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Efficacy of Cerebrospinal Fluid Beta-D-Glucan Diagnostic Testing for Fungal Meningitis: a Systematic Review

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ABSTRACT Several case reports and cohort studies have examined the use of (1,3)-beta-D-glucan measurement with cerebrospinal fluid to diagnose fungal meningitis. This systematic review aims to characterize the evidence regarding cerebrospinal fluid (1,3)-beta-D-glucan measurement to detect fungal meningitis. We searched PubMed for (1,3)-beta-D-glucan and each of several distinct fungi, cerebrospinal fluid, and meningitis. Summary data including diagnostic performance (where applicable) were recorded. A total of 939 records were examined via a PubMed search. One hundred eighteen records remained after duplicates were removed, and 104 records were excluded, as they did not examine cerebrospinal fluid, included animals, or focused on nonfungal infections. Fourteen studies were included in this systematic review. A variety of fungi, including species of *Candida*, *Aspergillus*, *Exserohilum*, *Cryptococcus*, *Histoplasma*, and *Coccidioides*, were studied, although most were case reports. Diagnostic accuracy was examined in 5 studies. Cerebrospinal fluid (CSF) (1,3)-beta-D-glucan measurement showed >95% sensitivity in the corticosteroid injection-related outbreak of *Exserohilum rostratum*. One study in *Histoplasma* meningitis found 53% (53/87) sensitivity and 87% (133/153) specificity, while another study of *Cryptococcus* meningitis found 89% (69/78) sensitivity and 85% (33/39) specificity. CSF (1,3)-beta-D-glucan testing may be useful, primarily as a nonspecific marker of fungal meningitis. Although the FDA black box warning states that *Cryptococcus* spp. do not make (1,3)-beta-D-glucan, the current evidence shows that (1,3)-beta-D-glucan is detectable in cryptococcal meningitis. Organism-specific testing should be used in conjunction with (1,3)-beta-D-glucan measurement.

KEYWORDS (1,3)-beta-D-glucan, *Coccidioides* meningitis, cryptococcal meningitis, *Exserohilum rostratum*, *Histoplasma* meningitis, cerebrospinal fluid, fungal meningitis

Meningitis may be caused by a diverse group of fungal pathogens, including molds, yeast, and dimorphic fungi. Symptoms such as headache, neck stiffness, and fever commonly occur, but their frequency varies by the type of fungi involved; typically, symptoms are subacute. Yet, fungal meningitis is often underrecognized as a cause of meningitis worldwide. For instance, cryptococcal meningitis is the most common cause of fungal meningitis worldwide and is the most common cause of meningitis in sub-Saharan Africa (1). Cryptococcal meningitis carries an average cost per case of $103,236, with an average length of hospitalization of 70.6 days in the United States (2). In Uganda, the estimated cost of initial diagnosis and treatment of cryptococcal meningitis in Uganda is $5.6 million (1). *Candida* meningitis is common in preterm infants and in persons with central nervous system (CNS) ventriculostomies or immunocompromised states (3). Further, although molds such as *Exserohilum rostratum* or

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Aspergillus species are generally uncommon causes of meningitis, iatrogenic outbreaks or sporadic cases may be devastating. Finally, endemic fungi such as *Coccidioides* or *Histoplasma* spp. are important causes of meningitis within their regions of endemicity (ever expanding due to a number of circumstances) (2, 4, 5).

Despite the importance of fungal pathogens as causes of meningitis, improved diagnostic tools are urgently needed in many cases. Classically, fungal meningitis is detected by culture or direct visualization of the fungus in cerebrospinal fluid (CSF) samples. While culture in many cases is fairly accurate, results often take at least 7 days, and so clinical utility is limited. The cryptococcal antigen (CrAg) lateral flow assay (LFA; Immuno-Mycologics, Norman, OK, USA) is the most rapid, effective way to diagnose cryptococcal meningitis, with sensitivity and specificity generally being >99% in CSF in testing of over 600 samples (6). While good performance has been noted for antigen detection in meningitis due to *Coccidioides* and *Histoplasma* spp., the diagnostic performance of antigen detection is less clear for *Blastomyces* meningitis (7–14).

