

EQUAL *Cryptococcus* Score 2018: A European Confederation of Medical Mycology Score Derived From Current Guidelines to Measure QUALity of Clinical Cryptococcosis Management

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Cryptococcosis is an opportunistic fungal infection with high morbidity and mortality. Guidelines to aid clinicians regarding diagnosis, management, and treatment can be extensive and challenging to comply with. There is no tool to measure guideline adherence. To create such a tool, we reviewed current guidelines from the Infectious Diseases Society of America, the World Health Organization, the American Society of Transplantation, and recent significant publications to select the strongest recommendations as vital components of our scoring tool. Items included diagnostic tests (blood, tissue, and cerebrospinal fluid cultures, *Cryptococcus* antigen, India ink, histopathology with special fungal stains, central nervous system imaging), pharmacological (amphotericin B, flucytosine, azoles) and nonpharmacological treatments (intracranial pressure management, immunomodulation, infectious disease consultation), and follow-up of central nervous system complications. The EQUAL *Cryptococcus* Score 2018 weighs and aggregates the recommendations for the optimal management of cryptococcosis. Providing a tool that could measure guideline adherence or facilitate clinical decision-making.

Keywords. *Cryptococcus*; fungal infection; guideline adherence; score; therapy.

Cryptococcosis is an invasive fungal infection caused by *Cryptococcus*, a ubiquitous pathogen with more than 70 species in the environment, but 2 species commonly causing disease, *Cryptococcus neoformans* and *C. gattii*, with the former being the most prevalent [1]. The infection typically affects patients with impaired cellular immunity and has a high morbidity and mortality [2]. Cryptococcosis is the most common systemic fungal infection worldwide among persons infected with HIV, with estimations in 2014 reporting an annual number of people with positive cryptococcal antigenemia of 278 000 and 223 000 incident cases of cryptococcal meningitis [3]. In the Western world, it seems to have lower mortality compared with organ transplant recipients and patients without either transplants or HIV [4].

Clinical presentation is variable, from asymptomatic localized disease (eg, lung nodules) to disseminated disease, preferentially

involving the central nervous system (CNS). Disseminated disease can involve any organ with a predilection for the CNS, lungs, skin, bone, or prostate [5]. Diagnosis via culture and histology tissue evaluation with the use of specific fungal dyes are considered the gold standard [5]. However, cryptococcal antigen (CrAg) testing by latex agglutination or lateral flow assay is highly sensitive and specific in both serum and cerebrospinal fluid (CSF) and is routinely used as the primary diagnostic method [6]. Mainstay therapy includes an induction phase with amphotericin B (Amb), either the lipid or deoxycholate formulation, combined with flucytosine (5-FC), followed by the consolidation and subsequent maintenance phases, where higher and lower doses of fluconazole are used [7]. Lipid soluble formulations of Amb are preferred over deoxycholate Amb due to their better tolerability and lower nephrotoxicity [8, 9]. However, cost and availability of lipid formulations of Amb and 5-FC are major limitations in resource-limited settings [10].

Guidelines devised to aid in the management of a disease often result in an extensive and detailed number of recommendations to tackle all possible clinical scenarios. The current Infectious Diseases Society of America (IDSA) guidelines have 86 recommendations [7]. This number of recommendations is based on the clear recognition that clinical manifestations, management, and prognosis can be different based on the host's immune system and, therefore, the guideline gives separate

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recommendations for the 3 distinct populations at risk, the HIV-infected individual, the organ transplant recipients, and the non-HIV, nontransplant host. Furthermore, the guidelines also highlight differences based on the burden of disease, additionally subdividing patients with localized, non-CNS, mild to moderate disease from those with moderately severe to severe, CNS, and/or disseminated disease. New data that could impact clinical management have been published since the IDSA guidelines were published in 2010.

All these tailored recommendations from the currently available guidelines make the management of such a complex infection more intricate. Previous scoring tools for candidemia and pulmonary aspergillosis that weighted and summarized guideline recommendations have been recently published [11, 12]. The aims of the EQUAL *Cryptococcus* Score 2018 are to provide a simple tool to summarize guideline recommendations that could be used to evaluate guideline adherence as a marker of quality of care and to support antimicrobial stewardship.

