Ocular Manifestations of Candidemia

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**Background.** Ocular candidiasis is a major complication of candidemia. The incidence, risk factors, and outcome of eye involvement during candidemia are largely unknown. We prospectively studied the ocular manifestations of candidemia in a large, worldwide, randomized multicenter trial that compared voriconazole with amphotericin B followed by fluconazole for the treatment of candidemia.

**Methods.** Nonneutropenic patients with blood cultures positive for *Candida* species were assigned treatment with voriconazole or with amphotericin B followed by fluconazole in a randomized 2:1 ratio. Dilated fundoscopy was performed in each patient at baseline, on day 7, at 2 and 6 weeks after the end of treatment (EOT), and, if clinically indicated, at 12 weeks after EOT.

**Results.** Of 370 patients, 49 had findings consistent with the diagnosis of ocular candidiasis at baseline, and an additional 11 patients developed abnormalities during treatment, totaling 60 patients with eye involvement (16%). Of these patients, probable *Candida* eye infection was diagnosed in 40 patients (6 with endophthalmitis, 34 with chorioretinitis), and possible *Candida* eye infection in 20 (all with chorioretinitis). The duration of candidemia was significantly longer in patients with ocular candidiasis (median, 4 days; range, 1–18 days) compared with patients without ocular involvement (median, 3 days; range 1–26 days; log rank, *P* = .026). Therapy with either voriconazole (44 cases) or amphotericin B followed by fluconazole (16 cases) was successful in 65% of patients; outcome was not evaluable in 32% and was unfavorable in 3%.

**Conclusions.** Ocular involvement occurred in 16% of patients with candidemia; however, endophthalmitis was uncommon (1.6%). Treatment with either voriconazole or amphotericin B followed by fluconazole was successful for ocular candidiasis in most cases with follow-up.

Candidemia is known to lead to hematogenous dissemination and metastatic ocular infection with potentially devastating consequences. Previous studies have described 2 distinct abnormalities: *Candida* endophthalmitis with vitritis, usually presenting as fluffy balls extending into the vitreous body, and *Candida* chorioretinitis, with abnormalities restricted to the chorioretinal layers. The extent of the ocular lesions may be related to the clinical setting. First, patients without a previous diagnosis of candidemia may present with *Candida* endophthalmitis. In such patients, the candidemia leading to ocular metastatic foci has not been noticed previously, and in the absence of antifungal therapy, a full-blown endophthalmitis has occurred [1]. Second, patients presenting with blood cultures positive for candidemia may also develop ocular candidiasis; however, timely antifungal therapy might limit their ocular manifestations, and the progression into endophthalmitis is rare. Until now, retinal lesions during candidemia have been described in small cohorts of patients [2–4]. Only 2 studies have investigated ocular lesions during candidemia; the investigators found *Candida* chorioretinitis in 2%–9% and *Candida* endophthalmitis in 1% of cases [1, 5].

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Ocular candidiasis can be treated with systemic antifungal therapy, or with intravitreal injection of an antifungal agent, sometimes combined with vitrectomy. Systemic amphotericin B and echinocandins do not penetrate well in the vitreous humor, whereas fluconazole and voriconazole reach vitreous concentrations between 25% and 100% of their serum concentrations [6–8]. However, few prospective studies have addressed the outcome of antifungal therapy on the incidence and course of ocular Candida infection.

In this study, patients with blood culture–proven candidemia were prospectively monitored to investigate the incidence of ocular manifestations during candidemia, and to assess the effect of antifungal therapy on the outcome of the ocular lesions.

**METHODS**

In this prospective study, we included 370 nonneutropenic patients ≥12 years of age with candidemia, defined as at least 1 blood culture positive for Candida species and clinical signs of infection (ie, fever, hypotension, or local inflammation at a site of Candida infection). The inclusion criteria, study population, and systemic treatment outcomes have been described in detail elsewhere [9]. The baseline characteristics of the study population are shown in Table 1.

All patients included in this study underwent dilated funduscopy at baseline, at day 7 of treatment, at 2 weeks and 6 weeks after the end of antifungal therapy (EOT) and, if clinically indicated, at 12 weeks after EOT. In cases of fundoscopic abnormalities, patients underwent a visual field examination (VF; using the confrontation method) and visual acuity (VA) tests when possible.