Given that for many types of fungal meningitis, diagnostic testing is inadequate, new diagnostic tests are needed. One test of interest is the detection of the polysaccharide glucose polymer 1,3-beta-D-glucan (BDG), a component of the fungal cell wall (15). Several studies have been conducted to evaluate the efficacy of this test on serum samples to diagnose invasive fungal infections, and more recently, studies have investigated the use of BDG testing on CSF (16–19). Although a review of BDG testing discussed CSF BDG testing for some fungal pathogens, a systematic review of CSF BDG testing has not been completed to date (18). This review aims to examine previous studies and reports of CSF BDG use in fungal meningitis to better understand the diagnostic utility of CSF BDG.

MATERIALS AND METHODS

This review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis of Diagnostic Test Accuracy (PRISMA–DTA) statement (20).

Search strategy. We searched PubMed (from inception until 7 February 2019) without any language restrictions using the terms "1,3 beta-D-glucan" AND each of the following: histoplasmosis, *Histoplasma capsulatum*, *Cryptococcus*, *Cryptococcus neoformans*, *Cryptococcus gattii*, cryptococcosis, coccidioidomycosis, *Coccidioides immitis*, blastomycosis, *Blastomyces dermatitidis*, aspergillosis, *Aspergillus flavus*, *Aspergillus fumigatus*, *Aspergillus niger*, mucormycosis, *Mucor mucedo*, *Candida*, *Candida albicans*, candidiasis, *Exserohilum*, *Exserohilum rostratum*, *Talaromyces*, *Talaromyces marneffei*, *Fusarium*, *Fusarium oxysporum*, *Paracoccidioides*, *Paracoccidioides brasiliensis*, *Paracoccidioides lutzii*, phaeohyphomycosis, *Scedosporium*, *Scedosporium prolificans*, sporotrichosis, *Sporothrix schenckii*, meningitis, and cerebrospinal fluid (Fig. 1).

Inclusion and exclusion criteria. Studies were included in the systematic review if they involved human subjects and measured BDG levels in CSF. Studies were excluded if they involved animal subjects or did not measure BDG in CSF (e.g., measured blood only). Due to the relative lack of cohort trials, case reports were also included.

Study selection and data extraction. Two authors (C.D. and N.C.B.) independently reviewed the studies and selected them for use in the review. The following data were then extracted from each study as available: details of publication (authors, country, and year of publication), organism(s) involved, study objective, number of patients, details of the diagnostic test, sensitivity and specificity, population, diagnosis of meningitis, intervention, follow-up period, control, and outcomes. No statistical analysis was completed, as a meta-analysis was not deemed feasible given the available studies.

RESULTS

The literature search produced 939 records, of which 118 remained after duplicates were removed. One hundred two studies were excluded due to not measuring CSF BDG levels. Sixteen full-text publications were examined, of which one additional study was excluded due to nonhuman subjects being included and another excluded due to its focus on *Nocardia* spp. rather than on fungal pathogens. Thus, of the 14 studies that were included in this systematic review (Fig. 1), 13 studies were from the United States, while one study included subjects from Uganda and South Africa. The causes of fungal meningitis examined in the studies are diverse and included *Cryptococcus*, *Coccidioides*, *Histoplasma*, *Aspergillus*, *Exserohilum*, and *Candida* spp. Eight studies were case reports or series, while seven were case-control studies. None of the studies included interventions based on BDG. Six of the studies determined diagnostic accuracy, although the cutoff level of CSF BDG used was not uniform. Twelve studies used the Fungitell assay (21–32). Two studies did not specify the method of BDG measurement (Table 1).

