Original Article / Özgün Araştırma

Meandros Med Dent J
doi:10.4274/meandros.galenos.2023.05925
Meandros Med Dent J 2023;24(1):78-84
78

Invasive *Candida* Infections in Children: Species Distribution, Antifungal Susceptibility, and Risk Factors Associated with Mortality

Çocuklarda İnvaziv *Candida* Enfeksiyonları: Tür Dağılımı, Antifungal Duyarlılık ve Mortalite ile İlişkili Risk Faktörleri

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Abstract

Objective: This study determined the distribution and antifungal susceptibility of *Candida* species, risk factors, and mortality in invasive candidiasis (IC).

Materials and Methods: The medical data of the pediatric patients with IC were analyzed retrospectively between September 2014 and September 2018. The first IC episodes were included, and the susceptibility was determined by the microdilution method performed according to The Clinical and Laboratory Standards Institute M27-A3 standards. Kaplan-Meier curves were prepared for survival on the 7th and 30th day after the first positive culture and the curves were compared with the log-rank test.

Results: Forty-eight *Candida* isolates were detected in 45 IC episodes. *C. albicans* and *C. parapsilosis* were the most common species (both 41.7%). Fluconazole, caspofungin, and amphotericin B resistance were 38.2%, 3.1%, and 2.9%, respectively. Fluconazole resistance was 73.3% among *C. parapsilosis*. The most common risk factors were underlying diseases (100%), previous antibiotic use (95.6%), and central venous catheter (73.3%). Six (13.3%) patients were deceased within the 30 days. Patients with neutropenia and dialysis had a higher rate of mortality and lower mean survival times for 7-day and 30-day mortality. Mean survival times for 7-day mortality were lower for the patients who had abdominal surgery (p=0.04).

Conclusions: There was high fluconazole resistance in *C. parapsilosis*, which was 73.3%. Neutropenia, dialysis, and abdominal surgery were associated with a significant increase in mortality. These data will help us identify patients who are at risk for IC and will guide us in the selection of empirical treatment.

Keywords: Antifungal susceptibility, amphotericin B, candidaemia, *Candida* spp., fluconazole resistance, pediatric

Öz

Amaç: Bu çalışma, invaziv kandidiyazise (İK) neden olan *Candida* türlerinin dağılımını, antifungal duyarlılığını, risk faktörlerini ve mortaliteyi belirlemek amacıyla yapılmıştır.

Gereç ve Yöntemler: Eylül 2014-Eylül 2018 tarihleri arasında İK'lı pediatrik hastaların tıbbi verileri retrospektif olarak incelendi. Çalışmaya hastaların ilk İK epizotları dahil edildi. *Candida* izolatlarının duyarlılığı, Klinik Laboratuvar Standartları Enstitüsü M27-A3 standartlarına göre yapılan mikrodilüsyon yöntemi ile belirlenmiştir. İlk pozitif kültürden sonraki 7. ve 30. gündeki sağkalım için Kaplan-Meier eğrileri oluşturulmuştur ve eğriler log-rank testi ile karşılaştırılmıştır.

Bulgular: Kırk beş IC atağında 48 *Candida* izolatı tespit edildi. *C. albicans* ve *C. parapsilosis* en yaygın türlerdi (her ikisi de %41,7). Flukonazol, kaspofungin ve amfoterisin B direnci sırasıyla %38,2, %3,1 ve %2,9 idi. *C. parapsilosis*'te flukonazol direnci %73,3 idi. En sık görülen risk faktörleri altta yatan hastalık (%100), önceden antibiyotik kullanımı (%95,6), santral venöz kateter (%73,3) idi. Altı (%13,3) hasta 30 gün içinde öldü. Nötropeni ve diyaliz hastalarında daha yüksek mortalite oranı ve 7-günlük ve 30-günlük mortalite

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Received/Geliş Tarihi: 17.12.2022
Accepted/Kabul Tarihi: 03.03.2023

için daha düşük ortalama sağkalım süreleri vardı. Abdominal cerrahi geçiren hastalarda 7 günlük mortalite için ortalama sağkalım süreleri daha düşüktü (p=0,04).

Sonuç: *C. parapsilosis*'te %73,3 oranında yüksek flukonazol direnci vardı. Nötropeni, diyaliz ve abdominal cerrahi, mortalitede önemli bir artışla ilişkilendirildi. Bu veriler, invaziv kandidiyazis riski taşıyan hastaları belirlememize yardımcı olacak ve ampirik tedavi seçiminde bize yol gösterecektir.