Proven ocular candidiasis was defined as ocular lesions in combination with positive histology or culture of a vitreous aspirate. Probable Candida endophthalmitis was defined as vitritis or fluffy lesions with extension into the vitreous. Probable Candida chorioretinitis was defined as deep focal white infiltrates in the retina. In addition, hemorrhages, Roth spots, or nerve fiber layer infarctions (cotton wool spots) in candidemic patients were classified as probable Candida chorioretinitis if no other cause for these abnormalities was present (eg, diabetes mellitus or hypertension). If signs of chorioretinitis were seen in patients with underlying systemic disease that may cause similar lesions (eg, diabetes, hypertension, or concomitant bacteremia), these cases were classified as possible ocular candidiasis [1].

We assigned patients in a randomized 2:1 ratio to receive either voriconazole or amphotericin B followed by fluconazole [9]. Voriconazole was given intravenously at 6 mg/kg every 12 hours for 24 hours, then at 3 mg/kg every 12 hours. Patients could be switched to oral voriconazole at 200 mg twice daily after 3 days. Amphotericin B was given intravenously at 0.7–1.0 mg/kg per day, followed, after 3–7 days, by oral or intravenous fluconazole (400 mg/d), with the following exceptions: (a) patients infected with an isolate found (or predicted on the basis of species) to have a fluconazole minimum inhibitory concentration (MIC) of ≥16μg/mL were to remain on amphotericin B; (b) patients infected with Candida lusitaniae were permitted to switch from amphotericin B to fluconazole earlier than day 3; and (c) patients unable to tolerate 3 days of amphotericin B could be switched to fluconazole even before day 4. Patients received treatment for at least 2 weeks after the most recent positive blood culture, for a maximum duration of 8 weeks. Patients were followed up until 12 weeks after EOT. To allow for an average of 2 weeks of treatment, all-cause mortality was assessed at 14 weeks after enrollment [9].

Successful treatment of ocular candidiasis was defined as disappearance of active inflammation within the eye and either disappearance or scarification of retinal lesions.

We based our statistical analysis on the modified intention-to-treat (MITT) population of all patients with a blood culture positive for Candida species within 96 hours of enrollment who received at least 1 dose of study medication. We compared patients with and without ocular Candida involvement by χ2 tests; we analyzed the time to the first negative blood culture using Kaplan–Meier methods.

**RESULTS**

Among 370 patients with candidemia treated in the MITT population, 60 (16%) had fundoscopic abnormalities suiting the definitions of probable and possible ocular candidiasis. Proven ocular candidiasis was not diagnosed, as none of the patients underwent vitreous sampling.

The groups with and without ocular involvement did not differ in demographic background, underlying disease, APACHE II score, or intensive care unit (ICU) admission (Table 1). However, patients with ocular candidiasis were significantly more often infected with Candida albicans (36 of 60 patients vs 123 of 310; \( P = .004 \)) and less often infected with Candida parapsilosis than patients without retinal lesions (3 of 60 patients vs 56 of 310; \( P = .011 \); Table 1).

Ocular abnormalities consistent with the diagnosis of ocular candidiasis were diagnosed at baseline in 49 patients, whereas 11 additional patients developed signs of ocular candidiasis during antifungal treatment of their candidemia, as assessed by follow-up fundoscopies (Figure 1). Of the 60 patients with fundoscopic abnormalities, 40 patients had probable ocular candidiasis and 20 patients were classified as having possible ocular candidiasis (Table 2). Of the 40 patients with probable ocular candidiasis, 6 had endophthalmitis with lesions extending into the vitreous, and 34 had chorioretinitis (Figure 1).
Visual Acuity and Visual Field Testing

Of 60 patients with ocular abnormalities, VA was assessed in 34 patients (57%), including 7 ICU patients. Due to severe underlying illness, 16 ICU patients and 10 non-ICU patients underwent no VA tests. Only 1 patient, with a history of macular degeneration, reported low visual acuity at baseline. Of 34 patients with baseline VA available, only 20 patients underwent follow-up VA assessment; 19 of those 20 patients had stable or improved VA, and 1 patient had worsening of perception associated with Candida endophthalmitis.