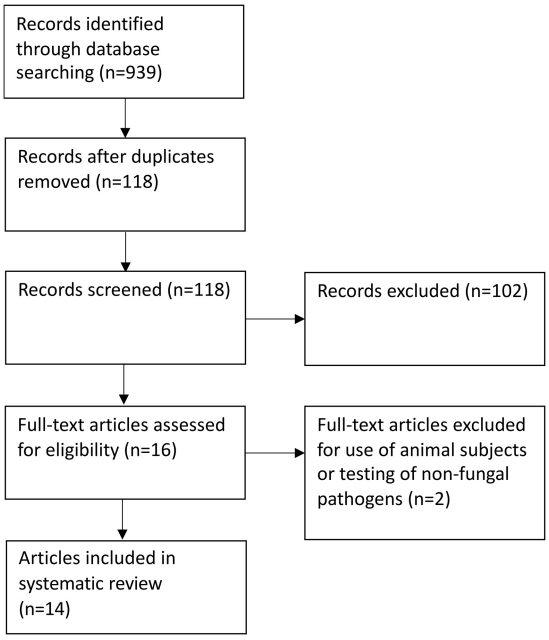

FIG 1 Flow chart of the study selection process demonstrating the number of records identified through PubMed queries. After duplicate records were removed, 118 studies were screened, and 104 studies were excluded based on the previously outlined criteria, which left a total of 14 records for this study.

***Candida*.** Ceccarelli et al. described persistent CSF BDG levels in a case of meningitis due to *Candida tropicalis* on proper treatment in the setting of negative CSF culture (21). Lyons et al. described the use of CSF BDG to monitor treatment efficacy in *Candida albicans* meningitis, finding a level of 500 pg/ml in CSF versus 74 pg/ml in serum (33). The positive CSF BDG levels preceded *Candida albicans* CSF culture growth. Myint and colleagues described two cases of *Candida* meningitis as part of a larger study of *Histoplasma* meningitis; one case had a CSF BDG level of 234 pg/ml, while the other had a level of <31 pg/ml (24). Finally, Salvatore and colleagues examined seven cases of *Candida* meningitis in children ($n = 4$, *Candida albicans*; $n = 2$, *Candida krusei*; $n = 1$, *Candida parapsilosis*), and two cases of *Aspergillus* meningitis were also included (29). This study described a median CSF BDG value of 230 pg/ml on initial testing and a decrease to <31 pg/ml in all successfully treated cases (29).

***Aspergillus*.** Salvatore and colleagues examined one proven and one possible case of *Aspergillus* meningitis (29). Mikulska and colleagues reported five patients with invasive CNS fungal infections, of which three were due to *Aspergillus* (27). The mean CSF BDG level for the three cases of *Aspergillus* meningitis was 383 pg/ml versus 41 pg/ml for 19 controls (27). Chen et al. reported a case of ventriculitis due to *Aspergillus fumigatus* which had elevated CSF BDG levels that seemed to rise in correlation with severity of magnetic resonance imaging (MRI) and clinical findings (34). Morgand and colleagues reported two cases of CNS infection due to *Aspergillus* spp. ($n = 1$ each of *Aspergillus fumigatus* and *Aspergillus flavus*), in which serum and CSF *Aspergillus* galactomannan antigen testing were negative, serum BDG was negative, and CSF BDG was positive (31). The previously noted paper by Myint and colleagues also reported two cases of *Aspergillus* meningitis, each with CSF BDG levels of >500 pg/ml (24).

***Exserohilum* spp. and other pathogens related to contaminated methylprednisolone.** *Exserohilum rostratum* gained notoriety as a potential human pathogen related to the widespread outbreak in the United States due to contaminated methylprednisolone acetate vials (22). Among 233 CSF specimens, including 28 proven cases of histopathological evidence of a fungal pathogen of fungal meningitis ($n = 27$ *E. rostratum*, $n = 1$ *A. fumigatus*), Malani et al. found a sensitivity of 96% (27/28) and a

TABLE 1 Characteristics of studies reporting the use of beta-D-glucan measurement in cerebrospinal fluid as a diagnostic test for fungal meningitis[a]