Anahtar Kelimeler: Antifungal duyarlılık, amfoterisin B, kandidemi, *Candida* türleri, flukonazol direnci, pediatrik

Introduction

Candidiasis is the most common fungal infection and usually affects children with chronic illness, prematurity, immunodeficiency, and critical diseases (1). In the United States, *Candida* spp. is the widespread cause of invasive fungal disease and is the second most common problem of central line-associated bloodstream infections (CLABSI) in pediatric patients (2).

Candidiasis leads to increased mortality, morbidity, prolonged hospitalization time, and health care costs in children (3). Regional distribution of *Candida* species, antifungal susceptibility and risk factors for invasive candidiasis (IC) are important for effective empirical treatment and prevention strategies.

We aimed to establish the distribution of *Candida* species, antifungal susceptibility, risk factors and mortality in hospitalized children with IC.

Materials and Methods

Patient Data and Definitions

This cross-sectional study was performed at a tertiary university hospital. Pediatric patients with culture-proven invasive *Candida* spp. infection during hospitalization during a four year (from September 2014 to September 2018). The demographic data, clinic features, and microbiological results of the pediatric patients with IC were analyzed retrospectively.

IC was characterized as the isolation of *Candida* spp. from sterile body fluids. Candidemia was described as the isolation of *Candida* spp. in blood culture from a peripheral vessel or a central venous catheter (CVC). The isolation of *Candida* spp. from any blood culture in a patient with a CVC or *Candida* spp. growth from a catheter-tip culture was defined as catheter-associated candidemia.

The previous hospitalization (history hospitalization) was defined as hospitalization history within three months before the IC (4). The presence of mechanical ventilation was recorded within two days before IC. Arterial catheter, CVC, urinary catheter, and use of total parenteral nutrition (TPN) were recorded within a week before infection. In the two weeks before infection, surgical intervention (abdominal and non-abdominal), broad-spectrum antibiotic use, immunosuppressive drug use, presence of neutropenia, and previous use of antifungal drugs were recorded. Initial therapy was deemed to be delayed when the time elapsed between taking the culture sample and the start of antifungal therapy was more than 72 hours. The time of first culture positivity was always considered as a benchmark to evaluate time to infection and mortality.

Identification of Organism and Susceptibility Testing

The isolates were cultured from several clinical samples (blood, CVC, and peritoneal fluid). Blood and sterile body fluid cultures were processed by the BACTEC FX 200 system (Becton Dickinson, United States of America). Growth was determined from the culture of specimens on blood and "Eosine Methylene Blue" agar plates. The colonies identified as yeast growth were transferred to the mycology laboratory for identification and antifungal susceptibility tests. The colonies were subcultured to "sabouraud dextrose agar" (Oxoid, England), and identification was performed after the strains were determined to be pure. Yeasts were identified by germ tube test, microscopic morphology on Cornmeal tween 80 agar (Oxoid, England) and CHROMagar *Candida* (CHROMagar, France), and API 20C AUX (BioMérieux, France).

The susceptibility of *Candida* isolates to fluconazole, amphotericin B (AmB), and caspofungin was determined by microdilution method performed based on The Clinical and Laboratory Standards Institute (CLSI) M27-A3 standards (5). Minimal inhibitory concentrations (MICs) for fluconazole, AmB, and caspofungin were evaluated according to the CLSI species specific clinical breakpoints. These were as follows: for fluconazole *C. albicans, C. tropicalis* and *C. parapsilosis* susceptible (MIC ≤2 µg/mL), susceptible-dose dependent (MIC 4 µg/mL), resistant (MIC ≥8 µg/mL); for fluconazole *C. glabrata* susceptible-dose dependent (MIC ≤ 32 µg/mL), resistant (MIC ≥64 µg/mL); for AmB susceptible (MIC ≤1 µg/mL), resistant (MIC >1 µg/mL); for caspofungin *C. albicans, C. krusei, C. tropicalis,* and *C. glabrata* resistant (MIC >0,5 µg/mL), *C. parapsilosis* resistant (MIC >4 µg/mL). *C. krusei* was considered as naturally resistant to fluconazole regardless of MIC (6).

