

The Incidence of Ocular Complications in Candidemic Patients and Implications for the Practice of Routine Eye Exams

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Background. Ocular candidiasis is a known complication of candidemia. Given the poor ocular penetration of echinocandins, there is some concern that the increasing use of echinocandins may portend an increased incidence of ophthalmic complications. We examined the changing trends in antifungal prescribing patterns and the incidence of ophthalmic complications after candidemia.

Methods. Patients with blood cultures positive for *Candida* species between January 2014 and June 2020 who underwent screening fundoscopic examination by an ophthalmologist were analyzed. The χ^2 analysis was used to compare antifungal prescriptions and ocular exam findings before and after 2016. Trend analysis was also performed to assess temporal changes in prescribing practices and eye exam findings.

Results. There were 226 candidemia cases during the study period, 129 (57.1%) of which underwent screening eye exams. From 2014 to 2015, 24 of 37 (64.5%) patients received eye-penetrating antifungals compared to 36 of 92 (39.1%) from 2016 to 2020 ($P = .008$). Overall, 30 of 129 (23.3%) patients had abnormal eye exams with the prevalence of abnormal findings being 7 of 37 (18.9%) before 2016 compared to 23 of 92 (25%, $P = .46$) thereafter. A trend analysis revealed an increase in abnormal eye findings over the study period ($P = .008$). Of the 30 patients who had abnormal eye exams, 9 (30%) had a change in systemic antifungal therapy from echinocandins to eye-penetrating antifungals. Echinocandin use was associated with abnormal eye findings.

Conclusions. Prescription of eye-penetrating antifungals for candidemia has trended down since 2016. This was associated with a concomitant increase in abnormal findings on screening fundoscopy. Abnormal eye exams were not uncommon throughout our study period.

Keywords. candidemia guidelines; echinocandins; endophthalmitis; ocular candidiasis; routine eye-screening.

The incidence of bloodstream infections with *Candida* species has risen over the last several decades, and the associated morbidity and mortality of such infections remains high [1]. Candidemia is known to cause disseminated infectious complications including endogenous fungal endophthalmitis, which can result in devastating outcomes such as vision loss. Despite the increasing incidence of candidemia, ocular complications of *Candida* bloodstream infections including chorioretinitis and endophthalmitis have decreased in recent decades due to the development of more effective antifungals [2–5]. The

Infectious Diseases Society of America (IDSA) guidelines currently recommend screening ophthalmic examinations in all patients with candidemia to identify evidence of ocular involvement [1, 6]. Due to declining rates of identified ocular involvement, the recommendation for routine screening for all candidemic patients has been challenged in recent years [7, 8]. Critics suggest a more focused strategy of screening based on identified risk factors to screen for ocular complications in a more cost-effective manner. In light of this, the American Academy of Ophthalmology recently published updated guidance that recommends ophthalmologic evaluation only in those candidemic patients who demonstrate signs or symptoms of ocular candidiasis [9]. However, other groups continue to recommend universal screening due to reported ocular complication incidence rates varying from 2% to 20% [2, 7, 10–14].

It should be noted that lower rates of endogenous fungal endophthalmitis have been observed in an era when azoles were recommended alongside echinocandins as first-line therapy for *Candida* bloodstream infections [5]. Azoles inherently have excellent penetration into ocular tissues, and thus their use as first-line agents likely contributed to the low rate of fungal endophthalmitis seen in the azole era [15]. In 2016, the IDSA

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guidelines were updated to recommend echinocandins as initial therapy for candidemia in neutropenic and nonneutropenic patients [1]. Echinocandins are known to have poor intraocular penetration [15, 16]. Current recommendations advise transitioning systemic antifungal therapy to an azole when ocular involvement of *Candida* species is identified, with intravitreal antifungals and surgical interventions as deemed necessary by the evaluating ophthalmologist for more severe cases [1].

