



Published in final edited form as:

Ophthalmology. 2014 December ; 121(12): 2334–2339. doi:10.1016/j.ophtha.2014.06.042.

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

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Abstract

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—348 inpatients at a tertiary care center between 2008–2012 with fungal positive blood cultures, 238 of whom received ophthalmologic consultation.

Methods—Inpatient charts of all fungemic patients were reviewed. Costs were standardized to the year 2014. Student's t-test was used for all continuous variables and Pearson's chi-squared 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—22 of 238 consulted patients with fungemia (9.2%) had ocular involvement. 20 patients had chorioretinitis and 2 had endophthalmitis. Only 9 patients (3.7%) had a change in management due to ophthalmic consultation. 1 patient had bilateral intravitreal injections. Thirty percent of consulted patients died prior to 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

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Portions of this data has been previously presented at ARVO Annual Meeting May 6, 2014

Conflicts of Interest: No conflicting relationship exists for any author

find one patient needing change in management with an average cost of \$5,620.33 per change in one patient's management.

Conclusions—Clinical management changes due to ophthalmic consultation in fungemic patients were uncommon. Associated costs were high for these consults in a patient population with a high mortality rate. Together, this data suggests that the utility of routine ophthalmic consultation for all fungemic patients is likely to be low.

Introduction

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 (IDSA) currently recommends that all patients with fungemia receive at least one dilated eye examination to rule out ocular involvement.³

Due to the large burden of 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 has also 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 Further, as 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.

Since 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, pharmacy, and laboratory data on all patients treated at the Hospital of the University of Pennsylvania was queried twice. The first query returned all inpatients that had a positive fungal blood culture. 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 two 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. Since there was often a delay of at least two days between blood culture sampling and results of the fungal culture, we excluded patients that were discharged or died prior to a positive fungal culture result.

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 REDCap (Research Electronic Data Capture) tools hosted at the University of Pennsylvania.¹¹ REDCap 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 etiology of fungemia, duration of antifungal therapy prior to consult, antifungal at time of consultation, time from positive culture to ophthalmic consult, ability to verbalize symptoms, visual symptoms, visual acuity, fundus examination findings, any recommended change in management from the consult, and whether the primary team followed through with the recommended change in management. We used the classification system for ocular fungemia proposed by Donahue et al.⁷ Chorioretinitis was defined as deep focal, fluffy white lesions localized within the chorioretinal layers. Vitritis 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 (CMS) 2014 Physician Fee Schedule.¹² Since 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. Consulted patients needing follow-up were presumably more complex, requiring additional medical decision-making and assigned a level 5 new visit. Consulted patients that 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 (CPT 99255) was \$204.19. The national average cost of a level 4 new inpatient consultation (CPT 99254) was \$138.63. The national average cost of a level 3 subsequent inpatient follow-up visit (CPT 99233) was \$104.24. All statistical analyses were performed with STATA® (College Station, TX). Student's t-test was used for all continuous variables and Pearson's chi-squared test was used for categorical variables. Two-sided p-values <0.05 were considered statistically significant. This study was approved by the University of Pennsylvania's Institutional Review Board (IRB) and adhered to the tenets of the Declaration of Helsinki.

Results

During the study period, 390 patients had a positive blood culture result 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 resulted only after death or hospital discharge, 4 were less than 18 years old, 1 patient was thought to have a contaminant rather than true positive fungal culture, and 1 patient was consulted only for diplopia without mention of positive fungal culture. Of the 348 patients meeting inclusion and exclusion criteria, ophthalmology was consulted on 239 patients (68.7%). Of these, 238 patients had 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 old (Table 1). The most common species identified on fungal culture were *Candida albicans*, *Candida glabrata*, and *Candida parailosis*, 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 ophthalmology was and was not consulted (Table 1). The rate of mortality or transfer to hospice was significantly higher for patients in 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 not differ significantly in gender, mean age, ability to verbalize symptoms, mortality/hospice rate, pathogen isolated on culture, and type of antifungal used ($p > 0.05$ for all comparisons). The average time between positive fungal culture and ophthalmic exam was significantly longer in those with eye disease, mean 6.72 days (SD 7.61), compared to those without eye disease, mean 4.76 days (SD 3.81) ($p = 0.04$). Patients with ocular involvement had on average been on systemic antifungal therapy significantly longer than those without ocular involvement, 6.64 days (SD 10.64) vs. 3.35 days (SD 4.16), respectively. This statistic, however, was largely influenced by a single outlier with ocular involvement who had been on caspofungin for 48 days prior to ophthalmology consult. Dropping this patient from analysis, the difference in duration of antifungal therapy between those with and without ocular involvement at time of consult was no longer significant ($p = 0.18$).

Of the 238 patients receiving ophthalmic consultation, 69.5% (166) were verbal. Of these verbal patients, 9.0% (15) had ocular signs such as red eye and visual symptoms such as blurry vision or floaters. 91% (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 was 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, 9 had their medical regimen altered per ophthalmology recommendation, and in 2 patients the primary team did not change the systemic antifungal despite recommendation. Only one patient had an intervention beyond medication change, and that patient had bilateral intravitreal antifungal injections. No patients were recommended to have a pars plana vitrectomy.