Statistical Analysis

Statistical analyses were performed using SPSS version 20 (SPSS, Inc, Chicago, IL) software. Categorical factors were shown as numbers and percentages. Shapiro-Wilk normality test was used for test normality. Non-normal distributed continuous variables were presented as medians and interquartile ranges unless stated otherwise. Qualitative data were compared using the chi-square test, while quantitative variables were compared between groups using the Mann-

Whitney U test or Fisher's exact test. The response variable of this study was mortality. Patients were right-censored at the 7th and 30th days after the initial positive culture. Kaplan-Meier survival curves were prepared, and the log-rank test was used to assess the differences between survival curves. Statistical analyses were applied in R (7) version 3.4.3, using the packages "survival" and "survminer". Significance was defined at the double-sided p-value of <0.05.

This study was approved by the Dokuz Eylül University Non-Invasive Research Ethics Committee (decision no: 2016/13-23, date: 12.5.2016).

Results

Demographics, Characteristics and Risk Factors

There were 45 IC patients during the four years. Four patients had one more recurrent episode, but only the first episodes were included. Two patients had more than one *Candida* spp. Two candida strains (*C. albicans, C. tropicalis*) were isolated in one patient, and three Candida strains (*C. parapsilosis, C. albicans, C. krusei*) in another patient.

Demographics and characteristics of the patients with IC are shown in Table 1. The most prominent risk factors were having underlying diseases (100%), a previous antibiotic use (95.6%), CVC (73.3%), and previous hospitalization (55.6%). *Candida* endocarditis and peritonitis developed in 2 (4.4%) and 1 (2.2%) patients, respectively.

Distribution and Antifungal Susceptibility of the *Candida* Species

Forty-eight *Candida* strains and seven different *Candida* species were isolated. The most common species were *C. albicans* and *C. parapsilosis,* both 20 (41.7%). Antifungal susceptibility testing was performed for 34 *Candida* isolates. The susceptibility of the isolates to the antifungal agents is shown in Table 2.

Therapy

Antifungal therapy was given in 42 episodes (93.3%), monotherapy in 17 (37.8%), and sequential treatment in 25 (55.6%) episodes. Twelve (26%) patients were receiving antifungal agents before IC. Initial therapy was delayed in seven patients (15.5%).

Table 1. Demographics of the patients with invasive candidiasis

	n (%)
Age, [Months, median (IQR)]	11.1 (3.88-53.02)
Minimum-maximum age, months	0-200.97
Length of stay [days, median (IQR)]	48 (32-95.5)
Time to infection [days, median (IQR)][a]	19 (10-30.5)
Length of stay to after onset of IC [days, median (IQR)]	26 (14.5-49.5)
Nosocomial infection	41 (91.1)
Catheter-related candidemia	32 (71)

[a]The time from admission to the date of the first positive culture for nosocomial acquired infection only. IC: Invasive candidiasis, IQR: Interquartile range

Table 2. *Candida* spp. isolates and antifungal susceptibility testing results

			Fluconazole		Caspofungin		Amphotericin B	
	n (%)	AST, n	MIC, Min-max	R, n	MIC, Min-max	R, n	MIC, Min-max	R, n
C. albicans	20 (41.7)	13	0.25-1	0	0.015-3	1	0.25-1	0
C. parapsilosis	20 (41.7)	15	0.5-32	11	0.25-1	0	0.25-1	0
C. tropicalis	3 (6.3)	2	1-32	1	0.015-0.06	0	0.5-1	0
C. krusei	2 (4.2)	1	NRF	NRF	0.13	0	2	1
C. glabrata	1 (2.1)	1	8	0	-	-	0.5	0
C. lusitaniae	1 (2.1)	1	2	0	-	-	0.5	0
C. pelliculosa	1 (2.1)	1	0.5	0	0.015	0	0.25	0

AST: Antifungal susceptibility testing, MIC: Minimum inhibitory concentration (Mg/Ml), R: Resistant, NRF: Naturally resistant to fluconazole, Min-max: Minimum-maximum

Outcome

Six of the patients died within 30 days following a positive culture, and the overall mortality rate was 13.3%. The demographic and clinical risk factors for 7-day and 30-day mortality were presented in Table 3. Patients with neutropenia and dialysis had a higher rate of mortality in 7-day (both p=0.02) and 30-day (p=0.04 and p=0.003, respectively). Mean survival times for 7-day mortality were lower for the patients with neutropenia (Mean ± SE: 5.86±0.97 vs 6.97±0.04), dialysis (Mean ± SE: 6.14±0.97 vs 6.92±0.06), and abdominal surgery (5.67±0.90 vs 6.97±0.03) when compared to patients who had not. Also, mean survival times for 30-day mortality were lower for the patients with neutropenia (Mean ± SE: 19.00±4.84 vs 28.29±0.97), dialysis (Mean ± SE: 15.86±4.36 vs 28.66±0.92) when compared to patients who had not (Figure 1).

