



## Funduscopy Screening of Fungemic Patients: where we Stand

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### Commentary

Candida and other fungal species account for approximately 9.5% of nosocomial bloodstream infections in the United States, with an incidence of 4.6 per 10,000 admissions [1]. Patients with a history of diabetes, indwelling lines/catheters, hyperalimentation, and immunocompromise are at increased risk for fungal bloodstream infections [2-5]. Dissemination of fungal organisms to the eye can occur via hematogenous seeding of small retinal and choroidal capillaries. Localized ocular fungal proliferation can progress to focal or multifocal inflammatory lesions manifesting as chorioretinitis and subsequent abscess formation and vitreous seeding can then lead to frank endophthalmitis. Fungal chorioretinitis and endophthalmitis carry the potential to cause devastating vision loss. Early recognition and prompt treatment can confer more favorable outcomes [6]. Previous studies in a variety of clinical settings not necessarily applicable to the modern tertiary care hospital demonstrated that patients with fungemia developed ocular involvement in 10% to 45% of cases [7-10]. These historically high rates have justified routine funduscopy screening of inpatients for ocular fungal involvement.

At our institution, as is the case for many tertiary care hospitals, the Ophthalmology service is routinely consulted to rule out ocular involvement in patients with positive fungal blood cultures. However, recent data has raised the question if inpatient funduscopy screening is necessary. Over the past 2 decades there has been a trend towards decreasing prevalence of ocular involvement and recent studies suggest that the prevalence of endogenous ocular fungal infections is much lower than previous reports [11-15]. This decline is thought to be due to advances in antifungal therapy, prophylactic systemic anti-fungal treatment in cases with high clinical suspicion, and prompt treatment once positive cultures are identified.

In the context of this evolving clinical issue, our group recently published a 6 year observational, retrospective study describing the microbial profile of fungal chorioretinitis and endophthalmitis at our tertiary care hospital and the impact of ophthalmologic consultation on inpatient management [16]. This study of 227 patients revealed a 4.8% (N=11) rate of ocular fungal involvement manifesting as chorioretinitis (N=7) or endophthalmitis (N=4). Eleven patients (4.8%) had non-specific fundus lesions including white/yellow retinal lesions, cotton wool spots, and retinal hemorrhages deemed to be inconsistent with ocular fungal involvement. Two additional patients were diagnosed with endogenous bacterial endophthalmitis in the setting of suspected fungemia and were treated with intravitreal antifungal medications in conjunction with intravitreal antibiotics. Additionally, 2.2% of patients (N=5) received intravitreal injections of antifungal medications for endogenous fungal endophthalmitis.

Our study also explored the utility of visual symptoms in predicting ocular fungal involvement. Seven of 156 patients (4.5%) who were able

to communicate and 4 of 156 patients (2.6%) who were unable to communicate had ocular involvement. Of the 11 patients with positive eye findings, 2 were asymptomatic and 4 were unable to verbalize symptoms, while the remaining 5 reported having visual symptoms. As the majority of patients with ocular involvement were either asymptomatic or were unable to communicate, we believe funduscopy screening of fungemic inpatients still has an important role. Our analysis indicates that the presence or absence of visual symptoms in verbal patients are not sufficiently sensitive or specific to predict the presence of ocular involvement. Furthermore, when fungal ocular involvement is present, it confers a poorer systemic prognosis and extends the timeline for systemic anti-fungal treatment [17]. Infectious disease guidelines dictate that evidence of ocular involvement should extend the duration of antifungal treatment to 4 to 6 weeks after signs of intraocular infection have resolved [18].

Several studies have suggested that ocular involvement in patients with known or suspected fungemia may be less than previously reported. A review of a large insurance claim database of 3,704 fungemic inpatients revealed a 0.4% rate of presumed endogenous endophthalmitis, with the leading predictors of ocular involvement being infectious meningitis, endocarditis, immunocompromise, extended hospital stay, and intensive care unit admission [5]. Another retrospective report analyzing 93 intensive care unit patients with candidemia disclosed a 2.9% rate of ocular candidiasis. In a 3 year retrospective study of 211 patients who underwent ophthalmic evaluation, Dozier et al. reported a rate of less than 1% (2/211) of fungal chorioretinitis or endophthalmitis [12]. Of note, in contrast to our study, no asymptomatic patients had evidence of ocular involvement. This finding prompted the authors to suggest that medical resources may be better utilized via a targeted screening approach. Differences in ocular involvement rates likely reflect regional epidemiologic factors, patterns of anti-fungal treatment, and microbial resistance, and the fact that our patient population did not include pediatric patients.

More recently, a retrospective report of 238 patients examining outcomes and cost effectiveness of ophthalmic consults to screen for ocular fungal involvement concluded that screening all fungemic inpatients may not be justified on the basis that changes in clinical management were uncommon. The authors reported 22 (9.2%) patients with ocular involvement, of which 9 (3.7%) patients had a change in management based on ophthalmic consultation. The authors estimated that to screen for a single patient requiring intervention with intravitreal injection of antifungal medications, the associated cost is greater than \$50,000 in a patient population with a high mortality rate. However, a critical limitation of this economic analysis is that true cost effectiveness of ocular fungal screening could not be calculated because final ophthalmic outcomes and visual acuities were not available.

Finally, in a recent 3 year, observational prospective study, Paulus et al reported on 125 fungemic inpatients where 7 cases of ocular involvement were identified (5.6%) [15]. Of these positive cases, 2 patients were diagnosed with endophthalmitis (1.6%). Two patients who had a negative initial examination subsequently had a positive examination. Visual symptoms, as similarly reported in our study, were neither sensitive nor specific for detecting ocular involvement, as 57% of patients with chorioretinitis who could verbalize symptoms were asymptomatic. Ocular involvement was found to confer a poor systemic prognosis; 57% of patients with chorioretinitis died while 32% of patient with ocular fungal involvement died. As reported previously [2-22], two patients developed chorioretinitis after an initial negative funduscopy screening, prompting the authors to conclude that two dilated ophthalmic examinations within a 2 week interval should be considered, even in asymptomatic patients. Limitations of this study include the low incidence of ocular involvement and associated inability to detect subtle risk factors for developing ocular involvement due to a lack of statistical power.

Despite the fact that multiple recent studies report very low rates of disseminated ocular involvement in patients with positive fungal cultures, continued inpatient funduscopy screening of all fungemic patients is justified. This practice is supported by the fact that the presence of ocular fungal involvement dictates the mode and duration of anti-fungal treatment [18]. Ocular involvement can still manifest after an initial negative funduscopy screening and over half of affected patients in our study and the prospective study by Paulus and colleagues were either asymptomatic or unable to communicate [15,16]. Furthermore, our data has shown that visual complaints in verbal patients is not predictive of ocular fungal involvement, underscoring the importance of ophthalmoscopic screening. Still, the issue remains under debate as reports with similar or lower rates of ocular fungal involvement have suggested that ophthalmic screening for all patients with positive fungal blood cultures may not be necessary [5,12,20]. Concerns regarding practicality and cost effectiveness of ophthalmic screening for all patients with positive fungal blood cultures certainly have validity, but any conclusions in this regard would be better substantiated by additional prospective studies. Future efforts examining screening for fungal ocular involvement should include portable fundus imaging to assess the utility of teleophthalmic screening, identify the strongest risk factors for developing ocular involvement, incorporate visual outcomes, and be multicentered to achieve adequate statistical power and control for regional differences in patient populations, microbiologic profiles, and antifungal treatment patterns. As of now, the current body of evidence supports routine funduscopy screening of inpatients with positive fungal cultures with two dilated examinations with a two week period.

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