Out of 60 patients with ocular abnormalities, VF tests were assessed in 33 patients. In only 1 patient, diagnosed with probable Candida endophthalmitis, VF results were abnormal at EOT but had normalized at 6 weeks after EOT.

### Table 1. Baseline Characteristics of 370 Patients With Candidemia

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>No ocular involvement (n = 310)</th>
<th>Probable or possible ocular candidiasis (n = 60)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candida albicans</td>
<td>123 (39.7)</td>
<td>36 (60)</td>
<td>.004</td>
</tr>
<tr>
<td>Candida glabrata</td>
<td>47 (15.2)</td>
<td>5 (8.3)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Candida tropicalis</td>
<td>57 (18.4)</td>
<td>8 (13.3)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Candida parapsilosis</td>
<td>56 (18.1)</td>
<td>3 (5.0)</td>
<td>.011</td>
</tr>
<tr>
<td>Candida krusei</td>
<td>2 (0.6)</td>
<td>2 (3.3)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Other and mixed</td>
<td>25 (8.1)</td>
<td>6 (10)</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

NOTE. ICU, intensive care unit; n.s., not significant (P > .05).

**Figure 1.** Outcome of ocular manifestations by fundoscopy results.
Table 2. Outcome of Ocular Involvement by Antifungal Treatment Arm

<table>
<thead>
<tr>
<th></th>
<th>Voriconazole n (%)</th>
<th>Amphi B/fluc n (%)</th>
<th>Total N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probable endophthalmitis</td>
<td>6 (50)</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Documented resolution (%)</td>
<td>3 (50)</td>
<td>0</td>
<td>3 (50)</td>
</tr>
<tr>
<td>Not evaluable (%)</td>
<td>2 (33)</td>
<td>2 (33)</td>
<td></td>
</tr>
<tr>
<td>Failure</td>
<td>1 (17)</td>
<td>1 (17)</td>
<td></td>
</tr>
<tr>
<td>Probable chorioretinitis</td>
<td>22 (71)</td>
<td>12 (63)</td>
<td>34 (71)</td>
</tr>
<tr>
<td>Documented resolution (%)</td>
<td>16 (73)</td>
<td>8 (67)</td>
<td>24 (71)</td>
</tr>
<tr>
<td>Not evaluable (%)</td>
<td>5 (23)</td>
<td>4 (33)</td>
<td>9 (7)</td>
</tr>
<tr>
<td>Relapsed (%)</td>
<td>1 (5)</td>
<td>1 (3)</td>
<td></td>
</tr>
<tr>
<td>Documented cure rate of probable infections</td>
<td>19/28 (68)</td>
<td>8/12 (67)</td>
<td>27/40 (67.5)</td>
</tr>
<tr>
<td>Cured probable infections/total probable infections (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Possible chorioretinitis</td>
<td>16 (63)</td>
<td>4 (50)</td>
<td>20 (64)</td>
</tr>
<tr>
<td>Documented resolution/stable (%)</td>
<td>10 (63)</td>
<td>2 (50)</td>
<td></td>
</tr>
<tr>
<td>Not evaluable (%)</td>
<td>6 (37)</td>
<td>2 (50)</td>
<td></td>
</tr>
<tr>
<td>Total documented cure rate</td>
<td>29/44 (66)</td>
<td>10/16 (62.5)</td>
<td>39/60 (65)</td>
</tr>
<tr>
<td>Cured evaluable patients/all evaluable patients (%)</td>
<td>29/31 (93.5)</td>
<td>10/10 (100)</td>
<td>39/41 (95)</td>
</tr>
<tr>
<td>Total cure rate in evaluable patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cured evaluable patients/all evaluable patients (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NOTE. Amphi B/fluc, amphotericin B followed by fluconazole.
* Outcomes were not significantly different between treatment arms (P > .05).