To help resolve this ongoing debate, we sought to examine whether patients who received empiric echinocandin therapy developed higher rates of ophthalmic complications of candidemia. We conducted a retrospective chart review to investigate the prevalence of ocular complications in candidemic patients in the current era when echinocandin use is becoming more common.

METHODS

Beginning in 2014, our health system instituted a policy requiring screening ophthalmology in all patients with identified candidemia. We identified the adult patients in our healthcare system who had blood cultures positive for *Candida* species and a completed ophthalmology consult between January 1, 2014 and June 30, 2020 (see Supplemental Figure 1). We collected demographic information including age and gender. Clinical data abstracted from the charts included medical comorbidities associated with an increased risk of underlying retinal or embolic disease (hypertension, diabetes, valvular vegetation on echocardiogram, or other known eye disease), known immunocompromised status (neutropenia with absolute neutrophil count [ANC] <500 cells/ μ L, history of solid organ or bone marrow transplant, human immunodeficiency virus, or currently prescribed immunosuppressive medications), and the presence of previously identified risk factors for ocular candidiasis (recent antibiotic exposure, presence of an indwelling catheter, recent incisional gastrointestinal surgery, parenteral alimentation, history of intravenous drug use, presence of concomitant bacteremia, and need for dialysis after a positive fungal blood culture) [2, 7, 8, 10–12, 17, 18].

Laboratory data (white blood cell count, ANC, serum albumin, and estimated glomerular filtration rate at the time of the first positive blood culture) and microbiological data (species of *Candida*, duration of candidemia, and total number of positive fungal blood cultures) were collected. Antifungal therapies administered before and after eye exam were recorded and classified as eye-penetrating (azoles, amphotericin) or noneye-penetrating (echinocandins).

The findings on ocular exam were documented in accordance with a previously established protocol [19]. “Specific” ocular exam findings were defined as clinical evidence of either chorioretinitis or endophthalmitis. Chorioretinitis was defined as deep white infiltrative lesions limited to the choroid or retina, and endophthalmitis was defined as inflammation extending

into the vitreous humor or vitreal “fluff balls” suggestive of vitreal abscess. This protocol also defines “nonspecific” fundus lesions including nerve fiber layer infarcts, intraretinal hemorrhages, and Roth spots without evidence of chorioretinal infiltration or vitreal extension.

Cases were reviewed for outcomes including documented findings on follow-up ophthalmic examination, resolution of significant findings, changes to management based on initial screening examination (change in antifungal agent, change in duration of therapy, intravitreal injection of antifungal agents, or surgical intervention), and mortality during admission.

Descriptive analyses were performed to examine the demographic and clinical characteristics of the study population; we also compared participants’ characteristics before and after 2016 and by the occurrence of ocular findings. *P* values for differences were estimated using χ^2 and Fisher exact test for categorical variables and using the Wilcoxon signed-rank test for continuous variables given their skewed distribution. To evaluate the trend in the use of ocular penetrating antifungals and of the ocular findings over time, we performed linear regression models of their prevalence as a function of time expressed in years. We subsequently examined the association between the era of prescription (whether before or after 2016) and ocular findings, adjusting for all covariates introduced in the model through forward selection with an entry *P* value of .10. This process computes the predictive value of the covariates and at each step, the candidate variable with more influence on the model is included until none of the covariates are significant. All our analyses were performed in SAS (version 9.4; SAS Institute, Cary, NC) and 2-sided *P* < .05 were considered statistically significant.

Patient Consent Statement

The study was conducted under University of Cincinnati Institutional Review Board (IRB) Number 2019-0592. The IRB determined that this protocol meets the criteria for exemption from IRB review in accordance with 45 CFR 46.104. Per 45 CFR 164.512, the IRB has granted a waiver from the requirement to obtain an authorization for the use and/or disclosure of protected health information.

