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MAJOR ARTICLE

Do Patients With Candidemia Need an Ophthalmologic Examination?

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Background. The Infectious Diseases Society of America recommends a screening dilated retinal examination by an ophthalmologist for all patients with candidemia. Conversely, the American Academy of Ophthalmology recommends against routine screening in patients with candidemia without symptoms.

Methods. In a collaborative effort between infectious diseases and ophthalmology, we examined the incidence of ocular complications in 308 patients with candidemia and subsequently measured the rate of fundoscopic examinations, risk factors for ocular complications, management changes, and outcomes.

Results. Among those who received fundoscopic exams, findings suspicious for ocular candidiasis were found in 12 patients (8%, 12/148). After independent review by ophthalmology and infectious diseases, 3 patients were found to have alternate pathologies that explained their ocular findings. Nine patients (6%, 9/148) were adjudicated as having presumed *Candida* chorioretinitis. Of these 9 patients, 4 (44%) were asymptomatic, and 2 (22%) were unable to declare symptoms. No patients were definitively determined to have *Candida* endophthalmitis. Ocular candidiasis was not found to have a statistically significant association with symptoms or comorbidities. Ocular candidiasis was more likely to be found at ophthalmology exams >7 days from first positive *Candida* blood culture. The number needed to screen to detect presumed *Candida* chorioretinitis among asymptomatic patients was 20.

Conclusions. Based on the available evidence and high risk of morbidity of eye involvement, continued ophthalmological screens seem prudent, but a definitive consensus was found to be challenging given a lack of outcome data. Additional investigations are warranted. Ophthalmology screenings have a higher sensitivity at >7 days from positive blood culture.

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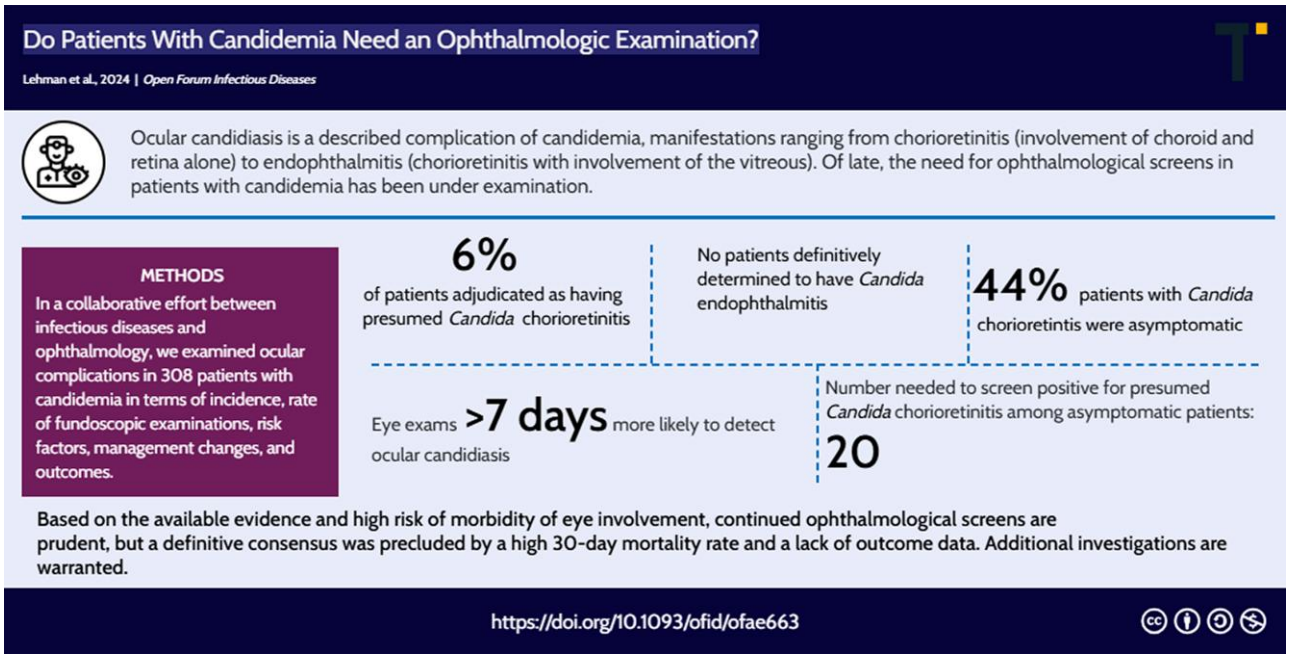
Graphical Abstract



This graphical abstract is also available at Tidbit: https://tidbitapp.io/tidbits/do-patients-with-candidemia-need-an-ophthalmologic-examination-a442ceb2-1509-4cb3-82ef-e42fcca30a19/update

Keywords. *Candida* endophthalmitis; candidemia; chorioretinitis; ocular candidiasis; ophthalmology screening.