Outcome of Ocular Candidiasis

*Candida* Endophthalmitis

We identified 5 cases of probable *Candida* endophthalmitis at baseline and diagnosed 1 additional patient with endophthalmitis at day 18 of antifungal therapy (Figure 1). This latter patient had negative fundoscopy results at days 1 and 8, but had multiple white fluffy lesions suggestive of *Candida* endophthalmitis and worsening VA at a repeat fundoscopy on day 18. Of note, this patient did not undergo central venous catheter exchange until day 10 of therapy. Voriconazole was substituted with fluconazole, and this treatment was discontinued for unknown reasons after 18 days without resolution of the abnormalities; therefore, this outcome was classified as unsuccessful. Of 6 patients with endophthalmitis, 4 had bilateral abnormalities. In 3 of these 6 patients, the abnormalities resolved during antifungal treatment. Furthermore, 2 patients, both with bilateral involvement and disturbed VA, died during treatment and before ophthalmologic follow-up was performed. In this study, none of the patients with endophthalmitis underwent intravitreal treatment or vitrectomy.

**Probable Candida Chorioretinitis**

Probable *Candida* chorioretinitis was diagnosed in 34 of 60 patients with ocular involvement. At baseline, the diagnosis was made in 28 of 34 (82%); 6 additional patients with negative fundoscopy at baseline were diagnosed during follow-up fundoscopy (each within 8 days of baseline).

Treatment of probable *Candida* chorioretinitis was successful, as confirmed by follow-up fundoscopies, in 24 of 34 patients (71%). Of 34 cases, 9 cases were not evaluable, largely because of lack of follow-up fundoscopy or death. Only 1 patient had documented relapse of candidemia with new ocular lesions after discontinuation of therapy. This patient with *C. albicans* candidemia had a retinal hemorrhage at baseline fundoscopy. He was treated with voriconazole for 21 days and was considered improved at EOT with complete resolution of the retinal abnormalities. During follow-up, candidemia relapsed with blood cultures positive for *Candida* and a new exudate in the other eye. Although these findings were likely because of a new episode of candidemia, the patient was classified as nonsuccessful outcome.

In all, 40 patients had probable *Candida* chorioretinitis or endophthalmitis. None of the lesions diagnosed as *Candida* chorioretinitis progressed to endophthalmitis during or after therapy. Whereas the outcome was not evaluable in 11 patients because of death or lack of follow-up fundoscopy, 27 of 29 patients in whom follow-up fundoscopy was performed responded well to systemic antifungal therapy with complete resolution of ocular lesions (93%).

**Possible Candida Chorioretinitis**

Possible ocular candidiasis was diagnosed in 20 of 60 patients with ocular abnormalities; 16 (80%) were diagnosed at baseline, and 2 patients were diagnosed within 2 weeks of treatment. The remaining 2 patients were diagnosed at later times: 1 patient who developed seizures while on treatment was diagnosed with a retinal hemorrhage at the end of 3 weeks’ treatment, and 1 patient with diabetic retinopathy was diagnosed with a new cotton wool exudate 14 days after completing 2 weeks of treatment. Both of these patients had candidemia for short durations (blood cultures became negative at days 1 and 2 of therapy); therefore, a causal relationship of these ocular lesions with *Candida* infection is unclear.
Of 12 patients who underwent repeat fundoscopies, the ocular lesions completely resolved in 9 patients, and exudates, cotton wool spots, and Roth spots remained stable in 3 patients without worsening of visual acuity. In the remaining 8 patients, outcome was not evaluable due to death or lack of follow-up fundoscopy.

**Antifungal Treatment Strategy and Outcome of Ocular Infection**
The antifungal treatment that was assigned, either voriconazole or amphotericin B followed by fluconazole, had no significant effect on the outcome of the ocular infection. Each treatment strategy led to confirmed resolution or stabilization of ocular abnormalities—in 93.5% of all evaluable patients treated with voriconazole (29 of 31 patients) and 100% of all evaluable patients treated with amphotericin B followed by fluconazole (10 of 10 patients; \( P = .41 \); Table 2).

**The Duration of Candidemia and Ocular Candidiasis**
The duration of candidemia from randomization day to first negative blood culture was significantly longer in patients with ocular candidiasis (median, 4 days; range, 1–18 days) compared with patients without ocular involvement (median, 3 days; range, 1–26 days; \( \text{log rank}, P = .026 \)). No significant difference was found between the time from first positive blood culture to start of treatment in patients diagnosed with or without ocular abnormalities (\( \text{log rank}, P = .98 \)).

