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Vitreoretinal Involvement in Patients With Fungemia at a Tertiary Care Hospital

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Abstract

Purpose: To identify the prevalence of fungal ophthalmic involvement and evaluate risk factors for positive screening for inpatients at an academic tertiary care hospital by assessing a priori screening criteria that may determine which patients need ophthalmic evaluation. **Methods:** This retrospective cohort study comprised patients with a documented positive blood culture for fungemia and an ophthalmic screening examination from January 1, 2015, to September 30, 2019. Ophthalmology notes and laboratory results taken during admission were evaluated. The primary outcomes were ocular involvement, the presence of visual complaints, and the duration of blood culture positivity. Variables assessed included recent gastrointestinal surgery, organ transplantation, HIV infection, diabetes mellitus, intravenous drug use, and central venous access. Analyses, including the Student *t* test, χ^2 test, and logistic regression, were performed. **Results:** Of 291 patients with fungemia, 7 had ocular involvement (3 with chorioretinitis; 4 with endophthalmitis). One patient with endophthalmitis required an intravitreal antifungal injection. No patient with chorioretinitis required injections or surgery. The mean culture positivity length was 5 days for those with vitreoretinal involvement and 4 days for those without vitreoretinal involvement ($P > .05$). Of patients with ocular involvement, 40.0% had a visual complaint compared with 4.2% without ocular involvement ($P < .05$). The negative predictive value was 99.3% for patients without complaints or persistent fungemia. **Conclusions:** Patients with visual complaints at the time of a positive blood culture for fungemia are at risk for ocular disease and require screening.

Keywords

fungemia, endophthalmitis, ophthalmic screening, chorioretinitis

Introduction

The incidence of fungal septicemia is increasing in the United States. Several factors are involved, including increased numbers of solid organ transplantations, rapid development of new immunosuppressive medications for immune and oncologic conditions, and overall improved mortality rates resulting from the conversion of once fatal diseases into chronic conditions.[1]

Fungemia can lead to multiorgan system failure in patients with the spread of infection, including the risk for fungal chorioretinitis and endophthalmitis, which may result in permanent vision loss or blindness. Triazole antifungal medications can clear fungal infection from the bloodstream within 72 hours and are known to have good penetration across the blood–brain barrier.[2] Therefore, these medications are used to prevent and treat end-organ fungal involvement, including intraocular disease.

Recent studies showing low rates of intraocular infections in patients with fungemia reflect the advances made in infectious diseases to treat the condition. This prompted the American Academy of Ophthalmology (AAO) to recommend that ophthalmic examinations be performed only for patients with fungemia who have signs and symptoms of ocular disease.[3]

Vision loss among patients with fungemia appears to be exceedingly rare.[4–6] A large systematic review of the literature reported a 0.9% rate of ocular involvement, with only 15.8% of those affected requiring ophthalmic intervention, with high mortality in that cohort.[7] This study was the motivation for the AAO's

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recommendation. The Infectious Disease Society of America (IDSA), however, has not yet changed its recommendation for universal ophthalmic screening on all non-neutropenic patients with fungemia within 1 week of a positive blood culture, despite the AAO guideline.[8] The current recommendation is deemed a strong one, with low-quality evidence by the IDSA; however, the AAO recommendation lacks the ability to provide specific criteria for which patients require screening, and thus disagreement persists.

Previously there was consensus that the management of patients with fungemia should consist of routine, universal ophthalmic examinations that include a dilated fundus examination to rule out ocular involvement. Previous studies reported rates of ocular involvement as high as 40% in patients with fungemia, representing a significant risk for severe vision loss.[4] As infectious disease treatments improved, however, ophthalmologists recognized that the incidence of positive screening examinations in this patient cohort was decreasing precipitously. More recent studies in the ophthalmic literature report a 1% to 9% incidence among these patients and, perhaps more important, an even lower rate of ophthalmic intervention or vision loss because most patients' disease will respond to intravenous therapy alone.[7]

Here, we present the findings of our study, which to our knowledge is the largest reported cohort to date of patients with fungemia screened by an ophthalmic consult service. We sought to identify clinically and statistically significant risk factors for fungal endophthalmitis that clinicians can reliably use as screening criteria.