Estimates from the Centers for Diseases Control and Prevention (CDC) suggest that ~23 000 cases of candidemia (7 per 100 000) occur in the United States each year as of 2017 [1]. Ocular candidiasis is a described complication of candidemia resulting from hematogenous seeding of the eye. However, of late the incidence of ocular complications has been under examination. Ocular candidiasis manifestations can range from chorioretinitis (involvement of choroid and retina alone) to endophthalmitis (chorioretinitis with involvement of the vitreous) [2, 3]. The Infectious Diseases Society of America (IDSA) recommends a screening dilated retinal examination by an ophthalmologist for all patients with candidemia [4]. On the contrary, the American Academy of Ophthalmology (AAO) recommends against routine screening in patients with candidemia [5]. The AAO supports ophthalmologic consultation for patients with signs or symptoms suggestive of ocular infection regardless of candidemia. This has led to uncertainty around whether ophthalmology screening is to be continued as a practice in patients with candidemia and no ocular symptoms.

The IDSA guideline recommendations for screening dilated examination were based on the need to determine the extent of ocular involvement in cases of ocular candidiasis, which in turn guides therapeutics [4]. In patients with candidemia without eye involvement, the IDSA recommends treatment with an echinocandin followed by an azole, for a total of 2 weeks after documented clearance of *Candida* species from the bloodstream and resolution of symptoms attributable to candidemia. In patients with eye involvement, at least 4–6 weeks of treatment with an azole is recommended, with the final duration depending on resolution of the lesions as determined by repeated ophthalmological examinations. Arguments for these recommendations include available evidence suggesting an inability of echinocandins to achieve adequate concentrations in the vitreous body, the sight-threatening nature of disease involving the macula, and poor outcomes seen with vitreous involvement. For patients with chorioretinitis with macular involvement and those with endophthalmitis, the IDSA additionally recommends close cooperation with ophthalmologists for (1) injection of either amphotericin B deoxycholate or voriconazole into the vitreous to achieve high drug concentrations in the posterior segment and (2) consideration of a pars plana vitrectomy to reduce disease burden, as needed.

The key arguments to the newer AAO guidelines include the following: (1) the incidence of *Candida* endophthalmitis in candidemia was found to be lower than historically reported (0.9%) in a recent systematic review [6], (2) previous classifications of ocular candidiasis lacked consistency and specificity, (3) ocular findings attributed to candidemia cannot be readily distinguished from findings in common comorbidities, and (4) intraocular diagnostics and therapeutics pose risks, and the benefits are not based on strong data [5]. The AAO recommends that any future recommendations be developed through

collaborative efforts between specialists represented by ophthalmology and infectious diseases.

In a collaboration between infectious diseases and ophthalmology, we examined the incidence of ocular complications in patients with candidemia and subsequently measured rates of fundoscopic examination, risk factors for ocular complications, management changes, and ophthalmologic outcomes.

METHODS

We performed a retrospective review of patients with candidemia at an academic medical center and 11 affiliated hospitals from a single community health system between January 2011 and June 2022. The study was approved by the Institutional Ethical Review Board at the University of Minnesota. We included patients of all ages who had a positive blood culture for *Candida* spp. Only the first positive blood culture showing *Candida* spp. during this period was included, and any subsequent positive cultures in unique patients were not assessed. International Classification of Diseases, 9th and 10th Revisions (ICD-9 and ICD-10), lab, and Current Procedural Terminology (CPT) codes were used to identify patients with positive blood cultures for *Candida* spp. and analyze for the presence of baseline characteristics (Supplementary Table 1). Patient charts were reviewed for ophthalmologic consultation, fundoscopic examination, ocular findings, antimicrobial medication management, repeat ocular examination findings, and 30-day mortality. Study objectives were to (1) summarize *Candida* endophthalmitis or chorioretinitis in those with candidemia, applying rigorous definitions of each, (2) determine the prevalence of ocular candidiasis in those with candidemia, (3) examine factors associated with ocular candidiasis, (4) describe outcomes including 30-day mortality and changes in medical management in patients with ocular candidiasis, (5) evaluate the role of signs and symptoms in predicting ocular candidiasis, and (6) evaluate the presence of comorbidities that may explain ocular findings in patients suspected to have ocular candidiasis. Records of all patients with eye findings suspicious for ocular candidiasis were independently reviewed by study team members from infectious diseases and ophthalmology, and differences were resolved by discussion.

Based on the definitions instituted in the recent Breazzano et al. systemic review, ocular outcomes were classified as presumed *Candida* chorioretinitis if classical ocular findings consistent with *Candida* chorioretinitis were present and no alternative etiology could explain the ocular findings, or presumed other chorioretinal disease if ocular findings were more suggestive of alternative etiologies or were nonspecific. Presumed *Candida* chorioretinitis was defined by the presence of focal, deep, white, infiltrative, chorioretinal lesions with no evidence of direct vitreous involvement. Chorioretinitis with extension of the surrounding inflammation into the vitreous or vitreous abscess manifesting as intravitreal fluff balls was designated as presumed *Candida* endophthalmitis [6].

Univariate analyses were done to investigate the study findings further. To investigate the association between potential risk factors and ophthalmology screening (yes/no), the chi-square, Fisher exact, and Wilcoxon rank-sum tests were used, when appropriate. To investigate the association between clinical features and ocular findings, the Fisher exact test was used. All reported *P* values are 2-sided, and a significance level of .05 was used. Statistical analyses were performed using R (version 4.1.2; R Core Team).