The duration of therapy after the first negative blood culture was median 14 days both in groups with (range, 0–57 days) and without (range, 0–65 days) ocular involvement, as we recommended per protocol.

**Mortality**
The mortality at 14 weeks after enrollment was 26 of 60 patients with ocular candidiasis (43.3%) and 113 of 310 patients without ocular lesions (36.5%, \( P = .31 \)). Among patients with endophthalmitis, the 14-week mortality was 50%.

**DISCUSSION**

This is the largest study to date that prospectively performed repeated dilated fundoscopies in patients with candidemia to assess the incidence and course of metastatic ocular candidiasis. Ocular abnormalities occurred in 16% of 370 patients. Probable *Candida* chorioretinitis was diagnosed most frequently (9.2%), whereas full-blown *Candida* endophthalmitis was rare (1.6%). Consistent with prior reports, patients with ocular candidiasis in this trial were mostly infected with *C. albicans*.

Few studies have prospectively assessed the incidence and course of ocular involvement in patients with candidemia. In a cohort of 118 candidemic patients, 9% had signs of *Candida* chorioretinitis, and endophthalmitis occurred in none of the patients [5]. In a more recent prospective series of 180 nonneutropenic patients with candidemia, Rodríguez-Adrián et al diagnosed endophthalmitis in 1% of patients and chorioretinal lesions related to candidemia in 2.7% [1]. Furthermore, 2 smaller, older prospective studies reported markedly higher incidences of ocular lesions in patients with candidemia (28%–37%) [2, 3]. It is likely that patient selection, and less advanced blood culture techniques that led to a prolonged time before detection and treatment of candidemia, may have led to a higher reported incidence of hematogenous dissemination of infection.

Most patients with ocular lesions found at fundoscopy did not exhibit symptoms of ocular involvement. The subclinical course of the ocular manifestations of candidemia could be explained either by underreporting due to the severity of illness or by the limited and peripheral nature of the lesions. Only 1 patient reported loss of VA at baseline. In another patient, loss of vision was identified during the VA test at baseline, and fundoscopy revealed bilateral endophthalmitis.

In most of our patients, the ocular lesions were present at baseline fundoscopy, before the start of antifungal therapy. However, in 18% of cases, baseline fundoscopy was negative, although new lesions were detected at scheduled follow-up fundoscopies after the start of treatment. This suggests that, in most cases, hematogenous inoculation has occurred early during candidemia, and that the ocular lesions require some time to evolve and become visible. Alternatively, persistent candidemia after the institution of antifungal therapy may have led to ocular foci. Indeed, in our study, *Candida* chorioretinitis and endophthalmitis were associated with persistently positive blood cultures during antifungal therapy for a median of 4 days, compared with 3 days in candidemic patients who did not develop ocular candidiasis (\( P = .026 \)).

Our findings support the notion that ocular candidiasis often is asymptomatic, and that retinal lesions do not always appear immediately after candidemia is detected. Previously, 3 studies noted an interval of ≤14 days between start of treatment and the first retinal abnormality consistent with candidal chorioretinitis [2–4]. Thus, it is recommended that in candidemic patients without visual symptoms, the fundoscopy be performed at least 1 week after the onset of therapy, to increase its sensitivity to detect ocular candidiasis [10].

Among all *Candida* species, *C. albicans* appeared to have the greatest propensity to cause ocular candidiasis. In contrast, *C. parapsilosis* was significantly less frequently associated with ocular manifestations. This is in agreement with earlier findings that *C. parapsilosis* is less virulent than other strains [9, 11].

All evaluable cases of probable ocular candidiasis resolved with systemic antifungal treatment, except for 2; 1 patient in whom a relapse of candidemia after discontinuation of
Antifungal therapy was associated with a new ocular lesion, and another patient in whom fluconazole was discontinued 18 days after diagnosis of endophthalmitis, without complete resolution of abnormalities. None of the cases of Candida chorioretinitis progressed to endophthalmitis during systemic treatment, and surgical intervention or intraocular administration of antifungal drugs was not required.

In our study, the incidence of Candida endophthalmitis was low (1.6%). This finding is likely because patient selection was based on positive blood cultures growing Candida species, and systemic antifungal therapy was promptly instituted. We defined endophthalmitis to be proven if the diagnosis was supported by histology or culture at vitreous sampling. However, vitreous sampling was performed in none of the 6 endophthalmitis patients, as the fundoscopic appearances were considered highly likely to be fungal in nature in the setting of candidemia.

