

# Incidence of Endogenous Fungal Endophthalmitis in Screening Dilated Exams in Patients with Elevated Beta-D-Glucan Levels versus Positive Fungal Blood Cultures

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**Purpose:** Endogenous endophthalmitis is a severe intraocular infectious condition requiring rapid diagnosis and treatment. This study examines the incidence of fungal endophthalmitis in patients with elevated beta-D-glucan (BG) levels and those with positive blood culture and the utility of ophthalmology consultation in these patients.

**Methods:** Single center retrospective consecutive cohort study was conducted on patients at Beaumont Health from 2016–2021 who either had positive fungal blood cultures or an elevated BG level.

**Results:** A total of 147 patients were examined by the ophthalmology department where 30 patients had an elevated BG level and 100 patients had a positive fungal blood culture. Incidence of fungal endophthalmitis was 0% in the elevated BG group and 1.5% in the positive fungal culture group, corresponding to a relative risk ratio of 0.0 ( $p = 0.31$ ).

**Conclusion:** BG testing may be useful in diagnosing isolated cases outside the standard screening paradigm, however the data within this study support the conclusion that there is no compelling evidence at this time to add or use BG as a surrogate for endophthalmitis screening. Further studies are required to further elucidate the role of BG in the care of critically ill patients.

**Keywords:** endophthalmitis, candidemia, chorioretinitis, infectious disease

## Introduction

Endophthalmitis is a severe intraocular inflammatory condition usually caused by infection. Exogenous endophthalmitis is more common and typically arises as a postsurgical complication or in the setting of trauma resulting in an open globe.<sup>1</sup> Endogenous endophthalmitis is a potentially visually devastating condition resulting from hematogenous spread of an infection from a systemic source to the eye.<sup>2</sup> Fungemia is more commonly observed in patients who are on chronic total parenteral nutrition or those who are immunocompromised, such as those with diabetes mellitus, malignancy, chronic steroid use, or those with human immunodeficiency virus (HIV).<sup>3</sup> As the prevalence of patients with health conditions that put them at risk for fungal infections increases,<sup>4</sup> it becomes increasingly important for rapid identification and treatment of systemic fungal infections and evaluation of possible ocular involvement. Since patients with fungemia may develop asymptomatic ocular involvement, the current recommendation from the Infectious Disease Society of America is for patients who have positive fungal blood cultures to undergo ophthalmic examination to evaluate for intraocular fungal infection.<sup>5</sup>

Recently, the beta-D-glucan (BG) assay has been used as a screening device for systemic fungal infections. The BG test is a quantitative assay approved by the Food and Drug Administration in 2004, and its goal is to provide early detection of invasive

fungal infections. As fungal species divide, the fungal cell wall is continuously remodeled and some BG is released into the bloodstream and can aid in the detection of systemic fungal infections.<sup>6</sup> In comparison, fungal cultures rely on growth of an entire organism rather than identification of molecular marker. Depending on the media used, the time to detection of fungal species in blood cultures can vary greatly, from within 24 hours to over 100 hours, with varying sensitivity.<sup>7,8</sup> Conversely, the BG test can be completed as quickly as 1 hour.<sup>9</sup> However, the literature regarding the necessity for inpatient ophthalmology consultation to rule out fungal endophthalmitis in cases of elevated BG levels without fungal blood culture data at the time of consultation is limited. This paper reports the incidence of fungal endophthalmitis in patients who have elevated BG levels without fungal blood culture data at the time of consultation and in patients who have positive fungal blood cultures and the utility of ophthalmology consultation in patients with elevated BG levels.