RESULTS

We included 308 patients with a first blood culture positive for *Candida* species during the defined study period. The cohort was 50% female and had a median age (range) of 57.9 (0.0–94.8) years. Forty-two percent required a critical care stay, 33% required a central venous catheter, and 79% received antibiotics within 30 days before positive culture. Many patients had chronic preexisting conditions such as hypertension (74%), diabetes (40%), or renal disease (42%). The 30-day mortality rate was at 34%. Less than half of the patients (48%, 148/308) received a dilated fundoscopic ophthalmologic examination. In patients without an examination, 46% died within 30 days of positive culture vs 22% among those with an examination ($P < .001$, Table 1). The median age was 61 years in patients who did not receive an ophthalmology screen, compared with 53 years in those who did ($P < .001$). Patients at the university adult and children's hospitals were more likely to have had an ophthalmology screen than patients at the community hospitals ($P < .001$). Patients who had symptoms were more likely to receive an ophthalmology screen ($P < .001$). Patients who received an ophthalmology screen were also more likely to have *Candida* endocarditis and to have needed central venous access, had neutropenia, or received antibiotics in the 30 days before positive blood culture ($P < .05$ for all). Abnormal ocular findings concerning for possible ocular *Candida* complications including chorioretinitis and/or endophthalmitis were found in 12 patients (8%, 12/148) (Table 2).

After review of the cases by the study team, 2 of these patients were determined to have presumed other chorioretinal disease due to characteristics of lesions suggesting an alternative etiology (Table 2). One patient who had a questionable diagnosis of *Candida* endophthalmitis, due to coexisting bacterial endophthalmitis, and negative *Candida* intravitreal cultures in the setting of having received systemic and intravitreal antifungals was excluded from subsequent analyses. This was the only patient who had intravitreal cultures performed and underwent intraocular therapeutics and surgery (enucleation). All the remaining 9 patients (6%, 9/148) had presumed *Candida* chorioretinitis.

Table 1. Comparison of Risk Factors by Ophthalmology Screening for Patients With Positive *Candida* Blood Culture

Variable	Patients With Ophthalmology Screening (n = 148)	Patients Without Ophthalmology Screening (n = 160)	*P* Value[a]
Sex, No. (%)			.820
Female	73/148 (49.3)	81/160 (50.6)	
Male	75/148 (50.7)	79/160 (49.4)	
Age			<.001
Mean (SD), y	47.4 (21.9)	57.5 (18.8)	
Median (range), y	53.1 (0.0–86.6)	61.1 (6.2–94.8)	
Hospital location, No. (%)			<.001
Community Hospitals	17/148 (11.5)	60/160 (37.5)	
University Children's Hospital	20/148 (13.5)	7/160 (4.4)	
University Adult Hospital	111/148 (75.0)	93/160 (58.1)	
Symptoms, No. (%)			<.001
Yes	23/148 (15.5)	4/160 (2.5)	
No	81/148 (54.7)	91/160 (56.9)	
Unable to ask	44/148 (29.7)	42/160 (26.2)	
Not asked	0/148 (0.0)	23/160 (14.4)	
Candida species, No. (%)			.666
Candida albicans	57/148 (38.5)	72/160 (45.0)	
Candida dubliniensis	5/148 (3.4)	7/160 (4.4)	
Candida glabrata	38/148 (25.7)	39/160 (24.4)	
Candida guilliermondii	2/148 (1.4)	3/160 (1.9)	
Candida kefyr	2/148 (1.4)	1/160 (0.6)	
Candida krusei	3/148 (2.0)	5/160 (3.1)	
Candida lusitaniae	2/148 (1.4)	5/160 (3.1)	
Candida parapsilosis	27/148 (18.2)	22/160 (13.8)	
Candida pelliculosa	1/148 (0.7)	0/160 (0.0)	
Candida tropicalis	11/148 (7.4)	6/160 (3.8)	
ICU during admission, No. (%)	65/148 (43.9)	63/160 (39.4)	.419
Candida endocarditis, No. (%)	8/148 (5.4)	0/160 (0.0)	.003
Diabetes before positive culture, No. (%)	58/148 (39.2)	65/160 (40.6)	.797
Hypertension before positive culture, No. (%)	113/148 (76.4)	115/160 (71.9)	.371
AKI or CKD 30 d before admission and through positive culture, No. (%)	60/148 (40.5)	68/160 (42.5)	.727
Prematurity at any time, No. (%)	4/148 (2.7)	0/160 (0.0)	.052
Cirrhosis before positive culture, No. (%)	22/148 (14.9)	18/160 (11.2)	.346
Neutropenia 30 d before admission and through positive culture, No. (%)	23/148 (15.5)	10/160 (6.2)	.008
Bacteremia 30 d before admission and through positive culture, No. (%)	52/148 (35.1)	45/160 (28.1)	.186
Anemia 30 d before admission and through positive culture, No. (%)	77/148 (52.0)	70/160 (43.8)	.146
Thrombocytopenia 30 d before admission and through positive culture, No. (%)	29/148 (19.6)	22/160 (13.8)	.168
Antibiotics 30 d before admission and through positive culture, No. (%)	124/148 (83.8)	118/160 (73.8)	.032
Immunosuppressant 30 d before admission and through positive culture, No. (%)	19/148 (12.8)	14/160 (8.8)	.247
Chemotherapy 30 d before admission and through positive culture, No. (%)	13/148 (8.8)	10/160 (6.2)	.398
Central venous access 30 d before admission and through positive culture, No. (%)	60/148 (40.5)	41/160 (25.6)	.005
Mortality within 30 d of positive culture, No. (%)	32/148 (21.6)	74/160 (46.2)	<.001

Abbreviations: AKI, acute kidney injury; CKD, chronic kidney disease; ICU, intensive care unit.