As previously reported, we diagnosed possible Candida chorioretinitis, as opposed to proven or probable Candida endophthalmitis or chorioretinitis, if chorioretinal lesions occurred in patients who had alternate potential causes for their retinal abnormalities, such as diabetes mellitus, hypertension, or concomitant bacteremia [1]. In 3 patients, retinal abnormalities were stationary and did not evolve during and after voriconazole therapy. These abnormalities did not progress to endophthalmitis after discontinuation of therapy, and therefore most probably were not Candida related. It has been noted earlier that nonspecific retinal lesions are common in critically ill adults [1]. However, in 11 of 20 patients, the lesions resolved at repeated fundoscopy during antifungal treatment, suggesting fungal infection as a cause.

Based on this study, it is recommended that dilated fundoscopy is performed in all patients with candidemia at least 1 week after the onset of therapy. Subsequent ophthalmological follow-up of those with ocular candidiasis is required, because antifungal treatment should be continued until ocular lesions are completely resolved.

The optimal treatment for endogenous ocular candidiasis had not been established, although fluconazole and voriconazole appear to be most favorable [12]. Systemic amphotericin B and echinocandins have limited ability to penetrate into the vitreous humor [13–15]. Flucytosine (combined with amphotericin B) has favorable pharmacokinetics; however, its side effects and limited availability in many countries preclude widespread use. Information on the treatment of ocular candidiasis with echinocandins is limited to case reports and animal studies [14–16]. The large randomized trials comparing echinocandins for treatment of candidemia and disseminated candidiasis [17–21] provide limited information on ocular manifestations. The penetration of echinocandins into the eye is poor [22], and these drugs are not considered the treatment of choice for ocular candidiasis [10]. Fluconazole has been well documented in the treatment of ocular candidiasis [23, 24]. However, its spectrum of activity against some Candida species is limited [10].

This is the first study to report successful treatment of ocular candidiasis with voriconazole in a large prospective cohort. Voriconazole has favorable pharmacokinetics and reaches high concentrations in the brain and ocular compartments [25, 26]. Breit et al described 5 patients with endogenous Candida endophthalmitis successfully treated with voriconazole [27]. In the present cohort of 248 candidemic patients who received voriconazole, repeated fundoscopy detected 28 cases of probable Candida chorioretinitis or endophthalmitis, and all but 2 evaluable cases were cured during voriconazole therapy.

In conclusion, this study found that ocular involvement occurred in 16% of patients with candidemia, mostly presenting as Candida chorioretinitis, whereas Candida endophthalmitis was rare in patients diagnosed with candidemia (1.6%). Patients with ocular candidiasis were characterized by a frequent involvement of C. albicans and a slightly longer duration of candidemia. In patients who received systemic antifungal treatment, the outcome of Candida chorioretinitis was favorable, and did not progress into endophthalmitis. In addition, our study has shown that voriconazole and amphotericin B followed by fluconazole are effective in the treatment of endogenous ocular candidiasis.

Acknowledgments

A. M. L. Oude Lashof was involved in the study design, data collection, data analysis and interpretation, writing the manuscript and final approval of the version submitted for publication.

B. J. Kullberg was the initiator of the study design, was involved in data collection, data analysis, and interpretation, writing the manuscript and final approval of the version submitted for publication.

A. Rothova was involved in data analysis and interpretation, writing the manuscript, and final approval of the version submitted for publication.

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C. Viscoli was involved in data analysis and interpretation, writing the manuscript, and final approval of the version submitted for publication.

I. T. Oborska was involved in data collection and final approval of the submitted version.

H. Schlamm was involved in data analysis, writing the manuscript, and final approval of the version submitted for publication.

J. Sobel was involved in data analysis and interpretation, writing the manuscript, and final approval of the version submitted for publication.

P. G. Pappas was involved in data analysis and interpretation, writing the manuscript, and final approval of the version submitted for publication.

J. H. Rex was involved in data analysis and interpretation, writing the manuscript, and final approval of the version submitted for publication.

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