expected that the titers should change after a few weeks of therapy, there is no evidence that titers predict or correlate with clinical and mycological outcomes (Kwon-Chung and Bennett, 1992).

The commercial (1,3) β-D-glucan assay detects a polysaccharide component of the cell wall of several pathogenic fungi, but given the limited experience to date with this test in cryptococcosis cases, there is no recommendation of using this test in the diagnosis of cryptococcosis.

Histological stains for tissue sections for revel *Cryptococcus* cells includes Gomori methenamine silver and calcofluor white, that are broad-spectrum fungal histochemical stains for fungi regardless of type. The best histological procedure uses mucicarmine, alcian blue, and periodic acid-Schiff that stain the capsule and Fontana-Masson stain, which interacts with the cell wall.

Culture techniques will remain the mainstay of the diagnosis of this infection. Culturing for *Cryptococcus* may be appropriate, even when the CSF profile is unremarkable. Blood, CSF, urine, and other clinical specimens should be cultured for fungi. Yeasts cells growth in 2 to 7 days in classical Sabouraud dextrose agar, typically as brilliant, mucous, pale colored colonies. Besides de capsular cell, one of the defining characteristics of *Cryptococcus neoformans* and *C. gattii* is its ability to synthesize a dark cell wall-associated pigment (melanin) when grow in media containing phenolic compounds, such Birdseed agar. Identification based on conventional biochemical and physiological assays, which are routinely used in a clinical laboratory for yeasts, can be difficult or even impossible for conclusive identification of *Cryptococcus* species. Laboratories should recognize that *C. gattii* cannot be differentiated from *C. neoformans* by conventional laboratory methods. *C. gattii* can only be differentiated from *C. neoformans* by specific biochemical or molecular testing. Laboratories should seek for definitive identification at an appropriate reference laboratory.

5. Conclusion

In conclusion, cryptococcosis remains a challenging management issue around the world and all patients presenting symptomatic increased intracranial pressure should be tested for HIC-infection, and screened for cryptococcal meningitis for receive early antifungal therapy. Relapses of symptoms and signs can occur during or after treatment and patients should be monitored for IRIS, drug resistance or compliance issues.

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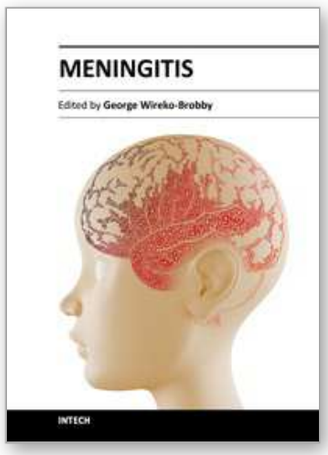

Meningitis

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Meningitis is a medical emergency requiring a rapid diagnosis and an immediate transfer to an institution supplied with appropriate antibiotic and supportive measures. This book aims to provide general practitioners, paediatricians, and specialist physicians with an essential text written in an accessible language, and also to highlight the differences in pathogenesis and causative agents of meningitis in the developed and the developing world.

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中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
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