Outcome(s) measured	No. of controls	No. of cases	Organism	Study type or objective	Country/ies	Type of study	Cohort[b]
CSF BDG persistence	NA	1	*Candida tropicalis*	Descriptive	USA	Case report	Ceccarelli et al. (21)
CSF BDG	NA	1	*Aspergillus* spp.	Descriptive	USA	Case report	Chen et al. (34)[c]
Sensitivity	66	108 (41 definite, 67 probable)	*Exserohilum rostratum*	Diagnostic accuracy and response to treatment	USA	Case-control	Litvintseva et al. (22)
CSF BDG	NA	1	*Candida* sp.	Descriptive	USA	Case report	Lyons et al. (33)[c]
NA	NA	5	Unknown	Descriptive	USA	Case series	Lyons et al. (23)
NA	66	9	*Cryptococcus* spp., *Histoplasma* spp., *Exserohilum* spp.	Diagnostic accuracy	USA	Case-control	Lyons et al. (32)
Specificity, sensitivity	153	47	*Histoplasma* spp.	Diagnostic accuracy	USA	Case-control	Myint et al. (24)[d]
Specificity, sensitivity, decline over time	39	78	*Cryptococcus* spp.	Diagnostic accuracy and response to treatment	Uganda, South Africa	Case-control	Rhein et al. (25)
Specificity, sensitivity, PPV, NPV, decline over time	11	26	*Coccidioides* spp.	Diagnostic accuracy	USA	Case-control	Stevens et al. (26)
CSF BDG	19	5 ($n = 3$, *Aspergillus* spp.; $n = 1$, *Histoplasma* sp.; $n = 1$, *Cryptococcus* sp.)	*Aspergillus* spp., *Histoplasma* sp., *Cryptococcus* sp.	Descriptive	USA	Case-control	Mikulska et al. (27)
Sensitivity, specificity	135	28 ($n = 1$, *Aspergillus* spp.; $n = 27$, *Exserohilum* spp.)	*Exserohilum rostratum*, *Aspergillus* sp.	Diagnostic accuracy	USA	Case-control	Malani et al. (28)
CSF BDG	NA	9 ($n = 7$, *Candida* spp.; $n = 2$, *Aspergillus* spp.)	*Candida* spp., *Aspergillus* spp.	Descriptive	USA	Case series	Salvatore et al. (29)
CSF BDG	NA	1	Phaeohyphomycosis (exact pathogen unclear)	Descriptive	USA	Case report	Nelson et al. (30)
CSF BDG	NA	2	*Aspergillus* spp.	Descriptive	USA	Case series	Morgand et al. (31)

[a]CSF, cerebrospinal fluid; BDG, beta-D-glucan; NA, not available; PPV, positive predictive value; NPV, negative predictive value.
[b]Sensitivity/specificity values are reported in Table 2 when available.
[c]Study did not specify the assay used; all others reported use of the Fungitell assay.
[d]This study had among its controls 13 cases of other fungal meningitis including meningitis due to *Cryptococcus* ($n = 5$), *Blastomyces* ($n = 3$), *Candida* ($n = 2$), *Aspergillus* ($n = 2$), and *Coccidioidomyces* ($n = 1$).

specificity of 95% (128/135) using a BDG cutoff of 80 pg/ml and a reference standard of any CSF culture or PCR positive (28). Control CSF samples were obtained from persons exposed to contaminated methylprednisolone. When the reference standard was liberalized to include 17 probable cases of fungal meningitis (e.g., signs or symptoms felt to be highly suggestive of fungal meningitis), the sensitivity was 84% (38/45), and the specificity was 95% (128/135) (28). Litvintseva et al. (22) examined 41 cases of definite *E. rostratum* meningitis and 66 controls (27 exposed to contaminated methylprednisolone without meningitis, nine with bacterial meningitis, eight with viral meningitis, 1 with toxoplasmosis, and 21 without a known infection) related to the same outbreak. Sensitivity and specificity were 100% (41/41) and 98% (65/66), respectively, using a cutoff value of 138 pg/ml, and they were 99% (40/41) and 98% (65/66) at a cutoff of 230 pg/ml, respectively (22). If 67 additional probable cases were included

TABLE 2 Beta-D-glucan diagnostic performance on cerebrospinal fluid in fungal meningitis by cohort

Organism(s)	% (no./total no.) for:		CSF BDG concn cutoff used (pg/ml)[a]
	Sensitivity	Specificity	
Exserohilum rostratum (23)	100 (41/41)	98 (65/66)	138
	99 (40/41)	98 (65/66)	230
Exserohilum rostratum, *Aspergillus* species (30)[b]	96 (27/28)	95 (128/135)	80
Histoplasma capsulatum (26)	53 (25/47)	87 (133/153)	80
Cryptococcus neoformans (27)	89 (69/78)	85 (33/39)	80
Coccidioides species (28)	96 (25/26)	82 (9/11)	31

[a]The clinically recommended cutoff value is 80 pg/ml.
[b]Multiple organisms included in the cohort.