METHODS

The EQUAL *Cryptococcus* Score 2018 (Table 1) is based on the recommendations of the most recent IDSA guidelines, World Health Organization (WHO) guidelines, guidance documents from the American Society of Transplantation (AST), and recent key studies with high potential to be included in updated versions of these guidelines [7, 13, 14]. For the purposes of the development of this score, studies published after 2010 were considered key if they were (1) original research, (2) provided new findings that impact treatment outcomes, and (3) confirmed optimal management through systematic review. Therefore, literature reviews, expert opinions or perspectives, case reports, and studies focusing on screening or prevention were not included.

Recommendations were grouped into 4 categories: diagnosis, antifungal treatment, nonpharmacological therapeutic interventions, and follow-up. Each recommendation included was considered an essential part in the management of cryptococcosis and was allocated a numerical value from 1 to 3, based on the strength of the recommendation and its level of evidence.

Given that some recommendations are organ or host specific, or conditioned by another variable (clinical, radiological, procedures), negative numbers were used to subtract from the score, when those interventions were not done in the appropriate clinical scenario. Penalizing with negative numbers allowed a homogenous maximum score to standardize optimal management, independent of the severity, organ localization, or immune status of the individual with cryptococcosis.

RESULTS

Current IDSA guidelines and the AST guidance document allocate a value to the strength of each recommendation (A to C) followed by the level of evidence supporting it (I to III), using a

modified version described in the Canadian Task Force report on periodic health examination [15]. The WHO guidelines used the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) method to rate the quality of the evidence and determine the strength of the recommendations [16].

Distinguishing between disseminated disease and localized pulmonary and asymptomatic disease is fundamental to guide therapy. Any patient with CNS disease, positive blood cultures, or elevated serum CrAg and those with severe pulmonary disease should be considered to have disseminated disease [7]. The choice of antifungal therapy is dependent on the site and extent of disease, net state of immunosuppression, and severity of illness.

Diagnosis

All patients should be evaluated for disseminated disease with serum CrAg (3 points) and fungal blood cultures (3 points). HIV-positive patients with CD4 \leq 100 cells/ μ L should also be evaluated for disseminated disease [17]. A lumbar puncture (LP) should be done in immunocompetent individuals who have CNS symptoms (headache, neck stiffness, confusion, ataxia, urinary incontinency, vomiting, photophobia) and in all patients with an underlying immunosuppression who have evidence of cryptococcal disease (ie, positive blood cultures, serum CrAg, or tissue biopsy; BII) [18]. At the time of the LP, opening CSF pressure should be measured, as high intracranial pressure (\geq 20 cmH₂O) is associated with increased mortality (AII; 3 points) [19]. CSF should be sent for fungal culture, and CrAg titers should be measured in the CSF (2 points each). Only if CrAg is not available, CSF India ink should be done instead (1 point) [5]. If the patient presents with focal neurological symptoms, either computed tomography (CT) or magnetic resonance imaging (MRI) should be done to rule out space-occupying lesions (BII; -1 point if not done) [20].

Patients with pulmonary involvement (infiltrates or nodule on imaging, respiratory symptoms) often undergo diagnostic bronchoscopy. If the procedure is done, tissue biopsy samples should be sent for histological evaluation with specific fungal dyes such as mucicarmine, Grocott-Gomori Methenamine Silver, Periodic Acid Schiff, and Fontana-Masson (-2 points if not done) [5]. Tissue and bronchoalveolar lavage samples should also be sent for fungal culture (-1 point if not done). If another organ is involved (skin, bone, etc.) and a tissue biopsy is performed, samples should be sent for fungal culture and histology evaluation with specific fungal dyes (-1 point each if not done) [5].