[a]To investigate the association between potential risk factors and ophthalmology screening, the chi-square, Fisher exact, and Wilcoxon rank-sum tests were used.

Patients with presumed *Candida* chorioretinitis were more likely to have had the eye exam >7 days into candidemia ($P < .05$) (Table 3). No statistically significant clinical risk factors for development of ocular candidiasis were found. The majority of patients with presumed *Candida* chorioretinitis had a change in management (78%, 7/9) from an

Table 2. Ocular Findings in Patients With Candidemia

	Candida spp.	Symptoms	Ophthalmologic Diagnosis	Ophthalmologic Findings	Intravitreal Culture Results	Duration of Candidemia	Antimicrobial Management	30- Day Mortality	Outcomes
1[a]	*C. glabrata*	Yes—pain, blurriness, vision loss	Endophthalmitis due to bacterial etiology	Left eye: hypopyon, dense vitritis, no retinal view, no retinal detachment on B-scan	Bacterial—*Enterobacter cloacae,* previous treatment with antifungals	3 d	Micafungin→intravitreal treatment + amphotericin B	No	Enucleation, transition to comfort care, death 6 wk after positive culture
2	*C. tropicalis*	No	Presumed *Candida* chorioretinitis	Right eye: small focal white retinal lesion near inferior arcade	Not performed	6 d	Micafungin→fluconazole	No	Resolved on repeat examination
3[b]	*C. tropicalis*	No	Presumed other chorioretinal disease	Right eye: retinal hemorrhages and roth spots	Not performed	10 d	Micafungin→voriconazole	Yes	Transition to comfort care, death 16 d after positive culture
4	*C. albicans*	Yes—blurry long-distance vision	Presumed *Candida* chorioretinitis	Right eye: single opalescent retinal lesion with surrounding heme midperiphery, cotton wool spots inferior arcade	Not performed	2 d	Micafungin→fluconazole	No	Transition to comfort care, death 8 wk after positive culture
5	*C. glabrata*	Yes—blurry vision	Presumed *Candida* chorioretinitis	Both eyes: retinal hemorrhage and scattered white lesions in macula and periphery	Not performed	4 d	Micafungin→voriconazole	Yes	Transition to comfort care, death 11 d after positive culture
6	*C. albicans*	No	Presumed *Candida* chorioretinitis	"Fungal retinitis" diagnosis by outside hospital retina specialist, no outside hospital notes available to review	Not performed	1 d	Micafungin→fluconazole	No	Initially resolved on repeat exam, then re-admitted with recurrent candidemia, endocarditis, death
7	*C. glabrata*	No	Presumed *Candida* chorioretinitis	Left eye: isolated retinal lesion along superior arcade without hemorrhage or vitritis	Not performed	1 d	Micafungin→voriconazole	No	Unknown, no follow-up
8	*C. albicans*	Unknown—intubated	Presumed *Candida* chorioretinitis	Right eye: yellow-white elevated retinal lesion along superior arcade with small hemorrhage	Not performed	18 d	Micafungin→amphotericin B + flucytosine	No	Stable on repeat examination, comfort care, death at 5 wk after positive culture
9	*C. dublinienesis*	No	Presumed *Candida* chorioretinitis	Right eye: retinal white lesion possible cotton wool spot	Not performed	1 d	Fluconazole →fluconazole, longer duration	No	Repeat examination improved, survived
10	*C. albicans*	Yes—floaters	Presumed *Candida* chorioretinitis	Bilateral cream-colored macular lesions and peripheral white-centered hemorrhages	Not performed	23 d	Micafungin→fluconazole then amphotericin B then fluconazole (fluconazole prescription missed at discharge)	No	Progression of lesions on repeat examination, death 5 wk after positive culture
11	*C. tropicalis*	Unknown—intubated	Presumed *Candida* chorioretinitis	Bilateral subretinal lesions along superior and inferior arcades	Not performed	1 d	Micafungin	Yes	Transitioned to comfort care, death
12[b]	*C. albicans*	No	Presumed other chorioretinal disease	Right eye: focal white clumping inferior vitreous (likely old blood vs fibrosis)	Not performed	2 d	Micafungin	No	Repeat examination stable, survived

[a]Patient with questionable diagnosis due to coexisting bacterial endophthalmitis.

[b]Patient with questionable diagnosis due to characteristics of lesions suggesting alternative etiology.