Methods

This retrospective cohort study included consecutive inpatients with fungemia and a documented ophthalmic evaluation from January 2015 to September 2019. Vitreoretinal involvement (ie, vitritis) was defined as evidence of active chorioretinitis and endophthalmitis. This study was approved by the Institutional Review Board, Icahn School of Medicine at Mount Sinai (IRB #20-01712), and adhered to the tenets of the Declaration of Helsinki.

The primary variables of interest were the presence of a visual complaint and the duration of positive blood cultures. Symptoms included vision loss, persistent blurry vision despite adequate ocular lubrication, new floaters or visual field loss, or persistent diffuse conjunctival injection and photophobia not otherwise explained by ocular surface disease. Patients who were nonverbal at the time of evaluation were excluded from the analysis of the symptomatic variable only. Persistent fungemia was defined as any patient with 2 positive blood cultures at least 48 hours apart, in line with IDSA criteria. Other variables (minor criteria) assessed included a history of gastrointestinal surgery in the preceding 6 months, solid organ transplantation, HIV infection, diabetes mellitus (DM), intravenous drug use, and concomitant or recent (<72 hours) central venous access.

Statistical analysis with the Student *t* test was performed using Stata 16 software (release 16, Stata Statistical Software, StataCorp LLC). The χ^2 test and then logistic regression were used to discern whether any factors were associated with positive blood cultures. Data were analyzed using SAS software (version 9.4, SAS Institute).

Table 1. Baseline Patient Characteristics (N = 291).

Characteristic	Value
Sex, n (%)	
Male	56.4
Female	43.6
Age (y)	
Median	57
Mean	54.0
Risk factors	
Mean number of positive blood cultures	2.85
Mean duration of positive blood cultures (wk)	0.59
Gastrointestinal surgery within the previous 6 months, n (%)	122 (41.9)
History of solid organ transplantation, n (%)	75 (25.8)
Immunocompromised status, n (%)	205 (70.4)
HIV infection, n (%)	12 (4.1)
Diabetes mellitus, n (%)	73 (25.1)
Intravenous drug use, n (%)	4 (1.4)
Central venous access, n (%)	126 (43.3)
Mean length of antifungal therapy (wk)	2.65
Ocular complaint, n (%)	14 (4.9)

Results

The study included 291 consecutive patients with fungemia; 93 patients were nonverbal and were excluded from the analysis of the symptomatic variable. Of the 291 patients, 7 had ocular involvement (2.4%), 4 with chorioretinitis and 3 with endophthalmitis (1.0%) (Table 1). One patient with endophthalmitis received a single intravitreal (IVT) antifungal injection (0.34%). Two patients with endophthalmitis improved on systemic antifungals alone. All patients with isolated chorioretinitis improved on systemic therapy alone.

Of the patients with ocular involvement able to verbalize, 40.0% had a visual complaint, such as new floaters or vision loss, at presentation compared with 4.0% without ocular involvement ($P < .05$). Patients with vitreoretinal involvement had an average culture positivity of 5 days, while those with normal findings had a mean of 4 days; the difference was not statistically significant ($P > .05$).

The most identified organisms were *Candida albicans* (89/291 [30.5%]) and *Candida glabrata* (89/291 [30.5%]) followed by *Candida parapsilosis* (49/291 [16.8%]) and 6 other less common *Candida* subspecies. One patient had *Fusarium* co-infection. The median positivity for the unaffected group was 2 days (Table 2).

Bloodstream infections in 116 patients were cleared within 1 day of a positive culture. Two of 93 intubated patients had persistent fungemia on blood cultures and a positive screening examination; however, there was no difference in ocular involvement

Table 2. Characteristics of Patients With Ophthalmic Involvement.