## Methods

### Study Design

This study was a retrospective, consecutive cohort study of patients at Beaumont Health, Royal Oak, Michigan. This study was performed with the approval of the Institutional Review Board and with the standards delineated in the Declaration of Helsinki. Using ICD-10 and ICD-9 codes, patients were identified who were admitted to William Beaumont Hospital, Royal Oak, diagnosed with positive fungal blood cultures or elevated BG levels, and had an inpatient ophthalmology consultation over a 63-month period from 2016–2021. Patient charts were then manually reviewed and patients were separated based on whether they had positive blood cultures or an elevated BG level. A BG level of at least 80 pg/mL was considered a positive test based on review of the literature.<sup>6</sup> Patients who received an initial ophthalmology consultation for an elevated BG result were included. The patient was examined within 24 hours of a positive fungal blood culture or elevated BG result. Exclusion criteria were history of previous severe intraocular inflammation or history of ophthalmic surgery within 1 month prior to consultation. At the admitting provider's discretion, micafungin was started within 24 hours prior to ophthalmic evaluation of the patient and within 24 hours of initial blood culture growth.

### Data Collection

Demographic data, visual acuity, intraocular pressure, pupil assessment, dilated funduscopic features, BG levels, fungal blood culture results, and systemic and intravitreal anti-fungal therapy utilized were obtained from patient charts. All patients were initially evaluated by a single ophthalmologist (LAS) during this time period. If there was clinical concern for fungal endophthalmitis, examination and treatment was then performed by a vitreoretinal specialist. The definition of fungal endophthalmitis was defined as chorioretinitis with surrounding vitreous inflammation or a vitreous abscess manifesting as intravitreal fluff balls.<sup>10</sup>

After the vitreoretinal specialist had diagnosed a patient with fungal endophthalmitis, the patient was then treated with oral or intravenous antifungals, intravitreal antifungal medication, and/or a vitrectomy. The decision for vitrectomy was based upon severity of retinal findings and inflammation at initial visit or response to intravitreal antifungals. In addition, the frequency of follow-up examinations were determined at the discretion of the vitreoretinal specialist taking care of the patient. Patients who had a completely unremarkable initial examination and were alert, oriented, and did not communicate any visual symptoms, were no longer followed by the ophthalmology department. If there were no signs of vitritis or chorioretinitis but retinal hemorrhages and cotton wool spots were present, as these may indicate possible chorioretinitis,<sup>10</sup> the patient underwent repeat examination in less than a week to ensure stability of findings. If these fundoscopic findings were found to be stable on two follow-up examinations, no further examinations were done. For patients who had no signs of fungal endophthalmitis or chorioretinitis but were altered and unable to communicate vision changes, a follow-up examination was performed in a week and, if findings were stable, no further examinations were performed.

### Statistical Analysis

A descriptive analysis was performed on the data collected. Visual acuity was measured using a near card and converted to logMAR equivalents using standardized methods. The incidence of presumed fungal endophthalmitis in the two

groups (patients with elevated BG level alone without fungal blood culture data at the time of consultation and patients with positive fungal blood cultures) was performed and a relative risk ratio was calculated.

## Results

After examination of the data, 147 patients were identified as having an inpatient ophthalmology consultation to rule out presumed fungal endophthalmitis and either an elevated BG level or a positive fungal blood culture at the time of consultation. In the elevated BG group, 60 eyes of 30 patients were included and 200 eyes of 100 patients in the positive fungal blood culture. Eleven patients were excluded for having an ophthalmology consultation and BG level below 80 pg/mL. Six patients were excluded because they had died before a full ophthalmic examination could be completed. At the time of consultation for patients in the elevated BG group, no fungal culture data were available. However on past review of patients in the elevated BG level group, 25% had negative fungal cultures. The mean age of patients was 58.3 years with a standard deviation (SD) of 16.9 years. Males made up 40% of the patients, and 60% of the patients were female. Mean visual acuity (VA) for patients with presumed fungal endophthalmitis was 20/190 (logMAR 0.98) and for patients without presumed fungal endophthalmitis VA was 20/35 (logMAR 0.25) (range 20/20 to NLP). Two patients had NLP vision in one eye on examination and based on clinical examination and history, it was determined to be from a prior ophthalmic artery occlusion and glaucomatous optic neuropathy. None of the patients diagnosed with presumed fungal endophthalmitis had a chronic indwelling catheter. All presumed fungal endophthalmitis patients had an intravitreal sample that was sent for culture, however all culture results returned negative. Out of the fungal endophthalmitis patients, 1 patient had a history of cancer undergoing active chemotherapy and radiation while 2 patients had a history of diabetes and intravenous drug abuse. All three patients in the positive fungal culture group grew *Candida albicans*. There were 0 of 60 eyes (0%) in the elevated BG level group and 3 of 200 eyes (1.5%) in the positive fungal blood culture group that had clinical features suspicious for fungal endophthalmitis (Table 1). Forty-nine patients or 98 eyes (33%) had no VA recorded in the electronic medical record as they were intubated and sedated at the time of examination. Additionally, all these patients were in the fungal culture group (Table 2). This corresponded to a relative risk