(108 cases total), sensitivity was 68% (73/108) and 65% (70/108) at cutoff values of 138 pg/ml and 230 pg/ml, respectively, with a specificity of 98% (65/66) in both cases (22). PCR was only 29% sensitive among cases of definite or probable *E. rostratum* meningitis (31/108) (22). Table 2 summarizes the diagnostic performace of CSF BDG measurement for various fungi based on the currently available evidence. The authors also noted that CSF BDG declined during testing of serial samples of 16 case patients who improved with treatment (22). In 3 patients, the CSF BDG level did not decline with treatment, and these patients all experienced worse clinical outcomes (22). Of note, this study did not use the cutoff value (80 pg/ml) listed on the package insert. Last, Lyons and colleagues reported that three of five cases of from the same outbreak (without a confirmed fungal etiology) had an elevated CSF BDG, with one that decreased with antifungal treatment (23); in another study, they reported two cases of *E. rostratum* meningitis with CSF BDG levels of 797 and 1,524 pg/ml, respectively (32).

Nelson and colleagues reported a case of a cerebral mycotic aneurysm presumed to be due to phaeohyphomycosis with symptom onset 17 days after a methylprednisolone infection (30). Although microbiological and molecular techniques were negative for a fungal pathogen, the CSF BDG level was >500 pg/ml (30). The patient received 32 weeks of antifungal treatment and was well a year after symptoms began (30).

***Cryptococcus*.** Rhein and colleagues examined CSF BDG in 78 subjects with cryptococcal meningitis and 39 controls suspected to have other forms of meningitis; all subjects were HIV infected, with low CD4 counts (25). The median CSF BDG levels were 343 pg/ml among cases and 37 pg/ml among controls (25). CSF BDG sensitivity was 89% (69/78), and specificity was 85% (33/39) using a cutoff value of 80 pg/ml (25). Additionally, the sensitivity improved to 98% when the initial fungal burdens were above or equal to 10,000 CFU/ml (25). Interestingly, CSF BDG levels did decrease more rapidly than did cryptococcal antigen levels (25). Among six cases of cryptococcal meningitis, Lyons and colleagues found that five cases had detectable CSF BDG (though all were <80 pg/ml). Among 66 persons without CNS fungal infections, the median CSF BDG level was 13.5 pg/ml (range, <4 to 109 pg/ml), well below 80 pg/ml, the typical cutoff used clinically (32). Myint and colleagues described five cases of cryptococcal meningitis as part of a larger study of *Histoplasma* meningitis, and three of the five cases had CSF BDG levels above 80 pg/ml (82, 221, and 500 pg/ml) (24). Mikulska and colleagues also reported one case of BDG measurement in cryptococcal meningitis (27).

***Histoplasma*.** Myint and colleagues (24) examined 47 persons with meningitis caused by *Histoplasma capsulatum*, including 9 confirmed via CSF culture, 33 probable via detection of *Histoplasma* antigen by enzyme immunoassay (EIA) or anti-*Histoplasma* antibodies in the CSF by immunodiffusion (ID) or complement fixation (CF), 5 possible with pulmonary or disseminated histoplasmosis with CSF pleocytosis but without laboratory confirmation of CNS involvement and no alternative etiology for the CSF pleocytosis, and 153 controls. They found CSF BDG levels of ≥80 pg/ml in 25/47 cases, with a median of 85 pg/ml among cases and a median of <31 pg/ml among controls (24). The sensitivity and specificity of CSF BDG were 53% (25/47) and 87% (133/153), respectively (24). Interestingly, 13 subjects with other fungal meningitis were among the controls (referred to in the paragraph related to the particular pathogen throughout the manuscript), with a median CSF BDG level of 82 pg/ml. Seven of those 13 controls with other fungal meningitis had CSF BDG levels of >80 pg/ml, and if those 13 subjects were excluded, specificity for *Histoplasma* meningitis rose to 91% (127/140) (24). Mikulska and colleagues (27) reported one case of BDG measurement in *Histoplasma* meningitis (282 pg/ml), as did Lyons and colleagues (110 pg/ml) (32).

