

## Perspective

Do *all* candidemic patients need an ophthalmic examination?Michael J. Vinikoor<sup>a,\*</sup>, Jonathan Zoghby<sup>b</sup>, Kenneth L. Cohen<sup>b</sup>, Joseph D. Tucker<sup>a</sup><sup>a</sup> Department of Medicine, University of North Carolina, 130 Mason Farm Road, CB #7030, 2<sup>nd</sup> Floor Bioinformatics Building, Chapel Hill, NC 27599, USA<sup>b</sup> Department of Ophthalmology, University of North Carolina, Chapel Hill, North Carolina, USA

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## SUMMARY

Intraocular candidiasis is a potentially sight-threatening complication of candidemia. While the incidence of candidemia in North America has increased, the prevalence of intraocular candidiasis appears to be decreasing. In the USA and Europe, an ophthalmic examination is recommended for all candidemic patients to rule out intraocular involvement. However, improvements in management, clarification of the diagnosis, and trends in the epidemiology of intraocular candidiasis suggest that some candidemia patients might be safely managed without the recommended dilated ophthalmic examination.

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## 1. Introduction

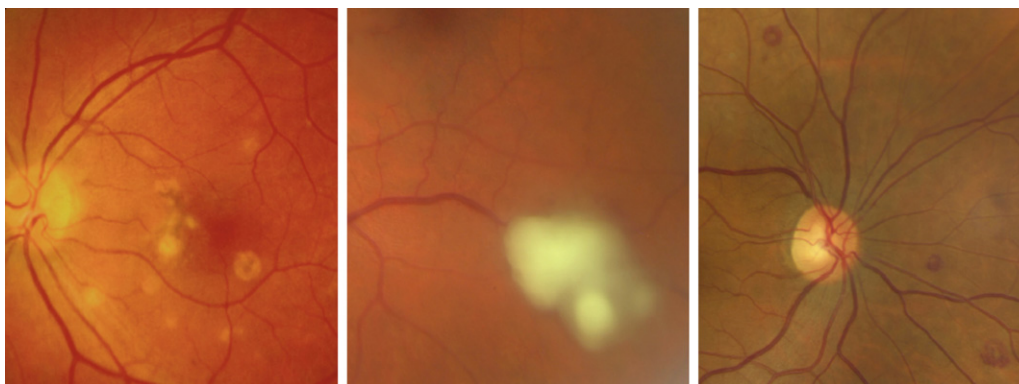
The incidence of invasive candidiasis is increasing.<sup>1,2</sup> An estimated 7–29 individuals per 100 000 population in North America will have an invasive *Candida* infection each year, with the majority being bloodstream infections.<sup>1</sup> Candidemia is usually a result of a central line-associated bloodstream infection and may lead to systemic manifestations. One of the most feared systemic manifestations of candidemia is eye involvement, which can result in loss of vision. The Infectious Diseases Society of America (IDSA) and European expert opinion currently recommend that all patients with documented candidemia receive at least one dilated eye examination, preferably by an ophthalmologist, to rule out intraocular involvement.<sup>3,4</sup> IDSA considers receipt of the ophthalmic examination a measure of quality of care for candidemic patients.<sup>3</sup> Timely diagnosis of intraocular candidiasis is critical because patients may require consideration for intravitreal antifungal therapy and/or vitrectomy. However, advances in the management, clarification of the diagnosis, and a possible decrease in the prevalence of intraocular candidiasis raise important questions about whether *all* candidemic patients should undergo an ophthalmic examination.

## 2. Intraocular candidiasis

Intraocular candidiasis is a spectrum of disease from chorioretinitis to gross infection of the vitreous body. Definitive diagnosis requires isolation of the organism from the eye in culture or histopathology. Usually a positive blood culture for *Candida* species and characteristic findings on ophthalmic examination are adequate evidence to justify treatment. During ophthalmic examination, chorioretinitis is characterized by the presence of deep focal, creamy white/yellow infiltrative lesions in the choroid or retina (Figure 1). Once identified, chorioretinitis rarely requires intraocular intervention. However, knowledge of the proximity of a lesion to the macula guides therapy, which usually consists of 4–6 weeks of systemically administered antifungal agents.<sup>3</sup> Ocular interventions are sometimes required when a vitreal abscess is found. A vitreal abscess presents as a fluffy white ball seen on ocular examination (Figure 1). Given the threat to vision and higher mortality associated with vitreal abscess, in addition to systemic therapy, intravitreal amphotericin and vitrectomy should be considered.<sup>3,5</sup>

The recommended ophthalmic examination for all candidemic patients is based partly upon studies from an era when less effective antifungal agents were used.<sup>6–8</sup> Systemic antifungals including amphotericin alone and echinocandins poorly penetrate the vitreous humor, and have been largely replaced by fluconazole in the treatment of most episodes of candidemia.<sup>3</sup> The regular use of a central nervous system (CNS) penetrating agent in cases of

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**Figure 1.** Dilated ophthalmoscopic images of chorioretinitis (left), vitreal abscess (center), and nonspecific fundus lesions (right). Images provided by Lee M. Jampol (Feinberg School of Medicine, Northwestern University) (left), James P. Gilman (Moran Eye Center, University of Utah) (center), and Glen S. Jenkins (Moran Eye Center, University of Utah) (right).

