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Outcomes, Impact on Management, and Costs of Fungal Eye Disease Consults in a Tertiary Care Setting

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Objective: To determine the frequency of clinical management changes resulting from inpatient ophthalmic consultations for fungemia and the associated costs.

Design: Retrospective case series.

Participants: Three hundred forty-eight inpatients at a tertiary care center between 2008 and 2012 with positive fungal blood culture results, 238 of whom underwent an ophthalmologic consultation.

Methods: Inpatient charts of all fungemic patients were reviewed. Costs were standardized to the year 2014. The Student *t* test was used for all continuous variables and the Pearson chi-square test was used for categorical variables.

Main Outcome Measures: Prevalence of ocular involvement, rate of change in clinical management, mortality rate of fungemic patients, and costs of ophthalmic consultation.

Results: Twenty-two (9.2%) of 238 consulted patients with fungemia had ocular involvement. Twenty patients had chorioretinitis and 2 had endophthalmitis. Only 9 patients (3.7%) had a change in management because of the ophthalmic consultation. One patient underwent bilateral intravitreal injections. Thirty percent of consulted patients died before discharge or were discharged to hospice. The total cost of new consults was $36 927.54 ($204.19/initial level 5 visit and $138.63/initial level 4). The cost of follow-up visits was $13 655.44 ($104.24/visit). On average, 26.4 patients were evaluated to find 1 patient needing change in management, with an average cost of $5620.33 per change in 1 patient's management.

Conclusions: Clinical management changes resulting from ophthalmic consultation in fungemic patients were uncommon. Associated costs were high for these consults in a patient population with a high mortality rate. Together, these data suggest that the usefulness of routine ophthalmic consultations for all fungemic patients is likely to be low. *Ophthalmology 2014;■:1–6 © 2014 by the American Academy of Ophthalmology.*

Systemic fungemia is a common cause of nosocomial infection. Risk factors for disseminated fungal infection include parenteral nutrition, indwelling intravenous lines, immunocompromised status, recent surgery, intravenous drug abuse, and diabetes.[1,2] Ocular involvement in fungemic patients is an uncommon, but potentially disastrous, cause of vision loss in hospitalized patients. The Infectious Diseases Society of America currently recommends that all patients with fungemia undergo at least 1 dilated eye examination to rule out ocular involvement.[3]

Because of the considerable burden presented by hospitalized patients with fungemia, consultations to rule out ocular involvement in fungemic patients is one of the most common reasons for inpatient ophthalmologic consultation.[4,5] The recommendation for routine consultation persists despite improved efficacy and side-effect profiles of newer generations of antifungal classes such as triazoles (fluconazole) and echinocandins (caspofungin). Quicker laboratory detection of systemic fungal infections also has allowed earlier and more consistent treatment in at-risk patients.[6] The earlier recognition of infection and use of systemic antifungal therapy have been suggested as the main reason for the decrease in the prevalence of ocular involvement in fungemia.[7–10] Furthermore, because many patients with fungal disease are already on systemic antifungals at the time of consultation, it is unclear how frequently ophthalmic consultation benefits these patients by altering their management.

Because disseminated ocular fungal infection is becoming less common and the need for intervention in those few patients is even more rare, routine ophthalmologic consultation on all fungemic inpatients may not be an efficient use of clinical resources.[7–10] The present report is the largest to examine the impact of ophthalmologic consultation on the management of fungemic patients and the costs associated with this care.

Methods

This study was a retrospective case series at the Hospital of the University of Pennsylvania conducted between January 1, 2008, and December 31, 2012. Penn Medicine's Clinical Data Warehouse containing clinical diagnostic codes and pharmacy and laboratory data for all patients treated at the Hospital of the University of Pennsylvania was queried twice. The first query returned all inpatients who had a positive fungal blood culture results.

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Fungal genera searched for included *Candida*, *Aspergillus*, and *Cryptococcus*. The second query returned all inpatients who were given systemic antifungal medications during the study period. The 2 lists were cross-referenced, and all patients appearing on both lists had their chart reviewed. Patients younger than 18 years of age were excluded. Repeat positive fungal cultures were considered new events if 90 days had passed since the previous positive culture results. Because there was often a delay of at least 2 days between blood culture sampling and results of the fungal culture, we excluded patients who were discharged or died before positive fungal culture results were reported.