***Coccidioides*.** Stevens et al. tested 26 CSF samples from 21 patients with confirmed coccidioidal meningitis and 11 control CSF samples (from 11 subjects). Any positive CSF coccidioidal antibody or culture in a subject with clinical meningitis was used as the reference standard (26). A cutoff value of 31 pg/ml was used. Sensitivity was 96%

(25/26), specificity was 82% (9/11), the positive predictive value was 93% (25/27), and the negative predictive value was 90% (9/10) (26). Performance with a cutoff of 80 pg/ml was not given, and exact CSF BDG values are not given here. Interestingly, some samples maintained positive CSF BDG levels for up to 8 years (26). One case of *Coccidioides* meningitis was also described by Myint and colleagues in their histoplasmosis study, in which the CSF BDG level was <31 pg/ml (24).

***Blastomyces*.** The study by Myint and colleagues (24) looking at CSF BDG diagnostic performance for *Histoplasma* meningitis described three cases of *Blastomyces* meningitis; all were CSF culture negative. Case one had a positive CSF *Blastomyces* antigen and bronchoalveolar lavage fluid culture with *Blastomyces* sp., and the CSF BDG level was 79 pg/ml. Case two also had positive CSF and urine *Blastomyces* antigen tests; postmortem leptomeningeal tissue Grocott's stain was consistent with *Blastomyces*, and the CSF BDG level was 176 pg/ml. Case three had a positive *Blastomyces* urine antigen result and bronchoalveolar lavage fluid culture, a negative CSF *Blastomyces* antigen test, and a CSF BDG level of 61 pg/ml (24).

DISCUSSION

Fungal meningitis is caused by several organisms, and testing accuracy varies with each organism. Delay in diagnosis and treatment leads to poor outcomes. While not specific for any particular cause of fungal meningitis, CSF BDG measurement may hold some utility as a marker of fungal disease, particularly in cases of subacute meningitis without clear etiologies.

This systematic review of the currently available studies of CSF BDG measurement has several limitations, primarily related to the small overall numbers of studies available, small overall numbers of cases (aside from *Exserohilum*, *Histoplasma*, and *Cryptococcus* spp.), and study heterogeneity. Due to the small numbers of studies and different CSF BDG cutoff values used, we felt that a meta-analysis could not be performed. Further, we can only comment on the specific fungi examined by the included studies and so cannot comment on the utility of CSF BDG measurement for other fungal causes of meningitis. In addition, we are not able to comment on the role of common causes of false-positive serum BDG results, such as bowel surgery treatment with immunoglobulin, albumin, or other blood products filtered through cellulose filters containing BDG, patients undergoing hemodialysis with cellulose membranes, or the use of certain antibiotics, as none of the studies addressed these issues (35–38).

In *Candida* meningitis, only case reports were available; thus, we cannot comment on diagnostic performance for CSF BDG measurement in this disease. Yet, some authors posited that CSF BDG may have a role in monitoring treatment response given the poor diagnostic performance of fungal culture. CSF BDG measurement in preterm infants with known *Candida* disease at other sites has also been considered. Whether or not CSF BDG can be relied upon in this situation is uncertain.

In meningitis due to *Aspergillus* or *Blastomyces* spp., though CSF BDG may be positive, its diagnostic performance (e.g., sensitivity, specificity, etc.) is unclear. CSF BDG measurement showed perhaps the most promise in a formal diagnostic study in persons with CNS infection due to *Exserohilum rostratum*. Yet, although one study found sensitivity and specificity at >98% (at higher cutoffs than typical), another study could not replicate these findings (22, 28).