candidemia is hypothesized as one factor in the observed decline in cases of vitreal abscess.<sup>2,9,10</sup>

While chorioretinitis and vitreal abscess are sought during the eye examination in the setting of candidemia, ‘nonspecific fundus lesions’ are by far the most common abnormalities found (Figure 1). Nonspecific fundus lesions include cotton wool spots, retinal hemorrhages, and/or white centered hemorrhages (Roth spots). Although they are not manifestations of intraocular candidiasis, these non-specific findings have been included in prior disease estimates, leading to inaccurate prevalence rates.<sup>6–8</sup> Such nonspecific lesions are associated with hypertension, atherosclerosis, renal failure, anemia, thrombocytopenia, and other comorbid conditions. Finding a nonspecific lesion during examination does not require a change in the standard 2-week duration of systemic antifungal therapy for uncomplicated candidemia.<sup>3</sup>

When candidemia is complicated by ocular involvement, speciation and resistance testing of all isolated *Candida* species should be performed to rule out fluconazole resistance. Fluconazole’s broad antifungal spectrum and wide therapeutic index have led to its widespread usage. More than 17 different species of *Candida* can cause bloodstream infections, and frequent use of fluconazole selects for resistant ones, namely *Candida krusei* and *Candida glabrata*.<sup>11</sup> *C. krusei* is usually intrinsically resistant to fluconazole through alteration in the target enzyme, 14 $\alpha$ -demethylase,<sup>12</sup> while *C. glabrata* rapidly develops resistance in the presence of the drug via efflux pumps.<sup>13</sup> Regardless of the mechanism of resistance, most fluconazole-resistant *Candida* species are sensitive to the echinocandins. However, in suspected

or confirmed intraocular infections, amphotericin plus flucytosine or voriconazole are preferred due to better CNS penetration.<sup>3</sup>

### 3. Discussion

While prompt diagnosis of intraocular candidiasis is critical to optimal management, trends in the epidemiology of the disease challenge the need to screen all candidemic patients with dilated ophthalmoscopy. In the setting of candidemia, the prevalence of intraocular *Candida* was estimated at 28–45% in studies that included nonspecific lesions (e.g., Roth spots) and utilized older antifungal agents.<sup>6–8</sup> More recent studies in the era of fluconazole and excluding nonspecific lesions have estimated the prevalence of true intraocular *Candida* at 1–16% (Table 1).<sup>14–20</sup> In addition to reclassification of nonspecific lesions, earlier diagnostic suspicion and prompt initiation of potent antifungals are likely to have contributed to the decrease in the rate of true intraocular disease.<sup>2,9,10</sup>

In the setting of decreasing prevalence, symptom-guided screening should be further evaluated as an approach to obviate the need for ophthalmic examinations in all candidemic patients. Many patients with candidemia are systemically ill and unable to articulate the presence or absence of visual symptoms. Intraocular disease can be present in the absence of symptoms, yet some studies have suggested that symptom reports among patients able to reliably communicate might be helpful in determining who should undergo dilated ophthalmic examination. During 118 examinations for candidemia, 50% of patients who reported visual symptoms (eye pain, red eyes, or floaters) were found to have

**Table 1**  
Prevalence of intraocular candidiasis among patients with candidemia<sup>a</sup>

First author	Year(s) of study or publication	Number of exams	Percent with intraocular candidiasis	Included nonspecific fundus lesions
Edwards	1974	34	44.6%	Yes
Parke	1982	38	28.9%	Yes
Brooks	1989	32	28.1%	Yes
Donahue	1994	118	9.3%	No
Rodriguez-Adrian	1993–1994	180	5.0%	No
Krishna	1996–1997	31	25.8%	No
Feman <sup>b</sup>	1995–2000	82	2.4%	No
Oude Lashof	1998–2003	370	10.8%	No
Popovich	2003–2005	80	6.0%	No
Shah	2006	38	7.9%	No
Dozier	2007–2009	211	0.9%	No

<sup>a</sup> Diagnosis based upon a positive blood culture and characteristic findings on ophthalmic examination (few cases were confirmed by intraocular culture or histopathology).

<sup>b</sup> Included patients with non-*Candida* fungal bloodstream infections.

intraocular candidiasis.<sup>15</sup> In a different study, symptom reports from patients who could communicate (which authors defined as anyone aged  $\geq 18$  years old who was not delirious and was examined outside of the intensive care unit) were analyzed. Among 211 candidemic patients who could communicate the absence of vision symptoms, none were found to have eye involvement.<sup>19</sup> In retrospective studies, symptom reports can be inaccurate and these findings require prospective confirmation.

In light of changes in the epidemiology, diagnosis, and treatment of intraocular candidiasis, and in order to improve the value of medical care, we suggest that further prospective research be done to refine the role of the ophthalmic examination for patients with candidemia. The cost-effectiveness of dilated ophthalmoscopy in cases of candidemia has not been assessed. Each examination can cost as much as US\$ 400 and carries a small risk of acute angle-closure glaucoma. Given the increased incidence of candidemia and decreased prevalence of intraocular disease, the requirement that every patient with candidemia have a dilated ophthalmic examination should be reconsidered.

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*Conflict of interest:* No conflict of interest to declare.

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