All eligible patient charts were reviewed for documentation of formal comprehensive ophthalmologic examination. Visual acuity was assessed with standard near card at the bedside or with Snellen chart in the clinic. The anterior segment was examined with either a penlight or portable slit lamp at the bedside and a standard slit lamp in the clinic. All dilated fundus examinations were performed with indirect ophthalmoscopy after pupillary dilation with mydriatic agents.

Study data were collected and managed using Research Electronic Data Capture tools hosted at the University of Pennsylvania.[11] Research Electronic Data Capture is a secure, web-based application designed to support data capture for research studies, allowing for data entry, tracking of data manipulation and export procedures, and an automated export procedure for data downloads to common statistical packages. Data extracted from the inpatient record included patient demographics, cultured fungal species, suspected cause of fungemia, duration of antifungal therapy before consultation, antifungal at time of consultation, time from positive culture results to ophthalmic consultation, ability to verbalize symptoms, visual symptoms, visual acuity, fundus examination findings, any recommended change in management from the consultation, and whether the primary team followed through with the recommended change in management. We used the classification system for ocular fungemia proposed by Donahue at al.[7] Chorioretinitis was defined as deep focal, fluffy white lesions localized within the chorioretinal layers. Vitreitis or endophthalmitis was defined as extension into the vitreous with fluff balls, vitreous haze, or vitreous abscess.

Costs of new inpatient and subsequent inpatient visits were obtained from the Centers for Medicare and Medicaid Services 2014 Physician Fee Schedule.[12] Because actual billing data were not available for review, total new patient costs were estimated by combining the costs of level 5 and level 4 new inpatient visits. Patients who received a consultation and needed follow-up presumably were more complex, requiring additional medical decision making, and were assigned a level 5 new visit. Patients who received a consultation and did not need follow-up presumably required less medical decision making, and thus a level 4 visit was used for cost calculations. The national average cost of a level 5 new inpatient consultation (Current Procedural Terminology code 99255) was $204.19. The national average cost of a level 4 new inpatient consultation (Current Procedural Terminology code 99254) was $138.63. The national average cost of a level 3 subsequent inpatient follow-up visit (Current Procedural Terminology code 99233) was $104.24. All statistical analyses were performed with STATA software (College Station, TX). The Student *t* test was used for all continuous variables, and the Pearson chi-square test was used for categorical variables. Two-sided *P* values of less than 0.05 were considered statistically significant. This study was approved by the University of Pennsylvania's Institutional Review Board and adhered to the tenets of the Declaration of Helsinki.

Table 1. Baseline Characteristics of Fungemic Patients Who Had Ophthalmology Consultation versus Those Who Did Not Have an Ophthalmology Consultation

	Ophthalmology Consultation	No Ophthalmology Consultation	*P* Value
Total no.	109	239	
Male gender (%)	56.9	55.6	0.83
Mean age (yrs)	57.8	56.9	0.62
Mortality + hospice rate (%)	56.9	28.9	<0.001
Pathogen			0.04
Candida albicans	50	108	
Candida glabrata	22	52	
Candida parasilosis	12	36	
Candida tropicalis	7	19	
Candida krusei	2	7	
Candida lusitaniae	2	3	
Candida dubliniensis	0	3	
Candida famata	0	2	
Candida guilliermondii	0	1	
Cryptococcus	12	3	
Malassezia	0	1	
Rhodotorula	0	1	
Fusarium	0	1	
Trichosporon	1	0	
Unspecified budding yeast	1	0	
Multiple species	0	2	

Results

During the study period, 390 patients had positive blood culture results for fungus. Of these, 42 patients were excluded for the following reasons: 23 did not have a complete inpatient record, 13 had positive fungal culture results only after death or hospital discharge, 4 were younger than 18 years, 1 patient was thought to have a contaminant rather than true positive fungal culture results, and 1 patient was consulted only for diplopia without mention of positive fungal culture. Of the 348 patients meeting inclusion and exclusion criteria, the ophthalmology department was consulted for 239 patients (68.7%). Of these, 238 patients underwent a complete ophthalmic examination and 1 patient declined examination.