Table 3. Clinical Features of Patients With and Without Ocular Candidiasis Among Those who Received Ophthalmology Screenings

Variable	All Patients With Ophthalmology Screening (n = 147[b])	Patients With Ocular Candidiasis (n = 9)	Patients Without Ocular Candidiasis (n = 138[b])	*P* Value[a]
Symptoms, No. (%)				.712
Yes	22/147 (15.0)	2/22 (9.1)	20/22 (90.9)	
No	81/147 (55.1)	4/81 (4.9)	77/81 (95.1)	
Unable to ask	44/147 (29.9)	3/44 (6.8)	41/44 (93.2)	
Candida species, No. (%)				.390
Candida albicans	57/147 (38.8)	4/57 (7.0)	53/57 (93.0)	
Candida dubliniensis	5/147 (3.4)	1/5 (20.0)	4/5 (80.0)	
Candida glabrata	37/147 (25.2)	2/37 (5.4)	35/37 (94.6)	
Candida guilliermondii	2/147 (1.4)	0/2 (0.0)	2/2 (100.0)	
Candida kefyr	2/147 (1.4)	0/2 (0.0)	2/2 (100.0)	
Candida krusei	3/147 (2.0)	0/3 (0.0)	3/3 (100.0)	
Candida lusitaniae	2/147 (1.4)	0/2 (0.0)	2/2 (100.0)	
Candida parapsilosis	27/147 (18.4)	0/27 (0.0)	27/27 (100.0)	
Candida pelliculosa	1/147 (0.7)	0/1 (0.0)	1/1 (100.0)	
Candida tropicalis	11/147 (7.5)	2/11 (18.2)	9/11 (81.8)	
ICU during admission, No. (%)	65/147 (44.2)	6/65 (9.2)	59/65 (90.8)	.184
Candida endocarditis, No. (%)	8/147 (5.4)	1/8 (12.5)	7/8 (87.5)	.404
Diabetes before positive culture, No. (%)	57/147 (38.8)	5/57 (8.8)	52/57 (91.2)	.310
Hypertension before positive culture, No. (%)	112/147 (76.2)	7/112 (6.2)	105/112 (93.8)	>.999
AKI or CKD 30 d before admission and through positive culture, No. (%)	59/147 (40.1)	6/59 (10.2)	53/59 (89.8)	.157
Prematurity at any time, No. (%)	4/147 (2.7)	0/4 (0.0)	4/4 (100.0)	>.999
Cirrhosis before positive culture, No. (%)	22/147 (15.0)	2/22 (9.1)	20/22 (90.9)	.624
Neutropenia 30 d before admission and through positive culture, No. (%)	22/147 (15.0)	2/22 (9.1)	20/22 (90.9)	.624
Bacteremia 30 d before admission and through positive culture, No. (%)	51/147 (34.7)	2/51 (3.9)	49/51 (96.1)	.497
Anemia 30 d before admission and through positive culture, No. (%)	76/147 (51.7)	4/76 (5.3)	72/76 (94.7)	.739
Thrombocytopenia 30 d before admission and through positive culture, No. (%)	28/147 (19.0)	2/28 (7.1)	26/28 (92.9)	.681
Antibiotics 30 d before admission and through positive culture, No. (%)	123/147 (83.7)	8/123 (6.5)	115/123 (93.5)	>.999
Immunosuppressant 30 d before admission and through positive culture, No. (%)	19/147 (12.9)	2/19 (10.5)	17/19 (89.5)	.328
Chemotherapy 30 d before admission and through positive culture, No. (%)	13/147 (8.8)	2/13 (15.4)	11/13 (84.6)	.182
Central venous access 30 d before admission and through positive culture, No. (%)	59/147 (40.1)	5/59 (8.5)	54/59 (91.5)	.485
Mortality within 30 d of positive culture, No. (%)	32/147 (21.8)	2/32 (6.2)	30/32 (93.8)	>.999
Days to eye exam, No. (%)				.035
≤7 d	112/147 (76.2)	4/112 (3.6)	108/112 (96.4)	
>7 d	35/147 (23.8)	5/35 (14.3)	30/35 (85.7)	
Days of positive blood culture, No. (%)				.728
<2 d	55/147 (37.4)	4/55 (7.3)	51/55 (92.7)	
≥2 d	92/147 (62.6)	5/92 (5.4)	87/92 (94.6)	
Mean (SD), d	4.0 (5.1)	6.3 (8.3)	3.9 (4.8)	.158
Median (range), d	2.0 (1.0–39.0)	2.0 (1.0–23.0)	2.0 (1.0–39.0)	

Abbreviations: AKI, acute kidney injury; CKD, chronic kidney disease; ICU, intensive care unit.

[a]To investigate the association between clinical features and ocular findings, Fisher exact tests were used.

[b]One patient who had a questionable diagnosis of *Candida* endophthalmitis, due to coexisting bacterial endophthalmitis, and negative *Candida* intravitreal cultures in the setting of having received systemic and intravitreal antifungals was excluded from analysis.

echinocandin-based regimen to an azole-based regimen, or to a longer duration of azoles. Most of the patients (67%, 6/9) with presumed *Candida* chorioretinitis were transitioned to comfort care and died within 8 weeks of initial candidemia. Among the patients with ocular findings, only 50% (6/12) underwent repeat fundoscopic examination. Among these, 3 patients who had been transitioned to an azole demonstrated resolved findings, 2 patients who had remained on an echinocandin showed

lesions that were without improvement, and 1 patient who did not receive a fluconazole prescription as intended at discharge demonstrated worsening ocular disease. Of the 9 patients with presumed *Candida* chorioretinitis, 4 patients (44%, 4/9) were asymptomatic, 3 patients (33%, 3/9) were symptomatic, and 2 patients (22%, 2/9) were unable to declare symptoms. The 4 asymptomatic patients with presumed *Candida* chorioretinitis were found by screening 81 asymptomatic patients with candidemia, making the number of asymptomatic candidemia patients needed to screen (NNS) to find 1 patient with presumed *Candida* chorioretinitis equal to 20 (absolute risk reduction [ARR] = 4/81 = 4.9; NNS = 1/ARR = 1/4.9 = 20.4).