Treatment

For nonimmunosuppressed patients with mild to moderate, non-CNS, and localized disease, the recommended treatment is oral fluconazole 400 mg daily (6 mg/Kg) for 6 to 12 months (BII; 3 points) [21, 22]. When fluconazole is unavailable or contraindicated, other azoles (itraconazole, voriconazole, posaconazole,

Table 1. EQUAL *Cryptococcus* Score 2018

Section	Intervention	Score		
		HIV ^a	Transplant	Non-HIV, Nontransplant
Diagnosis	In all patients irrespective of site			
	Blood fungal culture	3	3	3
	Serum CrAg	3	3	3
	Other sites explored based on clinical presentation ^b	-1	-1	-1
	- Tissue/fluid fungal culture not obtained if biopsy performed	-1	-1	-1
	- Histology with fungal stains not obtained if biopsy performed ^c			
	Immunosuppressed or CNS symptoms ^d			
	LP done and opening pressure measured	3	3	3
	CSF fungal culture	2	2	2
	CSF CrAg titers measured	2	2	2
	CSF India ink performed in the absence of CrAg	1	1	1
	Brain CT or MRI not performed before LP if focal neurological or immunosuppressed	-1	-1	-1
	Pulmonary ^e			
	If bronchoscopy done, no BAL/biopsy sent for fungal culture	-1	-1	-1
Antifungal treatment	Mild-moderate, non-CNS, or localized disease	Fluconazole for 6-12 mo		
		3	3	3
		Another azole for 6-12 mo ^f		
		2	2	2
		Any azole for <6 mo		
		1	1	1
	Moderately severe-severe, CNS, or disseminated disease ^g	Induction phase (1st choice only)		
		LFAmB plus 5-FC for ≥2 wk ^h		
		3	3	3
		AmBD plus 5-FC for ≥2 wk		
		2	2	2
		LFAmB alone for 4-6 wk		
		2	2	2
		LFAmB plus fluconazole for 2 wk		
		2	2	2
		Fluconazole with or without 5-FC for 6 wk		
		1	1	1
	Not extending for 4-6 wk when clinically indicated ⁱ			
	-2	-2	-2	
	Consolidation phase (1st choice only)			
	Fluconazole for ≥8 wk			
	3	3	3	
	Itraconazole or any other azole for 10-12 wk			
	1	1	1	
	Maintenance phase (1st choice only)			
	Fluconazole for ≥12 mo			
	3	3	3	
	Itraconazole for ≥12 mo			
	1	1	1	
	No TDM if itraconazole is used			
	-1	-1	-1	
	AmBD 1 mg/Kg IV/wk			
	1	1	1	
Nonpharmacological therapeutic interventions	Immunomodulation			
	ART started within 2 wk of diagnosis or not started at month 4	-3	NA	NA
	No decrease in net immunosuppression	NA	-1	NA
	Was immunosuppression ruled out?	NA	-2	-2
	a. HIV test not done	NA	NA	-1
	b. Full history and immunosuppressive drug not reviewed			
	Antifungal treatment stopped if IRIS developed	-2	-2	-2
	Management of ICH ^j			
	No decompression via LP or lumbar drain or ventriculostomy or VP shunt to maintain CSF pressure <20 cmH ₂ O	-3	-3	-3
	Corticosteroids (if no parenchymal edema) ^k	-2	-2	-2
	Acetazolamide	-1	-1	-1
Mannitol	-1	-1	-1	
Infectious diseases consultation ^l	2	2	2	
Follow-up	Repeat serum CrAg to monitor response	-1	-1	-1
	If CNS disease: not repeating CSF culture at day 14	-1	-1	-1

Table 1. Continued

Section	Intervention	Score		
		HIV ^a	Transplant	Non-HIV, Nontransplant
	If CNS disease: repeat CSF CrAg to monitor response	-2	-2	-2
	If HIV-positive, fluconazole was not stopped after 1 y of treatment on those on ART with a CD4 count ≥ 100 cells/ μ L	-1	-1	-1

Abbreviations: 5-FC, flucytosine; AmBD, Amphotericin deoxycholate; ART, antiretroviral therapy; BAL, bronchoalveolar lavage; CNS, central nervous system; CrAg, *cryptococcus* antigen; CSF, cerebrospinal fluid; CT, computed tomography; ICH, intracranial hypertension; IRIS, immune reconstitution inflammatory syndrome; LFAmB, lipid formulations of Amphotericin B; LP, lumbar puncture; MRI, magnetic resonance imaging; NA, not applicable; TDM, therapeutic drug monitoring; VP, ventriculoperitoneal.