**Table 1** Beta-D-Glucan and Fungal Culture Patient Demographics

	Elevated BG Level (>80 pg/mL) (No Fungal Endophthalmitis)	Positive Fungal Blood Culture (No Fungal Endophthalmitis)	Elevated BG Level (>80 pg/mL) (Fungal Endophthalmitis)	Positive Fungal Blood Culture (Fungal Endophthalmitis)
<b>Age (years)</b>				
Mean	58	59	–	45
Minimum	19	19	–	32
Maximum	86	91	–	63
<b>Visual Acuity</b>				
Snellen Visual Acuity				
Mean	20/21	20/21	–	20/133
LogMAR Visual Acuity				
Mean	0.018	0.017	–	0.83
<b>Sex (no. of patients)</b>				
Male	15	32	–	3
Female	15	65	–	0
<b>Incidence</b>	–	–	0.00%	1.50%
<b>Relative Risk Ratio</b>			0.0 (p=0.30)	

**Table 2** Characteristics of Patients with Clinical Fungal Endophthalmitis

	Age at Time of Consultation	Relevant Medical History	BCVA (Snellen Visual Acuity)	BG Level (pg/mL)	Fungal Culture	Intravitreal Culture		Initial Exam		Intravitreal Treatment	Intravenous Treatment	BCVA on Final Follow Up (Snell Visual Acuity)	Days between Inpatient Consultation and Last Follow Up	Duration of Therapy
<b>Elevated BG</b> Eye 1 (Ruled as not fungal endophthalmitis)	62	Type 2 DM, ESRD with dialysis catheter	CF 1ft	394	–	Negative culture	Vitreous Vitritis	Macula White chorioretinal lesion superiorly	Periphery Diffuse dot blot hemorrhages	Vancomycin Ceftazidime Voriconazole	Vancomycin	LP	467 days (expired after last follow up)	6 weeks Vancomycin
<b>Positive Fungal Blood Culture</b>														
Eye 2	65	Recurrent anal squamous cell carcinoma on chemotherapy and radiation	20/100	–	Candida albicans	Negative culture	Vitritis	Two chorioretinal lesions with overlying vitreous haze	Within normal limits	Voriconazole	Micafungin voriconazole	20/200	14 days (patient expired inpatient)	14 days
Eye 3	34	Type 1 DM, intravenous drug abuse	20/800	–	Candida albicans	Negative culture	Vitritis	2 large white chorioretinal lesions with pre-retinal hemorrhage	2 white chorioretinal lesions	Voriconazole	Voriconazole	CF 1ft	215 days (expired after last follow up)	6 weeks Fluconazole
Eye 4	40	Type 1 DM, intravenous drug abuse	20/30	—	Candida albicans	Negative culture	Vitritis	2 large white chorioretinal lesions with pre-retinal hemorrhage	5 white chorioretinal lesions	Voriconazole	Voriconazole	20/50	200 days (expired after last follow up)	6 weeks Fluconazole

ratio of 0 ( $p = 0.31$ ) when comparing the number of presumed fungal endophthalmitis cases in the BG level group to the positive fungal blood culture group (Table 1).

The remainder of patients that were followed closely by ophthalmology in the positive fungal culture group had evidence of fungal chorioretinitis without vitritis, which did not meet our criteria of presumed fungal endophthalmitis.