DISCUSSION

The systematic review by Breazzano et al., which serves as the basis for new AAO recommendations, considers the incidence of *Candida* ophthalmologic complications to be overestimated in historical medical literature [5, 6]. New definitions and recognition of confounding clinical variables are described as the basis for the determination of overestimation. Breazzano et al. defines concordant *Candida* endophthalmitis as *Candida* chorioretinitis with extension of the surrounding inflammation into the vitreous or vitreous abscess manifesting as intravitreal fluff balls, whereas discordant *Candida* endophthalmitis includes examination with nonspecific ocular findings and those without vitreous involvement, thus overlapping with chorioretinitis. Descriptive definitions such as these pose challenges to systematic and retrospective reviews as outcomes depend on subjectivity and quality in documentation of the fundoscopic examination. Breazzano et al. found incidence rates of concordant endophthalmitis to be at 0.9% and discordant endophthalmitis rates to be at 14.9%. However, a recent meta-analysis by Phongkhun et al. found a 10.7% pooled prevalence of ocular candidiasis, with the prevalence of concordant *Candida* endophthalmitis being 1.8%, and a 3.6% pooled prevalence among studies from Asian countries [7]. In the CANDIPOP prospective, multicenter candidemia surveillance study in Spain, a post hoc analysis found that only 46% (168/365) received a fundoscopic examination, of which 7.7% (13/168) had ocular lesions associated with ocular candidiasis [8]. Probable *Candida* endophthalmitis occurred in 1.2% (2/168) of patients in the CANDIPOP study, probable *Candida* chorioretinitis was present in 4.8% (8/168) of patients, and possible *Candida* chorioretinitis (with possible alternate causes of eye findings, such as diabetes, hypertension, or concomitant bacteremia) was found in 1.8% (3/168) of patients. Our study adhered to stringent definitions of ocular candidiasis as recommended by Breazzano et al. and found a 6% (9/148) incidence of presumed *Candida* chorioretinitis and no cases of definitive *Candida* endophthalmitis among the cohort that received fundoscopic examination. Differing rates in these studies can likely be attributed to the inability of cases included in retrospective reviews to consistently meet definitive definitions. The incidence of *Candida* ophthalmologic complications cannot truly be known unless studies perform fundoscopic screening in a prospective manner with documentation consistent with the new definitions.

Rapid initiation of targeted systemic antifungal therapy can reduce risk of *Candida* ophthalmologic complications; however, the optimal antifungal regimen remains largely uncharacterized for both *Candida* chorioretinitis and endophthalmitis. Seventy-eight percent (7/9) of patients in our cohort with presumed *Candida* chorioretinitis underwent a change in antimicrobial therapy per IDSA guidance [4]. While echinocandins are the initial antifungal deployed in candidemia, azole therapy has been described to have superior vitreal penetration, specifically with voriconazole in tissue studies [9]. The choroid plexus is a highly vascular tissue and hence theoretically allows for the possibility of vitreal penetration of echinocandins in *Candida* chorioretinitis with the enhanced breakdown of blood–retinal integrity [5]. This theory is not supported in observational clinical studies. The CANDIPOP study demonstrated resolution of ocular complications in 1 patient treated with micafungin; however, all other patients received a regimen that contained systemic fluconazole for varying durations [8]. In our study, 3 patients who had been transitioned to an azole demonstrated resolved findings, and 2 patients who remained on an echinocandin showed lesions that remained without improvement. The systematic review by Breazzano et al. demonstrated no treatment failures in surviving patients or those with repeat examination; however, the majority of these patients received regimens based on azoles and amphotericin B [6]. Small retrospective reviews suggest no correlation between ocular candidiasis and initial use of echinocandins in candidemia, and 1 study suggests that echinocandins may reduce ocular candidiasis risk [10, 11]. No clinical efficacy data on use of echinocandins in *Candida* ocular disease can be extrapolated from such small observational numbers. *Candida* spp. with intrinsic or high rates of resistance to azoles, such as *C. krusei* and *C. glabrata,* are another consideration. Among our patients with presumed *Candida* chorioretinitis, we had 2 patients with *C. glabrata,* both of whom were treated with voriconazole, and no patients with *C. krusei*. Voriconazole has been reported to exhibit in vitro activity against *Candida* species resistant to fluconazole and itraconazole, but clinical efficacy needs to be further elucidated [9, 12, 13]. Another recent collaborative review by infectious disease and ophthalmology providers acknowledges that evidence to support or refute use of echinocandins in ocular candidiasis is inconclusive [3]. Additional studies are warranted, but as echinocandins remain the recommended initial agent in candidemia, and as recommended duration of treatment differs

(2 weeks vs 4–6 weeks minimum) based on absence or presence of ocular findings, fundoscopic examination remains important to determine the possibility of ocular complications and guide therapy changes.