Of the 348 study patients meeting inclusion and exclusion criteria, 56% were male and the mean age was 57.2 years, with a range of 19 to 92 years (Table 1). The most common species identified on fungal culture were *Candida albicans*, *Candida glabrata*, and *Candida parapsilosis*, which were found 45.4%, 21.2%, and 13.8% of the time, respectively. *Cryptococcus* was identified in 4.3% of blood cultures. The most frequent primary suspected cause of fungemia was indwelling line, and the second most frequent was intravenous hyperalimentation. There were no significant differences in gender or mean age between patients for whom the ophthalmology department was and was not consulted (Table 1). The rate of mortality or transfer to hospice was significantly higher for patients for whom ophthalmology was not consulted ($P < 0.001$). Also, patients who did not receive an ophthalmology consult were significantly less likely to have *C. glabrata* identified on fungal culture ($P = 0.037$).

The overall incidence of ocular involvement in fungemic patients with ophthalmologic consultation was 9.2% (22 of 238 patients; Table 2). There were 20 cases of chorioretinitis (8 unilateral and 12 bilateral). There were 2 cases of endophthalmitis (both bilateral). Comparisons of the group of patients with and without ocular involvement are shown in Table 2. The groups did

Table 2. Comparisons of Fungemic Patients with Ocular Involvement Noted on Ophthalmic Examination versus Those without Ocular Involvement

	No Ocular Involvement	Ocular Involvement	*P* Value
Total no.	217	22	
Male gender (%)	55.3	59.1	0.73
Mean age (yrs)	56.9	56.6	0.93
Verbal (%)	70.0	63.6	0.53
Mortality + hospice rate (%)	28.6	31.8	0.75
Pathogen			0.72
Candida albicans	96	12	
Candida glabrata	48	4	
Candida parapsilosis	35	1	
Candida tropicalis	16	3	
Candida krusei	6	1	
Candida lusitaniae	2	1	
Candida dubliniensis	3	0	
Candida famata	2	0	
Candida guilliermondii	1	0	
Multiple species	2	0	
Other	6	0	
Average no. of days from positive culture to consultation	4.8	6.7	0.04
Antifungal treatment			
Fluconazole	89	13	0.12
Caspofungin	115	7	
Voriconazole	5	2	
Amphotericin	3	0	
None	3	0	
Mean duration of antifungal treatment (days)	3.4	6.6	0.005*

*Includes 1 outlier in the diseased category who had been taking caspofungin for 48 days before consultation. If this patient were removed, the difference in days for antifungal at the time of consultation would no longer be significant.

not differ significantly with regard to gender, mean age, ability to verbalize symptoms, mortality or hospice rate, pathogen isolated on culture, or type of antifungal used ($P > 0.05$ for all comparisons). The average time between positive fungal culture results and ophthalmic examination was significantly longer in those with eye disease, a mean of 6.72 days (standard deviation [SD], 7.61 days), compared with those without eye disease, a mean of 4.76 days (SD, 3.81 days; $P = 0.04$). Patients with ocular involvement had on average been receiving systemic antifungal therapy significantly longer than those without ocular involvement, a mean of 6.64 days (SD, 10.64 days) versus 3.35 days (SD, 4.16 days), respectively. This statistic, however, largely was influenced by a single outlier with ocular involvement who had been taking caspofungin for 48 days before the ophthalmology consultation. Dropping this patient from analysis, the difference in duration of antifungal therapy between those with and without ocular involvement at the time of consultation was no longer significant ($P = 0.18$).

Of the 238 patients receiving an ophthalmic consultation, 69.5% (n = 166) were verbal. Of these verbal patients, 9.0% (n = 15) had ocular signs such as red eye and visual symptoms such as blurry vision or floaters. Ninety-one percent (n = 151) of verbal patients had no signs or symptoms. The most common ocular signs and visual symptoms in decreasing frequency were blurry vision, floaters, and red eye. The sensitivity and specificity of ocular signs and visual symptoms among verbal patients as a predictor of ocular involvement were 28.6% and 92.8%, respectively. The positive predictive value and negative predictive value of ocular signs and symptoms predicting ocular involvement were 26.7% and 93.4%, respectively.

Of the 22 patients with ocular involvement, 11 patients had a recommended change in management after ophthalmic consultation. Of these 11 patients, 9 had their medical regimen altered per ophthalmology recommendation, and in 2 patients, the primary team did not change the systemic antifungal treatment despite recommendation. Only 1 patient underwent an intervention beyond medication change, and that patient underwent bilateral intravitreal antifungal injections. No patients were recommended to undergo a pars plana vitrectomy.