## Discussion

As the life expectancy of the average adult continues to increase, so does the chance for developing health conditions that put them at risk for developing an invasive fungal infection.<sup>4</sup> Proper care for these patients requires a multidisciplinary approach including internal medicine, ophthalmology, infectious disease, and potential other subspecialties depending on the underlying medical condition. One review at the University of California Los Angeles Medical Center showed ruling out fungal endophthalmitis was the second most common reason to request an inpatient ophthalmology consultation.<sup>11</sup> Fungal infections, whether intraocular or extraocular, carry a high morbidity and mortality rate and rapid detection and treatment of such infections becomes paramount.<sup>4</sup> With the increasing use of the BG test and limited literature regarding ophthalmology's role in ruling out fungal endophthalmitis in patients, we wished to initiate discussion regarding this subject.

Within this report, a diagnosis of presumed fungal endophthalmitis was made at incidence of 0% in the elevated BG group and 1.5% in the positive fungal blood culture group, corresponding to a relative risk ratio of 0.0 ( $p = 0.31$ ). Out of the 3 eyes that had presumed fungal endophthalmitis, 1 patient had a history of cancer undergoing active chemotherapy and radiation while 2 patients had a history of diabetes and intravenous drug abuse. All three patients in the positive fungal culture group grew *Candida albicans*. None of the patients with presumed fungal endophthalmitis had an indwelling urinary catheter. There was one eye in the BG group where there was clinical suspicion of fungal endophthalmitis. However 4 days after the initial ophthalmic examination, fungal blood cultures did not grow any organisms but a blood culture did grow methicillin-resistant *Staphylococcus aureus* (MRSA). This patient was taken for vitrectomy due to worsening vision and aerobic, anaerobic, and fungal cultures were done on the vitreous sample which was negative for infectious etiology, however this was approximately 1 week after intravenous antibiotics and intravitreal administration of antibiotics and antifungals. Based on blood culture results, this may represent a case of bacterial endophthalmitis rather than fungal endophthalmitis.

As part of a general overview of fungal chorioretinitis and fungal endophthalmitis, this is an entity that can be difficult to diagnose, especially within critically ill patients. Rodríguez-Adrián et al describe that fundusoscopic findings such as cotton wool spots, retinal hemorrhages, or Roth spots can be visualized in critically ill patients as they often have systemic conditions that can explain these findings compared with classically 3 dimensional lesions more indicative of an infectious process.<sup>12</sup> With these patients it becomes critically important to perform serial examinations to ensure stability of findings.<sup>12</sup> Therefore it becomes important to examine the importance of ancillary testing such as blood culture results and BG testing in guiding management and elevating clinical suspicion for endogenous intraocular infections.

Prior studies have commented on the importance of patient selection prior to performing a BG test, otherwise interpretation of the test can be difficult due to the factors that can cause false positive results.<sup>13,14</sup> For example, the BG test can be falsely elevated for the following reasons: hemodialysis with cellulose membranes,<sup>15,16</sup> administration of human blood products,<sup>17</sup> use of  $\beta$ -lactam antibiotics,<sup>18</sup> bacterial infections,<sup>19</sup> and even surgical gauze containing glucan.<sup>20</sup> Due to these confounding variables, having an elevated BG level may not necessarily correlate to an invasive fungal infection that would put a patient at risk for fungal endophthalmitis. Regarding this, it is likely then that our patient in the elevated BG level group had an elevated BG level due to systemic bacteremia.

Since the development of the BG assay, many studies have evaluated the diagnostic utility of this test. Multiple studies have commented on the statistical accuracy of the BG assay in detecting an invasive fungal infection. Pickering et al asserted that their study, among others, showed a very high negative predictive value (NPV) upwards of 95%, while having a lower positive predictive value (PPV) ranging from 51.9% with a specificity of 77.2% when patients had concomitant bacteremia and BG testing.<sup>19</sup> Of note, PPV and NPV range widely depending on the particular study, patient selection, and concurrent disease. A review by Theel et al describes PPV ranging from 30–89% and NPV ranging from 73–97%, hence further emphasizing patient selection prior to ordering a BG test due to the high number of false positives.<sup>21</sup> It is interesting to note that although fungal cultures are considered the gold standard for diagnosing invasive fungal infections, the sensitivity varies significantly based on the media used and is estimated to be 50%.<sup>7</sup>