Both the AAO and IDSA recommend fundoscopic screening in symptomatic patients [4, 5]. Within our cohort with presumed *Candida* chorioretinitis, the majority of patients were asymptomatic (44%, 4/9) or unable to declare symptoms (22%, 2/9). These findings are similar to those of the CANDIPOP study, where 92% (12/13) of the patients with ocular candidiasis were asymptomatic [8]. As such, significant amounts of ocular *Candida* complications would be missed if screening were limited to those with symptoms or those unable to declare symptoms. In fact, within our cohort of asymptomatic patients, the number needed to screen to find 1 case of ocular *Candida* chorioretinitis was 20. As such, identification of risk factors for ocular candidiasis remains important if selective screening is limited to only symptomatic patients. Previous literature correlates risks factors or predictors of ocular candidiasis to include *C. albicans* identification, prolonged positive cultures, presence of central venous catheters, prematurity in age, and immunocompromised states [14, 15]. The recent meta-analysis by Phongkhun et al. failed to identify predictors outside of *C. alibicans* spp. (pooled odds ratio [pOR], 3.02; 95% CI, 1.67–5.46; $P < .01$) and TPN (pOR, 6.92; 95% CI, 3.58–13.36; $P < .01$) [7]. However, other studies including our cohort have been unable to identify any significant clinical predictors for ocular candidiasis; thus, overall predictors are poorly defined, and triaging asymptomatic patients remains unvalidated [16].

A striking result in our study is the 67% mortality rate at 8 weeks seen in patients with presumed *Candida* chorioretinitis. Patients with candidemia tend to be an inherently critically ill population, with mortality rates up to 50% reported in the literature [17]. Our cohort of patients with candidemia was severely ill as well, with a 34% 30-day mortality and significant comorbidities. One can hypothesize that the subset with candida chorioretinitis was likely to be even sicker. Reported risk factors for ocular candidiasis often include markers of critical illness, such as prolonged positive cultures, and presence of central venous catheters [14, 15]. Ocular candidiasis has also been described as a marker of disseminated candidiasis [3]. Among patients with presumed *Candida* chorioretinitis, only 56% (5/9) underwent repeat fundoscopic examination. Of the remaining patients, 3 were transitioned to comfort care before an exam could be done, and 1 patient was lost to follow-up. Multicenter studies that can generate larger numbers and subsequently analyze clinical outcomes are essential to better decipher optimal management strategies for the spectrum of ocular candidiasis disease.

We also found that patients who received eye exams >7 days from first positive blood culture were more likely to have findings suggestive of ocular candidiasis. IDSA guidelines currently recommend eye exams in all patients with candidemia within the first week of therapy in non-neutropenic patients [4]. For neutropenic patients, it is recommended to delay the examination until neutrophil recovery. Sakamoto et al. have previously described patients with candidemia who showed no abnormal findings during a first ophthalmologic examination <7 days but who were diagnosed with ocular candidiasis during a second examination >7 days [15]. Others have recommended that the fundoscopy be performed at least 1 week after the onset of therapy in candidemia patients without visual symptoms to increase its sensitivity to detect ocular candidiasis [18]. Our study also suggests value in considering delayed or repeat eye exams. However, a consideration of delayed exams has to be carefully weighed against the risks of not identifying ocular involvement early.

Most patients did not receive an ophthalmologic fundoscopic examination, and thus the incidence of ocular candidiasis cannot truly be known based on these data. The rate of ophthalmologic examination in our study was similar to that of the CANDIPOP study in Spain, which found that only 46% received an ophthalmologic exam [8]. One hypothesis for the low rates of exam, based on what we see in practice, is that ophthalmology referrals were often intended for an outpatient consultation at discharge, but these did not occur if the patient died before discharge or if the patient was lost to follow-up. This is corroborated by our finding that in patients without an examination 46% died within 30 days of positive culture vs 22% among those with an examination ($P < .001$). The availability of ophthalmology resources at academic vs community hospitals is another factor likely at play here. We found that patients at the university adult and children's hospitals were more likely to have had an ophthalmology evaluation than patients at the community hospitals ($P < .001$). At our academic centers, there is usually an in-patient ophthalmology consultation service available. Residents and retina fellows help with the consultations, supervised by an attending ophthalmologist. The availability of ophthalmology services in community hospitals can vary widely—some may have a consulting ophthalmologist while others may not, in which case a referral to an academic center maybe needed when an ophthalmology evaluation is required, which often relies on bed availability and risk–benefit determinations for transfer decisions.

Among those who received ophthalmology exams in our cohort, 76% did so ≤7 days from onset of candidemia, which could have affected the sensitivity of the ophthalmology screens. Screening of patients being performed by multiple examiners could also have skewed the fundus exam descriptions. Furthermore, none of the patients had ophthalmology fundus images to corroborate the description of the clinical findings. Additionally, we defined ocular findings as presumed *Candida* chorioretinitis and presumed other chorioretinal disease given that definitive ocular candidiasis cannot be proven without

positive intravitreal cultures. However, intravitreal cultures are rarely done in clinical practice, and none of our patients with presumed *Candida* chorioretinitis had an intravitreal culture done, which limited the ability to meet this definitive definition. Finally, the high incidence of 30-day mortality and lack of follow-up exams in 50% of patients precluded the determination of meaningful clinical outcomes of ophthalmology screenings.

Unique in this study is the collaboration between infectious diseases and ophthalmology specialties, independent chart reviews by each specialty, and subsequent extensive analysis and discussion of results and determination of value. The process led to shared knowledge, widened perspectives between both specialties, and strengthened collaboration to develop systematic approaches to clinical operations as it pertains to infectious ocular diseases.

