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American Academy of Ophthalmology Recommendations on Screening for Endogenous *Candida* Endophthalmitis

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The American Academy of Ophthalmology evaluated the practice of routine screening for intraocular infection from *Candida* septicemia. In the United States, ophthalmologists are consulted in the hospital to screen for intraocular infection routinely for patients with *Candida* bloodstream infections. This practice was established in the era before the use of systemic antifungal medication and the establishment of definitions of ocular disease with candidemia. A recent systematic review found a rate of less than 1% of routinely screened patients with endophthalmitis from *Candida* septicemia. Other studies found higher rates of endophthalmitis but had limitations in terms of inaccuracies in ocular disease classification, lack of vitreous biopsies, selection biases, and lack of longer-term visual outcomes. Some studies attributed ocular findings to *Candida* infections, rather than other comorbidities. Studies also have not demonstrated differences in medical management that are modified for eye disease treatment; therefore, therapy should be dictated by the underlying *Candida* infection, rather than be tailored on the basis of ocular findings. In summary, the Academy does not recommend a routine ophthalmologic consultation after laboratory findings of systemic *Candida* septicemia, which appears to be a low-value practice. An ophthalmologic consultation is a reasonable practice for a patient with signs or symptoms suggestive of ocular infection regardless of *Candida* septicemia. *Ophthalmology 2021;■:1–4 © 2021 by the American Academy of Ophthalmology*

Instituting evidence-based guidelines for patient care helps to reduce care practices that are less cost-effective or lack benefit.[1,2] Low-value care not only is inefficient but also may be unsafe. Low-value care leads to an estimated $67 billion in unnecessary cost to the healthcare system annually in the United States.[1,2] Harm appears to be more challenging to quantify, although hospital-acquired complications are reported as high as 15% after procedures considered to be low value.[3] For example, when unrecognized, overdiagnosis (identifying indolent lesions otherwise not posing risk) leads to overtreatment and harm, a concept that has been used in reforming various cancer screening paradigms.[4]

We propose exploring the low-value care practice of routine screening for intraocular infection from *Candida* bloodstream infections (candidemia), one of the most common hospital consultations for American ophthalmologists.[5] We advocate to minimize candidemia-related screening examinations and share evidence in the literature that is based on numerous studies of endogenous *Candida* endophthalmitis. Two professional organizations internationally, the Royal College of Ophthalmologists and the Intensive Care Society, have recently implemented guidelines in collaboration that support these efforts.[6]

The root cause of this practice pattern can be traced to the Infectious Diseases Society of America (IDSA) Clinical Practice Guideline for the Management of Candidiasis, which advises an eye screening examination, "preferably performed by an ophthalmologist" for all (even asymptomatic) patients with candidemia.[7] The recommendation is made without participation by a body of similar stature representing ophthalmologists and is based on the presumption that such screening will prevent vision loss.[7] It is extracted from studies that are decades old, performed before implementing appropriate definitions of ocular disease with candidemia and before the era of systemic antifungal medication.[7–9] The "low-quality evidence" status has been recognized by the IDSA, whereas the guideline inflates the likelihood of sight-threatening disease and the benefits of ophthalmologic evaluation.[7–10] Because disagreement exists between specialists concerning the necessity and utility of these examinations,[8–14] the purpose of this position statement is to initiate steps to correct widespread misunderstanding and establish new recommendations.

Knowledge gaps in overuse and misuse, both within ophthalmology[9,15,16] and infectious diseases[7,11,17,18] literature, may explain the inconsistency in understanding between screening and vision loss.[1] Overuse (increased intervention with inefficacies and potentially harm) and misuse (an effective intervention in an inappropriate context) apply,[1] and include using advanced vitreoretinal surgical techniques with known risks[19] or alterations in systemic antifungal therapy that may be contrary to principles of

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antimicrobial stewardship (i.e., adding, switching, or extending agents with different side effect profiles for a theoretical rather than substantiated purpose).[20,21] Studies of examined patients have demonstrated the risks without demonstrating proven benefit. These risks result from intervening upon incidental findings due to the underlying conditions and comorbidities, yet not specifically from intraocular infection due to candidemia.[9,11,12,22,23]

Endophthalmitis from *Candida* septicemia occurs in less than 1% of routinely screened patients based on a systematic review of approximately 7500 examined patients, including more than 1000 identified prospectively.[9] Older definitions of endophthalmitis differ from current literature. For example, a study from 1982 in *Ophthalmology* reports an endophthalmitis incidence of 37%.[15] However, at least 1 photographic example was inconsistent with an endophthalmitis diagnosis.[15] A multicenter, prospective investigation in 1994 from the same journal helped clarify the discrepancy, by using rigorous definitions, with no cases of endophthalmitis identified among 3 different centers from screening over 2.5 years.[16]

Patients with candidemia generally have comorbidities that can explain intraocular findings: anemia, hypertension, and thrombocytopenia, among many other conditions simultaneously as critically ill patients.[16] Such abnormal, nonspecific retinal features include Roth spots or other hemorrhages, and cotton wool spots, and do not require ophthalmologic intervention.[16] Cotton wool spots can be challenging to distinguish clinically from a deeper chorioretinitis, even when using advanced imaging modalities such as OCT.[24,25] Histopathologic analysis in many of these cases is necessary for distinction but impractical outside of autopsy. These screening findings leave ophthalmologists with a diagnostic and therapeutic dilemma, given the lack of specificity for these lesions without established criteria for intervention in this context.