RESULTS

There were a total of 226 candidemia cases during the study period, 129 (57.1%) of which completed eye exams. We reviewed records of these 129 patients, and a comparison of the cohorts evaluated before and after 2016 revealed no major differences in demographics between the 2 groups except for a higher proportion of male patients in the cohort before 2016. There was an expected decrease in prescription of eye-penetrating antifungals, from 24 of 37 (64.9%) before 2016 to 36 of 96 (39.1%, *P* = .008) after 2016 (Table 1, Table 2, and Figure 1). It is notable that our data did not demonstrate a concomitant

Table 1. Demographic and Clinical Characteristics of Participants With Candidemia Before and After 2016

Characteristics	All (N = 129)	Before or After 2016		PValue
		Before (N = 37)	After (N = 92)	
Sociodemographic Characteristics				
Age (years), median (IQR)	52.9 (34.1–63.7)	53.5 (36.2–64.7)	52.5 (32.0–63.0)	.69
Male sex, N (%)	72 (55.8)	28 (75.7)	44 (47.8)	.004
Clinical Characteristics				
Diabetes, N (%)	39 (30.2)	10 (27.0)	29 (31.5)	.61
Hypertension, N (%)	53 (41.1)	16 (43.2)	37 (40.2)	.75
Immunocompromised, N (%)	30 (23.4)	6 (17.7)	24 (26.1)	.26
Antibiotics use, last 3 months, N (%)	107 (82.9)	28 (75.7)	79 (85.9)	.16
Indwelling IV catheter, N (%)	98 (76.0)	28 (75.7)	70 (76.1)	.96
GI surgery, last 6 months, N (%)	43 (33.3)	12 (32.4)	31 (33.7)	.89
Receiving TPN, N (%)	23 (18.1)	10 (27.0)	13 (14.4)	.09
Active intravenous drug abuse, N (%) ^a	13 (10.1)	3 (8.1)	10 (10.9)	.64
Concomitant bacteremia, N (%)	41 (31.8)	11 (29.7)	30 (32.6)	.75
RRT after candidemia, N (%)	28 (21.9)	6 (16.2)	22 (24.2)	.32
Vegetation on echocardiogram, N (%)				
No vegetation	103 (79.8)	31 (83.9)	72 (78.3)	
Vegetation	13 (10.1)	3 (8.1)	10 (10.9)	
Echocardiogram not performed	13 (10.1)	3 (8.1)	10 (10.9)	
Death during admission, N (%)	19 (14.7)	5 (13.5)	14 (15.2)	.80
Duration of candidemia, median (IQR)	2.9 (1.5–5.2)	3.0 (1.7–6.2)	2.8 (1.4–5.0)	.48
Number of positive cultures, median (IQR)	1.5 (1.0–3.4)	1.7 (1.0–2.8)	1.2 (1.0–2.8)	.62
Laboratory Findings				
eGFR, median (IQR)	46.0 (26.0–75.5)	72.0 (36.2–107.5)	37.5 (18.5–63.9)	<.001
WBC count, median (IQR)	10.9 (6.8–16.1)	11.5 (6.7–20.9)	10.7 (6.7–14.7)	.43
Antifungal Received				
Any ocular penetrating antifungal, N (%)	60 (46.5)	24 (64.9)	36 (39.1)	.008
Azoles, N (%)	57 (44.2)	21 (56.8)	36 (39.1)	.07
Amphotericin B, N (%) ^a	4 (3.1)	3 (8.1)	1 (1.1)	.07
Echinocandins, N (%)	100 (77.5)	29 (78.4)	71 (77.2)	.88
Eye Finding				
Any ocular finding, N (%)	30 (23.3)	7 (18.9)	23 (25.0)	.46
Nonspecific fundus lesion, N (%)	20 (15.5)	5 (13.5)	15 (16.3)	.69
Specific ocular finding, N (%)	11 (8.5)	2 (5.4)	9 (9.8)	.80
Chorioretinitis, N (%) ^a	10 (7.8)	1 (2.7)	9 (9.8)	.17
Endophthalmitis, N (%) ^a	1 (0.8)	1 (2.7)	0 (0.0)	N/A
Vitreous abscess, N (%) ^a	0 (0.0)	0 (0.0)	0 (0.0)	N/A

Abbreviations: eGFR, estimated glomerular filtration rate; IV, intravenous; IQR, interquartile range; NA, not applicable; RRT, renal replacement therapy; TPN, total parenteral nutrition; WBC, white blood cells.