Nevertheless, BG levels may still have a role in assisting with the diagnosis of fungal endophthalmitis. Chen et al described a short case series where 5 patients with clinically diagnosed fungal endophthalmitis had elevated intraocular BG levels and some of these cases had no systemic culture data.<sup>22</sup> Out of the 5 patients, 2 had either negative or no fungal blood culture data and these patients had improvement on appropriate intravitreal anti-fungal therapy. Ammar et al describes the use of BG testing in conjunction with patients who already have a clinical diagnosis of fungal endophthalmitis or positive blood cultures, stating that it may serve as a useful adjunctive test or if there is a high clinical suspicion of fungal endophthalmitis.<sup>23</sup> Kolomeyer et al discussed an interesting case where there was a clinical suspicion for fungal endophthalmitis and the elevated BG level helped guide the clinical management.<sup>24</sup> Despite this, few data exist on using BG as an initial screening tool to involve ophthalmology to rule out fungal endophthalmitis.

It is important to draw knowledge from current recommendations regarding screening ophthalmic exams regarding fungal endophthalmitis. In a study in 2019, Breazzano et al published a paper discussing that screening all patients with positive fungal blood cultures regardless of symptoms does not necessarily improve outcomes for patients.<sup>25</sup> This led to a recent change in the American Academy of Ophthalmology (AAO) recommendations that only symptomatic patients should be screened if they present with positive fungal blood cultures.<sup>26</sup> Although BG testing is an emerging test and there are no official recommendations regarding the utility of ophthalmology consultation together with elevated BG testing, preliminary results in our study show a statistically non-significant difference in incidence of fungal endophthalmitis between patients with initially elevated BG levels and positive fungal blood cultures. Likely future recommendations regarding BG testing may mimic official AAO recommendations regarding screening of patients with positive fungal blood cultures, however further studies with larger sample sizes will need to be conducted.

Limitations to this study included a relatively small sample size of patients with elevated BG levels. Having more patients to evaluate in this group would help increase the power of our study. In some cases, systemic micafungin may have been started as soon as an elevated BG level is seen and may have been done before an ophthalmologist, however we believe that this does not affect the results of our study as a Muñoz et al showed that intraocular fungal infections were not found to be more common between patients treated with echinocandins compared with candins or other antifungal regimens.<sup>27</sup> In addition, prior studies have shown that with intravenous therapy, micafungin has poor aqueous humor and vitreous penetration.<sup>28,29</sup> Lastly, our diagnosis of presumed fungal endophthalmitis was made on clinical features only and all patients had negative vitreous biopsy. However all patients had classic clinical features of endophthalmitis diagnosed by a vitreoretinal specialist, and we believe that due to significant vitreous inflammation, acquiring an adequate enough vitreous sample at the bedside to make a microbiological diagnosis of infectious endophthalmitis was why the cultures were negative.

The beta-D-glucan quantitative assay is a relatively new test that is gaining significant utility in critically ill patients. BG testing may be useful in diagnosing isolated cases outside the standard screening paradigm, however the data within this study support the conclusion that there is no compelling evidence at this time to add or use BG as a surrogate for endophthalmitis screening. Clinical correlation is crucial as there are multiple causes of a falsely elevated BG and these may lead to unnecessary examinations and overuse of invasive procedures which can be a significant cost to the patient. Continued study is needed to further elucidate the role of BG in guiding its use as ancillary testing and in ophthalmic screening exams for critically ill patients.

## Ethical Approval

This was conducted in accordance with the Declaration of Helsinki. The collection and evaluation of all protected patient health information was performed in a Health Insurance Portability and Accountability Act (HIPAA) compliant manner and under approval by the Institutional Review Board of William Beaumont Hospital (IRB Number 2020-441).

## Statement of Informed Consent

Informed consent was obtained prior to performing the procedure, including permission for publication of all photographs and images included herein.

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