Overall, there were 369 ophthalmic visits performed as a result of ophthalmic consultation because of fungemia. There were 238 new inpatient consultations, 178 of whom had follow-up visits and 60 of whom did not. Using level 5 for those needing additional visits and presumably more decision making and level 4 for those not needing follow-up, the estimated total costs of new inpatient consultations was $36 927.54. The cost of follow-up visits was $13 655.44 (131 visits × $104.24/visit). The total number of inpatient visits in patients with ocular involvement was 89 (mean, 4.05 visits). On average, 26.4 patients had to be evaluated to find 1 patient who had a management change resulting from the ophthalmic consultation, with an average cost of $5620.33 to alter 1 patient's management. Because only 1 patient underwent an ophthalmic intervention (bilateral intravitreal injections), the cost to find the single patient who required care beyond medication management was $50 582.98.

Discussion

In this report, we sought to identify the prevalence of ocular involvement in fungemia, to assess the frequency with which the patient's management is altered after ophthalmic consultation, and to examine the total costs associated with this care. Currently, the Infectious Disease Society of America recommends routine ophthalmic evaluation for all patients with fungemia.[3] This recommendation, however, may not be as relevant as it has been historically for a number of reasons. First, the high prevalence of ocular involvement in fungemia seems to be found only in older studies, where some reports demonstrated a 45% prevalence.[1,13–16] Although higher than some recent studies, the prevalence rate of 9.5% found in our study is consistent with contemporary publications that report a range of 2% to 16%.[5,6,8,10,17–19] Previous work by Donahue et al[17] reports that ocular involvement in fungemic children is less common than in adults. Because our study was limited to an adult population, this also may explain in part why our prevalence rate was slightly higher than some other recent studies that included both adult and pediatric examinations. Despite this, the true incidence of ocular involvement in our patient population actually may be higher than that found in our study. Nearly one-third of fungemic patients did not receive an ophthalmologic consultation, and the rate of fungemia may have been higher in this subgroup with poorer prognosis. Similar to the current literature, which found vitreous involvement to be quite uncommon, our study found very few instances of endophthalmitis.[7,20]

In parallel with the decreasing prevalence of ocular disease in fungemic patients, the role for ophthalmic intervention in the few patients with eye involvement also may be shrinking. In our study, the most common systemic

antifungals at the time of ophthalmology consultation were fluconazole and caspofungin. The choice of systemic antifungal was determined by the primary team in consultation with the infectious disease service. Although azoles frequently are used in tertiary care centers for their efficacy, caspofungin also is used frequently in our institution in immunosuppressed patients in whom azoles may have drug interactions with immunosuppressive medications such as tacrolimus and cyclosporine. Only 5 patients were receiving amphotericin at the time of initial consultation. The historical antifungal of choice, amphotericin, achieves very poor concentration in the posterior segment after systemic administration, possibly increasing the risk of developing endophthalmitis from vitreous extension.[21] This lack of intraocular therapeutic effect may have increased the need for ophthalmic intervention whether it was vitreous aspiration for culture and injection of intravitreal antifungal agents or vitrectomy to debulk infectious load.[22,23] The newer antifungals fluconazole and voriconazole have broad-spectrum coverage and excellent intraocular bioavailability, which may reduce the need for ophthalmic intervention in the treatment of fungal endophthalmitis.[21] Our data are consistent with several reports suggesting that in patients who are already receiving systemic antifungal therapy, ocular findings requiring additional treatment are very rare.[7,17]

This is the first study to examine the rate of change in management of fungemic patients after ophthalmic consultation and the largest to assess the costs of this care. The rate of actual management change was found to be very low in our study (3.7%; 9/238). In addition, only a single patient of the 238 who underwent an eye examination required an ophthalmic procedure, a process that cost more than $50 000 to find the 1 patient needing intervention. Half of those with eye involvement (11/22) had no recommended change in management. In our study, an average of 26.4 patients with fungemia needed to be examined at an average expense of $5620.33 before finding 1 patient in which the consult altered the management of the patient. One limitation to cost analysis is determining specific cost estimates for medical services. Although identifying the so-called true costs of providing a service would be useful, this information is difficult to standardize across different health systems and geographic regions of the country. Average national costs from Centers for Medicare and Medicaid Services data, which are widely accessible, were presented in this study to allow for generalization and meaningful comparisons for future studies. The Centers for Medicare and Medicaid Services data, however, may not reflect the real costs of these consultations because the average age of patients in our study was lower than Medicare eligibility, and it is unclear how a mix of uninsured, privately insured (which typically pays at a higher rate than Medicare), and Medicare patients would alter our results.