Overall, there were 369 ophthalmic visits performed as a result of ophthalmic consult due to fungemia. There were 238 new inpatient consultations, 178 of whom with follow-up visits and 60 of whom without. 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 \times \$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 one patient who had a management change resulting from the ophthalmic consultation, with an average cost of \$5,620.33 to alter one patient's management. Since only one patient had 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 2-16%.^{5,6,8,10,17-19} Previous work by Donahue *et al.* reported that ocular involvement in fungemic children is less common than adults.¹⁷ Since our study was limited to an adult population, this may also partially explain why our prevalence rate was slightly higher than some other recent studies that included both adult and pediatric exams. Despite this, the true incidence of ocular involvement in our patient population may actually be higher than found in our study. Nearly one-third of fungemic patients did not receive 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 may also 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. While azoles are frequently used in tertiary care centers for their efficacy, caspofungin is also frequently used 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 is 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 had an eye exam required an ophthalmic procedure costing over \$50,000 to find the one 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 \$5,620.33 prior to finding one patient in which the consult altered the management of the patient. One limitation to cost-analysis is determining specific cost estimates for medical services. While identifying the “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 CMS data, which are widely accessible, were presented in this study to allow for generalization and meaningful comparisons for future studies. The CMS data, however, may not reflect the real costs of these consultations as 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 better inform the discussion about the utility of ophthalmic consultations for fungemia. However, this data does not represent true cost-effectiveness due to one of the central limitations of this study, the inability to collect final visual acuity data on all fungemic patients (not just those consulted on). 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 from fungal eye disease. Since 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 29–68%.^{7,18,20,24,25} The mortality rate found in our study may even be underestimated due to

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.* found that no verbal patients who were asymptomatic had ocular involvement.⁶ As such, they recommended that routine ophthalmic consultation should only be performed on patients who were non-verbal 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 report by Lashof *et al.* that found that most patients with suspect fungal lesions did not exhibit visual symptoms.¹⁸ In our study and others, the lack of symptoms in some patients with positive ocular involvement may be due to 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.* looked to limit consultations to patients with prolonged sepsis, severe multisystem organ disease, and red eyes.⁷ The mortality rate in our study of fungemic patients in whom the primary team did not request ophthalmic consultation was 60% (66/110), which was much higher than in the group that received a consult (29%). Similarly, those found to have eye involvement had on average an extra 2 days between positive test result 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 prior to calling for an eye consult, and yet, the patients with worse underlying disease are also the most likely to be affected. Further work needs to be performed before a proper consult reduction strategy should be implemented, but severity of illness appears to be a key factor in determining which patients get ocular involvement. While 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 infirmed should have an opportunity to realistically maximize their visual potential.

Several other limitations to the present study should be addressed. First, this study only included inpatient records. Due to attrition from our hospital system, outpatient follow-up visits after discharge were not reviewed. It is possible outpatient exams 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 routinely followed with serial examinations and may have developed vitritis or fungal lesions after initial examination. Previous reports, however, have shown that the risk of developing endophthalmitis after initial inpatient normal fundus examination is rare.^{14,16} Lastly, 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 utility of ophthalmic consultation. Further prospective research including evaluation of visual outcomes in consulted and non-consulted patients would allow for the study of true costeffectiveness of ophthalmic consultations in fungemia. Future screening algorithms should weigh the risks of long-term visual sequelae versus the low yield of consultation due to the low prevalence of ocular involvement, even lower rate of change in clinical management, and the high costs associated with this care.

Acknowledgments

Financial Support: National Institutes of Health K12 Award (Dr. Brian VanderBeek), K12-EY015398. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH. Additional funding was provided by Research to Prevent Blindness and the Paul and Evanina Mackall Foundation. The sponsors had no role in the design or conduct of this research

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Table 1

Baseline characteristics of fungemic patients who had ophthalmology consultation vs. those that did not have ophthalmology consultation.

	Opth not consulted	Opth consulted	P value
Total	109	239	
Sex, male, %	56.9	55.6	0.83
Mean age, years	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 lusitane	2	3	
Candida dubliniensis	0	3	
Candidafamata	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	

Table 2

Comparisons of fungemic patients with ocular involvement noted on ophthalmic examination vs. those without ocular involvement.

	No ocular involvement	Ocular involvement	P value
Total	217	22	
Sex, male, %	55.3	59.1	0.73
Mean age, years	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
C. albicans	96	12	
C. glabrata	48	4	
C. parasilosis	35	1	
C. tropicalis	16	3	
C. krusei	6	1	
C. lusitaniae	2	1	
C. dubliniensis	3	0	
C. famata	2	0	
C. guilliermondii	1	0	
Multiple species	2	0	
Other	6	0	
Avg days from positive culture to consult	4.8	6.7	0.04
Antifungal			
Fluconazole	89	13	0.12
Caspofungin	115	7	
Voriconazole	5	2	
Amphotericin	3	0	
None	3	0	
Mean duration of antifungal, days	3.4	6.6	0.005*

* Includes one outlier in the diseased category that was on caspofungin for 48 days prior to consult. If this patient is removed, the difference in days on antifungal at time of consult is no longer significant