Bold values are statistically significant (i.e., PValue <.05).

^a P values calculated using Fisher's exact test due to small sample size.

Table 2. Prevalence and Trend of Ocular Penetrating Antifungals and Ocular Findings Over Time

	Before 2016	2016	2017	2018	2019	2020	Trend PValue
Ocular penetrating antifungals	24/37 (64.9)	8/17 (47.1)	7/19 (36.8)	12/28 (42.9)	7/20 (35.0)	2/8 (25.0)	.008
Azoles	21/37 (56.8)	8/17 (47.1)	7/19 (36.8)	12/28 (42.9)	7/20 (35.0)	2/8 (25.0)	.046
Amphotericin	3/37 (6.4)	0.0	0.0	0.0	0.0	0.0	N/A
Echinocandins	29/37 (78.4)	12/17 (70.6)	16/19 (84.2)	21/28 (75.0)	15/20 (75.0)	7/8 (87.5)	.88
Any ocular finding	7/37 (18.9)	1/17 (5.9)	4/19 (21.1)	5/28 (17.9)	8/20 (40.0)	5/8 (62.5)	.008
Nonspecific	5/37 (13.5)	0.0	2/19 (10.5)	5/28 (17.9)	5/20 (25.0)	2/8 (25.0)	.06
Specific	2/37 (5.4)	1/17 (5.9)	2/19 (10.5)	0.0	3/20 (15.0)	3/8 (37.5)	.10

Bold values are statistically significant (i.e., PValue <.05).

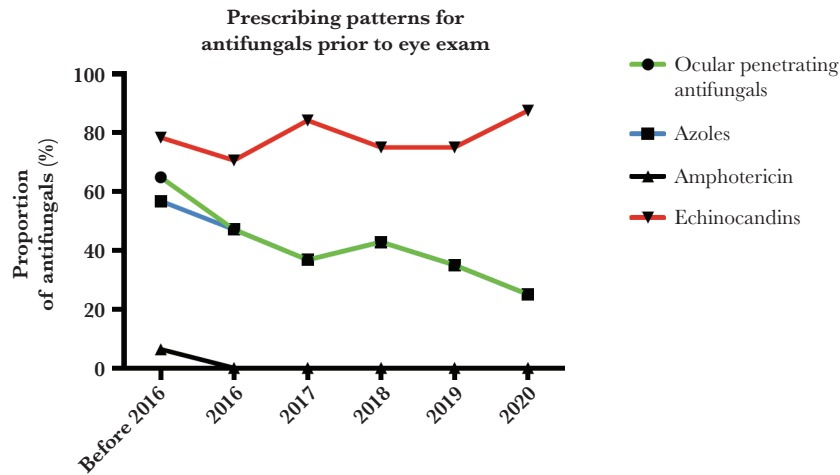


Figure 1. Prescribing patterns for antifungal before eye exam.

increase in treatment with echinocandins before eye exam. There was an overall increase in the incidence of ocular findings throughout our study period (Table 3 and Figure 2) as noted on the trend analysis. Before 2016, ocular findings were present in

7 of 37 cases (18.9%). In 2019, this rose to 8 of 20 (40%), and in the first 6 months of 2020, 5 of 8 patients were noted to have ocular findings (62.9%, trend $P = .008$). This trend was notably seen only when specific and nonspecific findings are combined

Table 3. Demographic and Clinical Characteristics of Participants by Ocular Finding