Costs are discussed in the study to inform better the discussion about the usefulness of ophthalmic consultations for fungemia. However, these data do not represent true cost effectiveness because of one of the central limitations of this study, the inability to collect final visual acuity data on all fungemic patients (not just those who received a consultation). Having all visual acuity data would allow for a true cost-effectiveness or cost-utility study of current screening guidelines and the relative efficacies of various systemic antifungals in preventing vision loss resulting from fungal eye disease. Because patient death is such a frequent outcome in fungemic patients, it is also an important part of any cost analysis. In our study, 38.6% of our fungemic patients with and without eye involvement died before discharge or were discharged to hospice. Other studies have reported mortality rates ranging from 29% to 68%.[7,18,20,24,25] The mortality rate found in our study may even be underestimated because of loss of follow-up. In summary, the low prevalence of ocular involvement, the rarity of ophthalmic intervention, a high mortality rate among fungemic patients, and the costs of screening suggest that the cost effectiveness of regular examination in fungemic patients is likely to be low.

Reducing the screening burden for fungemic patients has been discussed in several reports.[6,7,17] Dozier et al[6] found that no verbal patients who were asymptomatic had ocular involvement. As such, they recommended that routine ophthalmic consultation should be carried out only for patients who were nonverbal or who reported visual changes. In our study, this would have missed a large percentage of those who had eye involvement (10/14). This is similar to a study by Oude Lashof et al[18] that found that most patients with suspect fungal lesions did not exhibit visual symptoms. In our study and others, the lack of symptoms in some patients with positive ocular involvement may be the result of underreporting of symptoms secondary to the severity of systemic disease, thus making symptom-driven consults less reliable.[18]

A second strategy to reduce screening suggested by Donohue et al[7] looked to limit consultations to patients with prolonged sepsis, severe multisystem organ disease, and red eyes. The mortality rate in our study of fungemic patients in whom the primary team did not request an ophthalmic consultation was 60% (66/110), which was much higher than in the group who received a consultation (29%). Similarly, those found to have eye involvement had on average an extra 2 days between positive test results and consultation. Together, these findings suggest that the consulting team was likely dealing with the multitude of life-threatening urgent health issues that occur in these patients before calling for an eye consultation, and yet, the patients with worse underlying disease also were the most likely to be affected. Further work needs to be performed before a proper consultation reduction strategy should be implemented, but severity of illness seems to be a key factor in determining which patients have ocular involvement. Although the debate of whether to divert the allocation of limited resources away from patients with very poor systemic prognosis is beyond the scope of this study, it must be pointed out that all persons, whether healthy or infirm, should have an opportunity to maximize their visual potential realistically.

Several other limitations to the present study should be addressed. First, this study included only inpatient records. Because of attrition from our hospital system, outpatient follow-up visits after discharge were not reviewed. It is possible that outpatient examinations could have detected additional cases of fungal eye disease, but a recent long-term

follow-up study of 144 previously unexamined fungemia patients showed no cases of late-onset ocular involvement in those who received a full course of antifungal treatment.[26] Second, patients without ocular involvement were not followed up routinely with serial examinations, and vitreitis or fungal lesions may have developed after initial examination. Previous reports, however, have shown that the risk of developing endophthalmitis after initial inpatient normal fundus examination is low.[14,16] Finally, the nature of our study adds the possibility of shortcomings inherent to all retrospective data, such as inconsistencies in documentation and variability in clinical recommendations among ophthalmic clinicians.

In conclusion, this study demonstrates that changes in clinical management from routine ophthalmic consultation for fungemia are rare and are associated with high costs. The high mortality rate in fungemic patients, especially those who were too sick for consultation, suggests a low usefulness of ophthalmic consultation. Further prospective research, including evaluation of visual outcomes in patients with and without a consultation, would allow for the study of true cost effectiveness of ophthalmic consultations in fungemia. Future screening algorithms should weigh the risks of long-term visual sequelae versus the low yield of consultation because of the low prevalence of ocular involvement, even lower rate of change in clinical management, and the high costs associated with this care.

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Abbreviation and Acronym:
SD = standard deviation.

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