^aHIV-infected individuals with CD4 ≤ 100 cells/ μ L should be screened with serum CrAg, regardless of clinical manifestations.

^bSome examples of sites that can be sampled based on clinical presentation include skin lesions and prostate tissue.

^cSpecific fungal dyes include mucicarmine, Grocott-Gomori Methenamine Silver, Periodic Acid Schiff, and Fontana-Masson.

^dCNS disease symptoms include headache, neck stiffness, confusion, ataxia, urinary incontinuity, vomiting, photophobia. In all patients with disseminated disease or an underlying immunosuppression and evidence of cryptococcal disease (ie, positive blood cultures, serum CrAg, or tissue biopsy), a lumbar puncture should be even if asymptomatic.

^eRespiratory symptoms or pulmonary infiltrates or nodule on imaging.

^fIn the case of itraconazole, liquid formulation or capsules can be used, although the former is recommended.

^gIn each phase, treatment options are mutually exclusive.

^hOne week of AmB plus 5-FC is acceptable in resource-limited settings.

ⁱNontransplant, non-HIV patients and pregnant women may require at least 4 weeks. Extending to 6 weeks is recommended in the presence of cryptococcomas, neurological complications (eg, deterioration, persistent coma, or seizures), severe uncorrected immunosuppression, and positive fungal CSF culture at the end of 2 weeks of treatment.

^jIf intracranial hypertension is present (≥ 20 cmH₂O), this intervention to decrease it should be continued until the intracranial pressure remains < 20 cmH₂O for 2 days. There are no data on the maximum volume of CSF that can be safely drained during a lumbar puncture. CSF pressure should be rechecked periodically afterwards.

^kUse of steroids for other indications specific to each individual patient should not penalized (eg, transplant patients, chronic steroid use, etc.)

^lRecently published data not contained in the IDSA guidelines.

or isavuconazole) can be used for the same length of therapy (BII; 2 points) [23–25]. Treatment with any of these agents for less than 6 months is superior to no treatment (BII; 1 point) [7].

Treatment in those with moderately severe to severe, disseminated, or CNS disease is divided into 3 phases: induction, consolidation, and maintenance. During each phase, there are several treatment options, which are mutually exclusive. For the induction phase, lipid formulations of AmB (LFAmB) plus 5-FC for ≥ 2 weeks is preferred (AI; 3 points). AmB deoxycholate plus 5-FC (AI), LFAmB alone for 4–6 weeks (AII), and LFAmB plus high-dose fluconazole (≥ 12 mg/Kg; 1200 mg daily favored; BI) are alternative options (2 points). Nontransplant, non-HIV patients and pregnant women may require at least 4 weeks of induction therapy (BII; -2 point if not done). Extending

induction therapy to 6 weeks is recommended in the presence of CNS parenchymal involvement (eg, cryptococcoma), neurological complications (eg, deterioration, persistent coma, or seizures), severe uncorrected immunosuppression, and positive fungal CSF culture at the end of 2 weeks of treatment (BII; -2 points if not done) [9, 26–28]. When AmB is unavailable or contraindicated, high-dose fluconazole with or without 5-FC for 6 weeks can be used (BII; 1 point) [29, 30].

For the consolidation phase, fluconazole 800 mg daily for ≥ 8 weeks is the preferred drug (AI; 3 points) [27]. Other azoles (CIII), including itraconazole (CII) [31], for 10–12 weeks are alternative options (1 point). Fluconazole 200 mg daily for ≥ 12 months is preferred for the maintenance phase (AI; 3 points). Twice-daily itraconazole and LFAmB 1 mg/Kg once per week are alternatives (CI; 1 point) [32, 33]. Therapeutic drug monitoring (TDM) is recommended if itraconazole is used (CI; -1 point if not done) [7]. If the patient develops inflammatory immune reconstitution syndrome (IRIS), antifungal therapy should be continued (BIII; -1 point if not done) [7]. In HIV-positive patients on ART with a CD4 count ≥ 100 cells/ μ L, fluconazole should be stopped after 1 year of treatment (BII) [34].