Characteristics	Ocular Finding		PValue
	No (N = 99)	Yes (N = 30)	
Sociodemographic Characteristics			
Age (years), median (IQR)	52.9 (33.8–65.1)	49.0 (34.0–61.7)	.82
Male sex, N (%)	57 (57.6)	15 (50.0)	.46
Clinical Characteristics			
Diabetes, N (%)	30 (30.3)	9 (30.0)	.97
Hypertension, N (%)	42 (42.4)	11 (36.7)	.57
Immunocompromised, N (%) ^a	25 (25.5)	5 (16.7)	.32
Antibiotics use, last 3 months, N (%)	81 (81.8)	26 (86.7)	.54
Indwelling IV catheter, N (%)	74 (74.7)	24 (80.0)	.56
GI surgery, last 6 months, N (%)	34 (34.3)	9 (30.0)	.66
Receiving TPN, N (%) ^a	17 (17.3)	6 (20.7)	.68
Active intravenous drug abuse, N (%) ^a	8 (8.1)	5 (16.7)	.17
Concomitant bacteremia, N (%)	29 (29.3)	12 (40.0)	.27
RRT after candidemia, N (%)	19 (19.2)	9 (31.0)	.17
Vegetation on echocardiogram, N (%)			
No vegetation ^a	82 (82.8)	21 (70.0)	
Vegetation ^a	7 (7.1)	6 (20.0)	
Echocardiogram not performed ^a	10 (10.1)	3 (10.0)	
Death during admission, N (%)	11 (11.1)	8 (26.7)	.04
Duration of candidemia, median (IQR)	3.1 (1.5–5.5)	2.5 (1.5–4.4)	.36
Number of positive cultures, median (IQR)	1.4 (1.0–2.8)	1.9 (1.0–4.5)	.19
Laboratory Findings			
eGFR, median (IQR)	47.5 (25.5–77.5)	37.7 (22.2–66.7)	.70
WBC count, median (IQR)	10.7 (6.3–15.8)	12.2 (8.4–16.4)	.34
After 2016 guideline, N (%)	69 (69.7)	23 (76.7)	.46
Ocular penetrating antifungal, N (%)	47 (47.5)	13 (43.3)	.69

Abbreviations: eGFR, estimated glomerular filtration rate; GI, gastrointestinal; IV, intravenous; IQR, interquartile range; RRT, renal replacement therapy; TPN, total parenteral nutrition; WBC, white blood cells.

Bold values are statistically significant (i.e., P Value $< .05$).

^a P values calculated using Fisher's exact test due to small sample size.

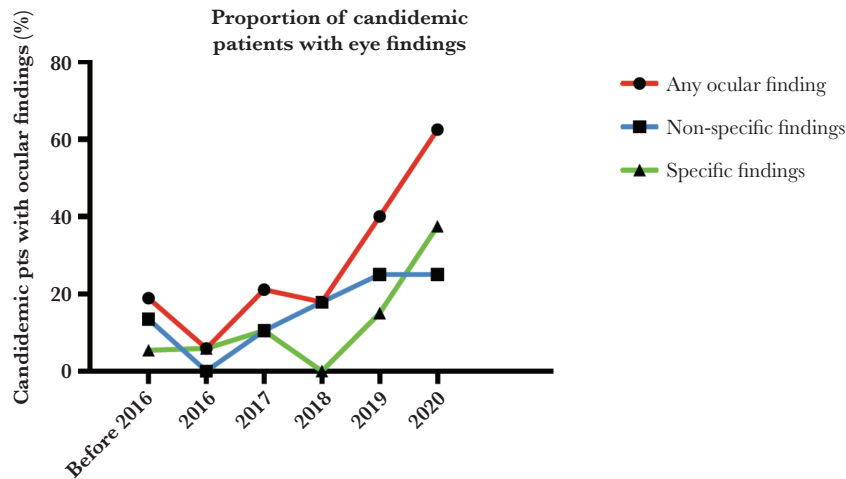


Figure 2. Proportion of candidemic patients with eye findings.

as a composite outcome, and not observed when either outcomes were evaluated individually.