Numerous recent studies perpetuate deficiencies, including selection bias, lack of vitreous biopsies, absent criteria for intervention or change in management based on screening, inaccurate or misleading ocular disease classification, and exclusion of critical outcomes data.[26–30] For example, in 2019, Ueda et al[26] reported a retrospective, multicenter study from 15 medical centers in Japan with an incidence of 13% when ophthalmologists examined non-neutropenic patients and 43% of these with endophthalmitis or macular involvement. Although the authors concluded that routine screening is warranted, the quality of data is limited with a high risk of bias. The weaknesses found in this report include the following: (1) Only 71.7% of the cohort was screened; (2) 0% of the screened cohort had vitreous confirmed biopsy; (3) the positive cases were considered "probably or possible ocular candidiasis"; (4) no vitrectomies were performed; (5) only 2 patients received intravitreal therapy; (6) and all positive cultures were exclusively obtained from the blood.[26] Thus, the data from this study are insufficient to support the authors' conclusions.

A major shortcoming throughout the literature is the failure of recognizing the prevalence of ocular findings in critically ill patients without candidemia. A notable exception is the study by Rodríguez-Adrián et al,[31] who examined a cohort of patients in a critical care unit regardless of candidemia status, representing a control group, and identified abnormal retinal findings in 19%.[31] The IDSA guidelines cite a comparable rate (16%) of associated ocular findings in patients with candidemia.[7] Given the lack of control groups among remaining candidemia studies, there is concern of potential harm from interventions that arises from screening because retinal findings in contemporary studies are often attributed to candidemia rather than associated comorbidities.[12,22,23] Perhaps, the question is not *if* unnecessary intervention and misuse[1] are occurring, but *how much*. Overuse of interventions[1] is challenging to quantify,[3,4] particularly with cases of mild endophthalmitis (e.g., peripheral vitreoretinal lesions) or chorioretinitis that may resolve without any intervention.[25,32] Screening has not been proven beneficial and may lead to harm, especially given poor outcomes that have been associated with invasive intervention.[9] Furthermore, mortality rates of patients with systemic candidemia approach 30%,[33] and adherence to screening is missed beyond 30% without evidence of unfavorable outcomes.[12,22,26]

Optimizing systemic treatment of the underlying conditions, the *Candida* bloodstream infection itself, and related comorbidities appear to be most important in successful management of incidentally associated ocular disease and the overall survival of the patient.[9,19,33] Early suspicion and detection of systemic candidemia are essential, in addition to appropriate systemic antifungal therapy for a minimum of 2 weeks after negative blood culture growth and clearance of other infectious sources with immediate exchange of indwelling catheters, as advocated by the IDSA.[7,18] At least 2 patients from 2 studies developed endophthalmitis after failure to exchange indwelling catheters for more than 1 week,[17] or having received systemic antifungal therapy for just 2 days,[18] after detection of systemic candidemia. Interestingly, 1 patient had resolution of endophthalmitis after removal of an indwelling catheter without any systemic antifungal therapy or invasive ophthalmologic intervention.[34]

Experimental evidence suggests that voriconazole has superior vitreous penetration from the bloodstream,[35] lending potential credence to continuing screening examinations to tailor medical management, even if invasive intervention is not performed.[17,36] However, these data have not been replicated in clinical literature.[17,37] One large, prospective study by Oude Lashof et al[17] was unable to demonstrate an advantage of systemic voriconazole to amphotericin B followed by fluconazole. Post hoc analysis of another prospective, multicenter study of candidemia (CANDIPOP) examined the systemic efficacy of echinocandins (speculated to have relatively poor vitreous penetration)[36] and did not show a difference in associated ocular findings when compared with other drugs.[8,37] It is unknown if other organ systems are affected by a change in systemic antifungal therapy based on ocular findings (including extensions in treatment duration). In our experience, many infectious diseases physicians feel compelled to adjust systemic management on the basis of the evidence of retinal findings. This practice does not appear substantiated given the lack of specificity of the lesions and a multitude of potential complications from altering systemic agents.[18,21] Thus,

systemic management should be tailored to the underlying candidemia, rather than associated ocular findings.

The pathophysiology of endogenous *Candida* endophthalmitis can largely explain many of these clinical findings and outcomes as they relate to bloodstream infections. Experimentation, autopsy, and conventional imaging have all demonstrated that the origin of typical lesions is localized to the inner choroid.[25,38,39] The choroid is the most vascular tissue of the body,[40,41] and therapeutic systemic antifungal drug levels should be easily achieved without regard to vitreous penetration. A direct relationship between increased microcirculatory blood flow and greater antibiotic concentration has been supported in a study of human volunteers.[42] Vitreous penetration from systemic therapy may be enhanced by the breakdown of the outer blood-retinal barrier known to occur with intraocular inflammation.[43]

In conclusion, the American Academy of Ophthalmology recommendations are as follows. Ophthalmologic consultation is reasonable for anyone with a clinical rationale including signs or symptoms concerning for an ocular infection. However, because current evidence does not support a routine ophthalmologic consultation after laboratory findings of systemic *Candida* septicemia, this low-value practice should be de-adopted. Any future recommendations should be developed through collaborative efforts between specialists represented by ophthalmology and infectious diseases. Such efforts and any future studies must eliminate discrepancies regarding the incidence of sight-threatening disease and potential benefit of ophthalmologic screening for candidemia within the literature after carefully applying rigorous definitions, reviewing associated clinical data, including control groups, and including long-term visual outcomes data. These recommendations are based on, but not limited to, safety, efficacy, epidemiology, and pathophysiology of endogenous *Candida* endophthalmitis.

Footnotes and Disclosures

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