Pt	Age (y)	IVT Injection?	Endophthalmitis vs Chorioretinitis	Time +BCx (d)	Chief Complaint	Initial VA	Duration Culture+ (wk)	Treatment[a]	Organism
1	20	No	Chorioretinitis	4	Unable	N/A	2.00	Caspofungin, voriconazole	*Candida tropicalis*
2	76	No	Endophthalmitis (bilateral)	4	Floaters/ vision loss	20/20 OU	0.14	Fluconazole	*Candida albicans*
3	52	No	Chorioretinitis	5	Floaters/ vision loss	20/20 OU	1.14	Fluconazole	*Candida albicans*
4	53	No	Chorioretinitis (bilateral)	1	None	20/40 OU	0.14	Caspofungin	*Candida glabrata*
5	67	No	Chorioretinitis	1	None	20/20 OU	0.43	Caspofungin	*Candida albicans*
6	52	Yes	Endophthalmitis	3	Unable	N/A	0.29	Caspofungin, fluconazole, IVT voriconazole	*Candida albicans*
7	47	No	Chorioretinitis	2	None	20/20 OU	0.29	Caspofungin, fluconazole	*Candida albicans*

Abbreviations: BCx, blood culture; IVT, intravitreal; N/A, not applicable; Pt, patient; VA, visual acuity.
[a]Systemic and/or IVT.

between the verbal patients and nonverbal patients on subgroup analysis. One patient improved on systemic medication alone while the other received 1 IVT voriconazole injection. One patient with a positive screening was transferred from an outside hospital after approximately 2 weeks of persistent fever and did not have a blood culture until the day of transfer. Another culture, which was negative, was not taken until 1 week later, after the patient started antifungal systemic medications.

When grouped together, complaints of vision loss or new floaters and persistent fungemia were found to be significant predictors of ocular involvement ($P < .01$). Evaluated separately, symptoms of ocular involvement, but not persistent fungemia, were found to be significant ($P < .05$). The sensitivity and specificity were 83.3% and 49.1%, respectively. No other risk factors were significant ($P > .1$). The negative predictive value among nonverbal patients who did not have persistent fungemia was 92.0%. The underlying organism was not associated with a risk for ocular involvement. The negative predictive value was 99.3% for patients who did not endorse the previously mentioned complaints or have persistent fungemia. Applying the significant criteria a priori would have resulted in a reduction in ophthalmic consultations of 50.1%.

Conclusions

Among this large cohort of inpatients with fungemia, the prevalence of fungal endophthalmitis was approximately 1%, in agreement with a previous large systematic review of the literature.[7] An additional 1% of patients may develop less severe ocular involvement such as chorioretinitis, which usually resolves with systemic treatment alone. Visual symptoms such as floaters and blurry vision or vision loss were found to be significant predictors of ophthalmic involvement. Persistent fungemia, defined by 2 positive cultures 48 hours or more apart, showed a trend toward a positive screening examination but did not meet statistical significance. Previous reports of gastrointestinal surgery being a primary risk factor for persistent fungemia led to its consideration initially; however, this was indicative of the risk for fungemia and not for ophthalmic screening positivity in this cohort, such as central venous access and other known risk factors.[4]

Additional criteria were also evaluated, including immunocompromised status, history of transplantation, indwelling or recent (<72 hours) central venous access, and DM. None of these criteria was found to significantly increase the risk for screening positivity and likely only increase the risk for fungemia in general (Table 3). Baseline antifungal medication at the time of consultation was not found to be predictive of a positive screening examination ($P > .1$), with caspofungin the most common medication reported (67.5%) followed by fluconazole (27.6%) and voriconazole (2.0%). Two patients with chorioretinal but not vitreous involvement were treated with caspofungin alone, likely indicating that this drug may be a reasonable option for patients without endophthalmitis who require caspofungin for nonocular reasons. Causative organisms identified did not show significance for the prediction of disease. There is good evidence for IVT penetration of triazole antifungals; however, there is concern about the poor penetration of echinocandins, such as caspofungin, based on limited human and animal models.[9] However, no difference was found in this cohort. Based on these results, which are likely the result of the rarity of the primary outcome, we cannot recommend systemic antifungals as a primary choice. The duration of baseline antifungal treatment, a mean of 2.62 weeks for the patients with a positive screening, was also not significantly different.

A significant proportion of the patients did not undergo daily or every-other-day blood culture draws as recommended by the IDSA, which may have skewed the data toward a longer duration of infection, even in patients who had cleared the infection.[8] For the purposes of the current study, patients with an excessively long time between cultures (last culture 72 hours or more

Table 3. Differences in Patient Risk Factors Based on the Presence of Endophthalmitis.