Outcomes of Patients With Abnormal Eye Findings

Of the 30 patients with abnormal eye findings, 11 patients were on ocular-penetrating agents and therefore warranted no changes. Seven of these patients had follow-up exams. At the time of follow-up, 2 of those 7 (28.6%) patients improved, 2 of 7 (28.6%) patients worsened, and 3 of 7 (42.9%) patients remained stable. Nineteen of the 30 patients with abnormal findings did not receive eye-penetrating antifungals before ocular exam. Nine of the patients with abnormal eye exams (30%) had a change in therapy from an echinocandin to ocular-penetrating antifungals. Eight of these patients had follow-up exams: 1 (12.5%) had a worsening eye exam at follow up whereas the rest remained stable. Of the 10 patients (47.6%) who remained on nonocular- penetrating antifungals despite eye findings, 5 of the 10 patients died during admission and 6 (60%) of the 10 patients had follow-up eye exams. One of the 6 (16.7%) patients worsened, and 5 of the 6 (83.3%) patients remained stable. None of these patients improved at follow-up exam. When comparing demographic and clinical characteristics of participants by ocular finding, it was notable that patients with ocular finding had higher mortality (26.7 vs 11.1; $P = .04$) (Table 3). It was also notable that on multivariate analysis, echinocandin use was associated with the observation of eye findings on eye exam (Table 4).

Outcomes of Patients With Specific Versus Nonspecific Eye Findings

Of the 11 patients with specific findings, 8 had a change in antifungal treatment (72.7%). Of these, 10 had follow up exams: 1 improved, 1 worsened, and the rest were stable. Nineteen patients had nonspecific ocular findings, and 1 had a change in antifungal treatment (5.3%) after initial exam. Ten had follow-up exams: 3 patients (30%) had worsening eye exams on follow up, and only 1 patient improved (10%). The rest were stable.

DISCUSSION

The utility of eye exams for patients with candidemia has been the subject of ongoing debate in the literature. To date, one post hoc analysis of a prospective cohort study has evaluated whether the incidences of endophthalmitis and chorioretinitis are higher in candidemic patients initially treated with echinocandins [4]. Since that study predates the updated guidelines, the majority of patients found to have ocular involvement had empirically received nonechinocandin therapy for candidemia [18]. The analysis did not demonstrate increased risk of ocular involvement in patients initially treated with echinocandins, although the study had significant limitations including the fact that fewer than half of all patients with candidemia underwent screening ophthalmoscopy.

To accurately estimate the utility of these exams, 2 questions need to be addressed. (1) Is the incidence of ophthalmologic

Table 4. Multivariate Analysis of Antifungal Type and Ocular Findings

	Any Ocular Finding		Nonspecific Ocular Finding		Specific Ocular Finding	
	OR (95% CI)	<i>P</i>	OR (95% CI)	<i>P</i>	OR (95% CI)	<i>P</i>
Echinocandin use	2.82 (1.07–7.42)	.036	1.69 (0.57–5.06)	.34	1.89 (0.39–9.08)	.43

Abbreviations: CI, confidence interval; OR, odds ratio.

Bold values are statistically significant (i.e., P Value < .05).

complications high enough to warrant routine exams? (2) Will a change in management after an abnormal exam improve outcomes in candidemia patients? The second question becomes particularly relevant only if patients are frequently receiving nonpenetrating antifungals to begin with, and thus, in such scenarios, the change in management will accord the use of eye-penetrating antifungals. It is unfortunate that there are very few studies reported that address these questions, and none have done so contemporaneously. Previous studies done to address some of these questions were conducted before the 2016 guidelines were published; therefore, the current incidence of ophthalmic complications after candidemia has been difficult to estimate because routine eye exams were not done in many institutions. Although a randomized controlled trial will provide the ultimate level of evidence, retrospective studies can provide valuable insights. In certain aspects, this study, although retrospective, is in itself a natural history experiment that has the potential to address some of these questions.

Furthermore, the impact of changes in prescribing patterns was impossible to evaluate in prior studies because no major shift in prescribing patterns occurred during those studies. Another strength of this study is that a subset of patients with abnormal eye exams had follow-up exams, and thus we were able to assess response to therapy and disease progression for this group. We were able to make key observations indicated below.