Patients with HIV should be started on antiretroviral therapy between 2 and 10 weeks after antifungal therapy starts, as earlier initiation has been associated with increased mortality (AI; -3 points if not done) [35]. Transplant recipients should have a net decrease in the amount of immunosuppression received (BII; -1 if not done) [36]. In non-HIV, nontransplant individuals, immunosuppression should be ruled out with a thorough medical history, including a review of potential immunosuppressive drugs and a CD4 lymphocyte count (-1

Table 2. EQUAL *Cryptococcus* Score 2018

Section	Maximum Score	
	Mild–Moderate, Non-CNS, or Localized Disease	Moderately Severe–Severe, CNS, or Disseminated Disease
Diagnosis	6	13
Treatment	Antifungal	3
	Immunomodulation	0
	ICH management	NA
	ID consult	2
Follow-up	0	0
Total	11	24

Abbreviations: CNS, central nervous system; ICH, intracranial hypertension; ID, infectious diseases; NA, not applicable.

point for each item not done) [37, 38]. An HIV test should be performed in all patients with unknown status (−2 points if not done) [7]. In CNS disease, intracranial hypertension (ICH) should be managed aggressively with mechanical decompression via daily LP, lumbar drain, ventriculostomy, or ventriculoperitoneal shunt placement, with the goal of maintaining CSF pressure <25 cmH₂O (BIII; −3 points if not done) [39, 40]. The use of corticosteroids for this purpose is contraindicated as it has shown to increase morbidity and mortality (AII; −3 points if used) [41]. Acetazolamide (AII) and mannitol (AIII) to decrease ICH are not useful in CNS cryptococcosis (−1 point each if used) [7, 42].

Regardless of the localization or severity of the disease, patients with cryptococcal infection should receive an infectious diseases consultation, if available, as this has been shown to decrease 90-day mortality (2 points) [14].

Follow-up

Repeat serum CrAg to monitor clinical response is not recommended (−1 point if done) [43]. In patients with CNS disease, repeating a CSF culture after 2 weeks of treatment is recommended (BII; −1 point if not done) [27]. However, monitoring CSF CrAg titers is not recommended (−2 points if done) [43].

The maximum score is 11 points for patients with mild to moderate, non-CNS, or localized disease and 24 points for patients with moderately severe to severe, CNS, or disseminated disease (Table 2).

DISCUSSION

The EQUAL *Cryptococcus* Score 2018 is a 47-item scoring tool, derived from current IDSA guidelines and recent key publications, to inform about quality of clinical cryptococcosis care. We weighed the items recommended by these documents, based on the strength of the endorsement and the level of evidence, to provide a score that could reflect the ideal management of cryptococcosis. The maximum score, reflection of complete adherence to current guideline recommendations, is 11 points for patients with mild to moderate, non-CNS, or localized disease and 24 points for moderately severe to severe, CNS, or disseminated disease. However, this would require validation through retrospective or prospective analysis, measuring different outcomes (eg, mortality, microbiologic clearance, time to clinical improvement, etc.) in distinct patient populations before being widely used.

The score is applicable to all patients with *Cryptococcus* infection regardless of the site and severity of disease or the immune status of the individual. This generalizability is also a major limitation of the EQUAL *Cryptococcus* Score 2018, which, at first glance, seems more cumbersome than scores recently published for other invasive fungal infections [11]. Although this reflects the complicated management of cryptococcosis in every potential clinical scenario, from the 47 items included in the score, more than half are conditioned by the site of disease, the host's

immune status, or the mutually exclusive options provided, thus tailoring down the actual number of items to be reviewed.

The EQUAL *Cryptococcus* Score 2018 is a tool envisioned to improve quality of care by aligning patient management, facilitating antimicrobial stewardship and comparability between health care facilities. The validity and ultimate utility of the proposed scoring system can only be established by evaluating the correlation between the score and outcomes in future studies.

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