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EDITORIAL

On the American Academy Recommendations for cancelling routine screening for ocular candidiasis - are we being too hasty?

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Candidemia is an important cause of morbidity and mortality among immunocompromised and acute care patients, requiring prompt systemic antifungal treatments. Ocular involvement from hematogenous seeding via retinal and choroidal vessels is a well-known complication, affecting between 2% and 20% of candidemic patients, with potentially visually devastating outcomes. Of these, it is estimated that 40–60% are unable to self-report symptoms and up to 50% and 85% of patients with endophthalmitis and chorioretinitis, respectively, are asymptomatic [1]. For this reason, routine ophthalmological screening of candidemia patients for rapid diagnosis and treatment has been accepted as the standard of care.

Indeed, while azoles may still be used as an initial treatment, since 2016 the Infectious Diseases Society of America (IDSA) clinical practice guidelines have recommended echinocandins as first-line therapy in most settings due to its efficacy, favourable safety profile and limited concerns regarding resistance. However, echinocandins are known to provide lower ocular penetrance with subtherapeutic concentrations in the vitreous and aqueous humour reported after systemic dosing. Suspicion of ocular involvement may prompt a switch of antifungal therapy to prevent vitreous extension of chorioretinal disease and justify tighter ophthalmological follow-ups.

Recently, the American Academy of Ophthalmology (AAO) published recommendations against routine ophthalmology consultations for candida septicaemia, recommending instead to only examine patients with signs and symptoms suggestive of ocular infection [2]. The recommendations mainly stemmed from the results of a systematic review by Breazzano et al. that pooled 38 studies with 7472 patients and reported a less than 1% rate of endophthalmitis [3]. These were "concordant" cases of *Candida* endophthalmitis, defined as having evidence of vitreous involvement. For "discordant" cases (defined as absence of vitreous involvement) or probable chorioretinitis, they found a rate of 14.6%, with an overall difference in rate between concordant and discordant cases of 13.8%. The authors concluded that ophthalmologic examination provided limited therapeutic value and invasive management including intravitreal injections or vitrectomy was associated with poorer outcomes and a higher rate of vision loss.

Though well-conducted, the report was limited by the paucity of available data. Studies do not always systematically screen all patients, report outcomes, or provide microbiological confirmation of ocular involvement. For example, none of the endophthalmitis cases included had intraocular histologic or microbiologic confirmation of *Candida*. The conclusion regarding worse vision prognosis in patients treated with additional invasive intervention compared to systemic antifungal therapy alone was based on the data of only 12 patients, after excluding 6 deaths. The studies were retrospective in nature which introduces potential selection bias, for example with patients having more significant ocular involvement being allocated to more invasive intraocular treatment. Variable definitions for endophthalmitis, surgical success and failure and extent of ocular involvement across studies may bias analyses. These limitations undermine the ability of the current study to conclude on the value of the current IDSA screening guidelines for ocular candidiasis.

In fact, the current guidelines meet most expectations of a good screening test. The dilated fundus exam is simple, non-invasive, and cheap, allows for detection of a disease that is potentially devastating and may lead to change in management and outcomes. Specifically, this may engender a switch from echinocandins to azoles to achieve superior vitreous penetrance. Recently, a study comparing the incidence of ocular findings in candidemic patients before and after the IDSA recommendations in 2016 found a temporal increase in chorioretinal findings in the era of echinocandins. The authors reported an increase rate of ocular findings (both specific and non-specific) from 18.9% in 2016 to 60% in 2020 with an overall rate of 23.3%, in contrast to previously reported rates of 16% [4]. Additionally, more recent studies have been reporting higher rates of *Candida* endophthalmitis, with one study on persistent candidemia reporting a rate of 8.3% [5]. Until more conclusive studies are published, this alone may lend credence to continue screening to adjust antibiotherapy as needed even if invasive treatment is not performed.

This should also be considered when referring to the study by Breazzano et al. [3] Of the 38 studies, only one study was published after 2016 (Munoz et al., 2017) and only two of the patients for which treatment regimen and outcome data were complete had been treated with echinocandins, with the rest being treated with voriconazole, fluconazole, amphotericin B or an unspecified anti-fungal. Though the authors state that discovery of endophthalmitis during screening exams did not lead to a change in management in 12 of the 19 patients, this may in part be because patients were already on an antifungal with optimal ocular coverage.

In conclusion, the AAO recommends that symptomatic patients be evaluated, appearing to acknowledge that detection of ocular candidiasis in these patients would at least warrant revisiting management options. However, as brought forth by O'Donnell et al. [1], there is no reliable way to stratify patients with candidemia who would most benefit from an evaluation and no evidence to suggest that ocular candidiasis cases in patients that are asymptomatic or unable to verbalise should be treated differently from symptomatic cases.

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The discrepancy in approach between the AAO and IDSA guidelines appears to be that the AAO accepts the possibility of missing true positives in favour of saving negative patients from unnecessary examination, while the IDSA accepts subjecting negative patients to unnecessary examination to identify all true positives including potentially non-specific findings. This difference in priorities is anchored in the belief that examinations would only lead to harm from acting on "incidental findings." However, upon review of the included citations, no actual data is presented to substantiate the claims. Furthermore, the claim that alterations in systemic antifungal therapy are contrary to principles of antimicrobial stewardship is equally unsupported by IDSA guidelines which endorses fluconazole as an acceptable alternative to echinocandins (strong recommendation, high-quality evidence).

The authors believe until more convincing data is released, it is most judicious to continue with ophthalmologic screening. At a minimum, well-conducted prospective double-blinded randomised controlled trials comparing antifungals (particularly echinocandins and azoles) for ocular outcomes and/or evaluating the outcomes of screening among asymptomatic patients should be done prior to establishing a new standard of care.

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AUTHOR CONTRIBUTIONS

MJA conceived of the presented idea and supervised the overall work. ELY and MH wrote the manuscript with support from MJA and SFD. All authors provided critical feedback and contributed to the final version of the manuscript.

COMPETING INTERESTS

The authors declare no competing interests.