Prescription Practices Are Changing

Our healthcare system instituted routine ophthalmology for candidemia before the 2016 IDSA guidelines were published. This contributed to a more robust study because the prescribing patterns before publication of the guidelines were not overrepresented by echinocandins use, and a fair mix of agents that had varying ocular penetrating abilities could be evaluated. It is notable that over recent years, there has been a statistically significant trend away from the use of eye-penetrating antifungals (azoles and amphotericin) (see [Table 2](#)). Our study shows that only 1 in 4 patients with candidemia receive eye-penetrating antifungals currently. This shift in prescribing patterns is likely to be driven by the publication of the updated candidemia guidelines in late 2015 that recommended echinocandins as first-line therapy. The concern among practitioners has been that this shift in prescribing patterns where noneye-penetrating antifungal agents dominate clinical management could lead to an increased incidence of ocular complications. Our finding that echinocandin use was associated with ocular complications suggests this is an issue that warrants further investigation and the true significance of some of these complications needs to be established. A recent publication by Sng et al [20] in which the initial use of an echinocandin was

associated with ocular complications and poor outcomes highlights these concerns.

Eye Findings Are Common in Patients With Candidemia, and the Incidence of Eye Findings Is Increasing

Overall, it is notable that eye findings were common in our patient population. We noted an overall rate of approximately 23.3% with approximately 25% being *Candida*-specific eye findings. This compares with published studies that reported rates of 16% [1]. The prevalence threshold of specific findings for which routine eye exams will provide more benefit than harm remains unclear.

A trend analysis indicates that there is a statistically significant increasing prevalence of ocular findings from 18.9% in 2016 to over 60% in 2020 ([Table 3](#)). It is notable that these findings were mostly nonspecific findings that may not necessarily be attributable to candidemia. There was also a trend towards an increase in candidemia-specific eye findings, although this did not reach statistical significance. Despite a directive to halt nonemergent eye exams due to coronavirus disease 2019 (COVID-19), the rate of completed eye exams remained stable from 57% in the overall study period to 62% during the first 6 months of 2020. Although only 6 months of data were available for that year, it is notable that specific eye findings were noted in 3 of 8 examined patients (37.5%).

Nonspecific Eye Findings Did Occasionally Demonstrated Dynamic Changes on Follow-Up Exam

The vast majority of eye findings in this study were nonspecific (findings other than endophthalmitis and chorioretinitis), and the significance of these nonspecific eye findings remains unclear. However, it is notable that of the patients with nonspecific eye findings who underwent follow-up examination, 3 of 10 had worsening findings. This speaks against arguments that these nonspecific findings represent stable chronic conditions that are inactive.

Our study has several limitations that are worth noting. This is a retrospective study conducted across multiple centers within a single healthcare system. The rate of completed eye exams in the candidemic population in our healthcare system was only 57% despite an institutional protocol. Additionally, ophthalmology practice changed after the start of the pandemic and this could in theory affect the results of this study. However, only five patients were included in the study after March 2020 when COVID was declared a pandemic. Only one of these patients had specific eye findings, and another had nonspecific findings. Despite these limitations, our study adds to the body of work evaluating the impact of the use of echinocandins on the development of ophthalmic complications after candidemia. Furthermore, our study is one of few studies that reports follow-up ophthalmologic assessments of candidemic patients.

CONCLUSIONS

Comparing ocular complication rates for candidemia before 2016 to rates thereafter when use of echinocandins is prominent could provide some insights into the impact of these agents on the incidence of ophthalmic complications. It is notable that there has been a decrease in the use of ocular penetrating antifungal over the last several years, and the use of nonocular penetrating agents (echinocandins) was associated with the observation of abnormal findings on eye exam in our study. In addition, we report data indicating that although abnormal findings were common and increasing in prevalence, a statistically significant increase in *Candida*-specific findings was not noted, probably due to sample size limitations. It must also be noted that several patients with nonspecific findings had worsening findings on follow-up exam.

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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