Cryptococcus spp. are often thought not to have sufficient BDG levels to cause positive test results based on a small study of seven subjects without HIV infection with pulmonary cryptococcosis and negative plasma BDG levels; in cryptococcal meningitis, this is clearly not true (25, 39). In the only study to systematically investigate CSF BDG in cryptococcal meningitis, sensitivity was 89% (69/78) (25). Although CSF BDG was not as effective as a cryptococcal antigen, it may have some role in differentiating immune reconstitution inflammatory syndrome (IRIS) from true relapse of disease, as it cleared quickly from the CSF in one study (25). This finding, however, has not been duplicated, and the ability of CSF BDG to differentiate IRIS from relapse is conjecture at this point. Probably the most important take-home point in regard to *Cryptococcus* and CSF BDG

is that a positive CSF BDG may, in fact, be due to *Cryptococcus* spp. (e.g., one should not presume noncryptococcal fungal disease on the basis of a positive CSF BDG result alone). CSF cryptococcal antigen remains the test of choice for cryptococcal meningitis.

The performance of CSF BDG was inadequate for meningitis due to both *Histoplasma* spp. (sensitivity, 53%) and *Coccidioides* spp. (specificity, 82%). Interestingly, a positive CSF BDG was noted up to 8 years after initial diagnosis in some cases of coccidioidomycosis meningitis, as opposed to its rapid clearance with cryptococcal meningitis (24, 26). Yet, the use of 31 pg/ml as a cutoff value in this study makes this finding (and the overall accuracy of the test) difficult to interpret for *Coccidioides* meningitis.

One advantage of the CSF BDG test compared to waiting for fungal cultures is that the turnaround time is relatively brief. Of the studies examined in this systematic review, only one study had information on the length of time needed to process CSF BDG. This study demonstrated that assays performed by Beacon Diagnostics Laboratory had a turnaround time of 48 to 96 h for CSF BDG (29). In Kansas City, a local laboratory typically gets results back to our facility in ~48 h.

Clinically, the role of monitoring CSF BDG during treatment has been demonstrated to be potentially useful in some settings. Rhein and colleagues showed that CSF BDG decreased more rapidly than did the CSF cryptococcal antigen during treatment (25). Litvintseva and colleagues also studied this effect and found that CSF BDG levels declined with treatment except in patients who had poor clinical outcomes in their study of *Exserohilum rostratum* cases (22). Clearly, additional data are needed to draw stronger conclusions; however, in cases of fungal meningitis with high CSF BDG levels at baseline, it may be reasonable to track levels with any repeat lumbar puncture to assess treatment response. Whether or not this also indicates that antifungal therapy prior to CSF BDG measurement might decrease levels is unclear, though this would be theoretically possible. None of the studies comment on the timing of antifungal therapy relative to initial CSF BDG testing.

Despite our intensive search, we found no reported cases of measuring CSF BDG in patients with meningitis caused by *Talaromyces*, *Fusarium*, *Paracoccidioides*, or *Scedosporium* spp. or sporotrichosis.

Future studies must address potential causes of false-positive BDG results, and particular focus should be given to those causes of fungal meningitis without adequate current methods of diagnosis if feasible. Further, any study of CSF BDG for fungal meningitis should report test performance using the approved cutoff of 80 pg/ml, even if other experimental cutoffs are reported as well. In one case, one of the few indications of ongoing infection was an elevated CSF BDG level, suggesting a possible role as a screening test in persons without a clear cause of subacute meningitis (30). One may consider CSF BDG measurement as a screening tool for fungal meningitis broadly, but to do so, one must also recognize inadequate specificity for any particular fungal etiology as well as inferior performance for some more specific tests, such as cryptococcal antigen testing, and uncertainty for many types of fungal meningitis. Thus, the use of CSF BDG measurement should be considered with caution and should not replace more specific testing.

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C.D. was involved in the literature search, data collection, data interpretation, writing, and figures. L.J.W., T.M., and D.R.B. performed a critical review of the manuscript and data interpretation. N.C.B. was involved in the literature search, data collection, data interpretation, writing and revision of the manuscript, and study design.

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