Risk Factor	Ocular Involvement (n = 7)	No Endophthalmitis (n = 284)	*P* Value
Mean number of positive blood cultures	3	2.85	.892
Mean duration of positive blood cultures (wk)	0.67	0.60	.795
Ocular complaint, n (%)	2 (33.3)	12 (4.2)	.012
Gastrointestinal surgery in previous 6 mo, n (%)	3 (50.0)	119 (41.8)	.942
History of solid organ transplantation, n (%)	1 (16.7)	74 (26.0)	.607
Immunocompromised status, n (%)	4 (66.7)	201 (70.5)	.961
HIV infection, n (%)	0	12 (4.2)	.606
Diabetes mellitus, n (%)	1 (16.7)	72 (25.3)	.618
Intravenous drug use, n (%)	0	4 (16.0)	.915
Central venous access, n (%)	5 (83.3)	121 (42.5)	.792
Mean length of antifungal therapy (wk)	2.62	2.66	.996

than the previous) were deemed to have persistent fungemia by default, capturing more potential cases and reducing false negatives. In doing so, the positive criteria are overestimated, as is the number of patients with persistent fungemia. It is likely that bloodstream infections in many of these patients cleared before the delayed serum culture collection.

The 99.3% negative predictive value remained high despite an unreliable estimate of the time of culture positivity. This suggests that the primary criteria may be used to exclude those at low risk for ocular disease and safely reduce unnecessary ophthalmic examinations by approximately 50%.

One patient with a positive screening did not have cultures before arrival at our institution, decreasing the negative predictive value despite the their likely having persistent fungemia at that time. Without this outlier, the negative predictive value would be 100%. Variable adherence to culture recommendations is common, with 1 large retrospective multicenter study reporting a 41.7% deviation from IDSA recommendations.[1] Because of the relative efficacy of newer generation antifungal medications, which may clear a bloodstream infection within 72 hours, it is likely that ocular involvement will not develop in patients with rapidly cleared bloodstream infections. Indeed, at least 116 patients cleared the infection within 1 day, which is underestimated given the limitations of inconsistent retesting. In this study's cohort, we were unable to determine which antifungal may reduce the risk for ocular involvement.

In our cohort, 93 of 291 patients were intubated and unable to communicate visual changes and were excluded from the analysis of the symptomatic variable only. Two of those patients had positive screenings, and both had fungemia for at least 2 or more days, meeting the criteria for persistent fungemia. Neither patient had observable signs such as injection or hypopyon. One patient improved sufficiently on systemic treatment alone, and the other received an IVT injection without the need for vitrectomy, reflective of the overall data. Intubated patients appeared to have similar rates of ocular involvement and similar clinical treatment courses, despite the inability to report new symptoms. Although significance was not met in this cohort for persistent fungemia alone, we recommend considering this as a screening tool for nonverbal patients. Many of these intubated patients require pupil examinations for monitoring. For these patients, repeated dilated examinations introduce the possibility of harm given the decreased ability to monitor neurologic function.

The data presented here lead to the following recommendations: (1) all inpatients with fungemia who have ophthalmic complaints, such as new floaters or vision loss, should undergo universal ophthalmic screening examinations and (2) persistent fungemia may be considered a criterion in nonverbal patients to trigger screening when pupil dilation places a patient at risk.

These criteria present a broad and reasonable approach toward an evidence-based screening protocol through which patient harm and unnecessary ophthalmic evaluations are minimized. In addition, the potential for incidental disease to be missed can be reduced by intentional overscreening.

Authors' Note

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Ethical Approval

This study was performed in compliance with the tenets of the Declaration of Helsinki and in compliance with US Health Insurance Portability and Accountability Act of 1996 regulations. Approval from Icahn School of Medicine at Mount Sinai Institutional Review Board was obtained (IRB #20-01712) for this study.

Informed Consent

Informed consent was waived for the present study because inclusion in the study posed no substantial risk to participants and data analysis consisted of de-identified data obtained through retrospective chart review.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of the article: Dr. Wilkins is a consultant to EyePoint Pharmaceuticals. None of the other authors declared potential conflicts of interest with respect to the research, authorship, and/or publication of the article.

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