This study has certain limitations. Cohort and risk factor determination was facilitated by lab, ICD-9, ICD-10, and CPT codes with subsequent chart review, with the inherent possibility of missing some elements in this retrospective methodology. Furthermore, analysis of the first candidemia blood culture allowed for a defined correlation to ocular candidiasis; however, often the clinical care of patients with candidemia is more complex, with multiple incidents of candidiasis over time, which likely impact development of ocular complications.

CONCLUSIONS

Based on the available evidence and high risk of morbidity of eye involvement, continued ophthalmological screenings seem prudent, but we found a definitive consensus to be challenging given the high 30-day mortality and inability to obtain outcome data in 50% of patients in our study [19]. Ocular candidiasis was more likely to be diagnosed >7 days from candidemia onset. Interdisciplinary discussions and decisions involving ophthalmology and infectious diseases at the national level can help inform best practices for screening eye exams in patients with candidemia until more definitive evidence is available. Future studies could evaluate ocular photography and teleophthalmology as screening strategies [3] that could be particularly helpful in low-resource settings and at institutions without ophthalmology consultation. Prospective, multicenter studies need to focus on clarifying preferred treatments and providing equitable ophthalmologic access [19].

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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References

1. Tsay S, Williams S, Mu Y, et al. National burden of candidemia, United States. Open Forum Infect Dis **2018;** 5(Suppl 1):S142–3.
2. Donahue SP, Greven CM, Zuravleff JJ, et al. Intraocular candidiasis in patients with candidemia. Clinical implications derived from a prospective multicenter study. Ophthalmology **1994;** 101:1302–9.
3. O'Donnell M, Eller AW, Waxman EL, Clancy CJ, Nguyen MH. Screening for ocular candidiasis among patients with candidemia: is it time to change practice? Clin Infect Dis **2022;** 75:1092–6.
4. Pappas PG, Kauffman CA, Andes DR, et al. Clinical practice guideline for the management of candidiasis: 2016 update by the Infectious Diseases Society of America. Clin Infect Dis **2016;** 62:e1–50.
5. Breazzano MP, Bond JB 3rd, Bearelly S, et al. American Academy of Ophthalmology recommendations on screening for endogenous *Candida* endophthalmitis. Ophthalmology **2022;** 129:73–6.
6. Breazzano MP, Day HR Jr, Bloch KC, et al. Utility of ophthalmologic screening for patients with *Candida* bloodstream infections: a systematic review. JAMA Ophthalmol **2019;** 137:698–710.
7. Phongkhun K, Pothikamjorn T, Srisurapanont K, et al. Prevalence of ocular candidiasis and *Candida* endophthalmitis in patients with candidemia: a systematic review and meta-analysis. Clin Infect Dis **2023;** 76:1738–49.
8. Vena A, Muñoz P, Padilla B, et al. Is routine ophthalmoscopy really necessary in candidemic patients? PLoS One **2017;** 12:e0183485.
9. Hariprasad SM, Mieler WF, Lin TK, et al. Voriconazole in the treatment of fungal eye infections: a review of current literature. Br J Ophthalmol **2008;** 92: 871–8.
10. Sakai D, Matsumiya W, Kusuhara S, et al. Factors associated with the development of ocular candidiasis and ocular prognosis with echinocandin therapy for candidemia. J Ophthalmic Inflamm Infect **2021;** 11:17.
11. Hautala N, Köykkä H, Siiskonen M, et al. Effect of first-line antifungal treatment on ocular complication risk in *Candida* or yeast blood stream infection. BMJ Open Ophthalmol **2021;** 6:e000837.
12. Pfaller MA, Diekema DJ, Gibbs DL, et al. *Candida krusei*, a multidrug-resistant opportunistic fungal pathogen: geographic and temporal trends from the ARTEMIS DISK antifungal surveillance program, 2001 to 2005. J Clin Microbiol **2008;** 46: 515–21.
13. Varma D, Thaker HR, Moss PJ, Wedgwood K, Innes JR. Use of voriconazole in *Candida* retinitis. Eye (Lond) **2005;** 19:485–7.
14. Festekjian A, Neely M. Incidence and predictors of invasive candidiasis associated with candidaemia in children. Mycoses **2011;** 54:146–53.
15. Sakamoto T, Gotoh K, Hashimoto K, et al. Risk factors and clinical characteristics of patients with ocular candidiasis. J Fungi (Basel) **2022;** 8:497.
16. Khalid A, Clough LA, Symons RC, et al. Incidence and clinical predictors of ocular candidiasis in patients with *Candida fungemia*. Interdiscip Perspect Infect Dis **2014;** 2014:650235.
17. Horn DL, Neofytos D, Anaissie EJ, et al. Epidemiology and outcomes of candidemia in 2019 patients: data from the Prospective Antifungal Therapy Alliance registry. Clin Infect Dis **2009;** 48:1695–703.
18. Oude Lashof AM, Rothova A, Sobel JD, et al. Ocular manifestations of candidemia. Clin Infect Dis **2011;** 53:262–8.
19. You EL, Hébert M, Dufresne SF, et al. On the American Academy recommendations for cancelling routine screening for ocular candidiasis—are we being too hasty? Eye **2024;** 38:2483–4.