Of the total of 32 patients with CLABSI, 29 had a catheter removed following positive culture, and 16 of them were removed within 72 hours. There was no difference for mortality (both p=0.33) between catheter withdrawals within 72 hours and those not withdrawn within 72 hours.

Discussion

In our study, 58.3% and 41.7% of IC episodes were related to non-albicans *Candida* species and *C. albicans*, respectively. *C. albicans* and *C. parapsilosis* were the most common isolated species (both 41.7%). Fluconazole, caspofungin, and AmB resistance rates were 38.2%, 3.1%, and 2.9%, respectively. 73.3% of *C. parapsilosis* isolates were resistant to fluconazole. Risk factors associated with mortality were neutropenia, dialysis, and abdominal surgery. Also, most of the IC cases were catheter-related candidemia and nosocomial candidiasis.

According to recent studies, non-albicans *Candida* species cause more than half of IC cases in children (8). Neu et al. (9), 74% of 203 episodes of pediatric candidiasis were found to be related to non-*albicans* species (43% *C. parapsilosis*). Our study confirmed that non-*albicans Candida* species have been increasing in recent years in IC as in previous studies, and it was remarkable that the frequency of *C. parapsilosis* was at least as frequent as *C. albicans*.

Various risk factors have been identified in candidiasis, and these are the presence of immunodeficiency, underlying

Table 3. Comparison of demographic and clinical features for 7-day and 30-day mortality among survivors and deceased

	7-day mortality			30-day mortality		
	Survivors (n=40)	Deceased (n=5)	p-value	Survivors (n=39)	Deceased (n=6)	p-value
Gender, boys	22 (88)	3 (12)	>0.99	21 (84)	4 (16)	0.68
Age [months, median (IQR)]	11.15 (4.17-56.89)	1.43 (1.07-104.78)	0.43	11.2 (4.27-54.77)	1.37 (0.83-62.53)	0.19
Lenght of stay [days, median (IQR)]	52 (37.25-110.50)	27 (6.5-39.5)	0.02	53 (37-112)	29 (7.75-43.5)	0.02
Prematurity	12 (85.7)	2 (14.3)	0.64	11 (78.6)	3 (21.4)	0.36
Previous hospitalization	23 (92)	2 (8)	0.64	23 (92)	2 (8)	0.38
Abdominal surgery	4 (66.7)	2 (33.3)	0.13	4 (66.7)	2 (33.3)	0.18
Immunosupression	9 (81.8)	2 (18.2)	0.58	9 (81.8)	2 (18.2)	0.62
Neutropenia	4 (57.1)	3 (42.9)	0.02	4 (57.1)	3 (42.9)	0.04
Mechanical ventilation	19 (82.6)	4 (17.4)	0.35	18 (78.3)	5 (21.7)	0.19
Dialysis	4 (57.1)	3 (42.9)	0.02	3 (42.9)	4 (57.1)	0.003
Total parenteral nutrition	17 (81)	4 (19)	0.17	16 (76.2)	5 (23.8)	0.08
Nosocomial infection	37 (90.2)	4 (9.8)	0.39	36 (87.8)	5 (12.2)	0.45
Central venous catheter	28 (84.8)	5 (15.2)	0.30	27 (81.8)	6 (18.2)	0.17
Urinary catheter	15 (83.3)	3 (16.7)	0.36	15 (83.3)	3 (16.7)	0.67
Arterial catheter	8 (72.7)	3 (27.3)	0.09	8 (72.7)	3 (27.3)	0.15
Catheter removal after 72 h[a]	11 (84.6)	2 (15.4)	0.33	11 (84.6)	2 (15.4)	0.33

[a]Catheter removal were evaluated among the patients with central line-associated bloodstream infections (n=32), IQR: Interquartile range

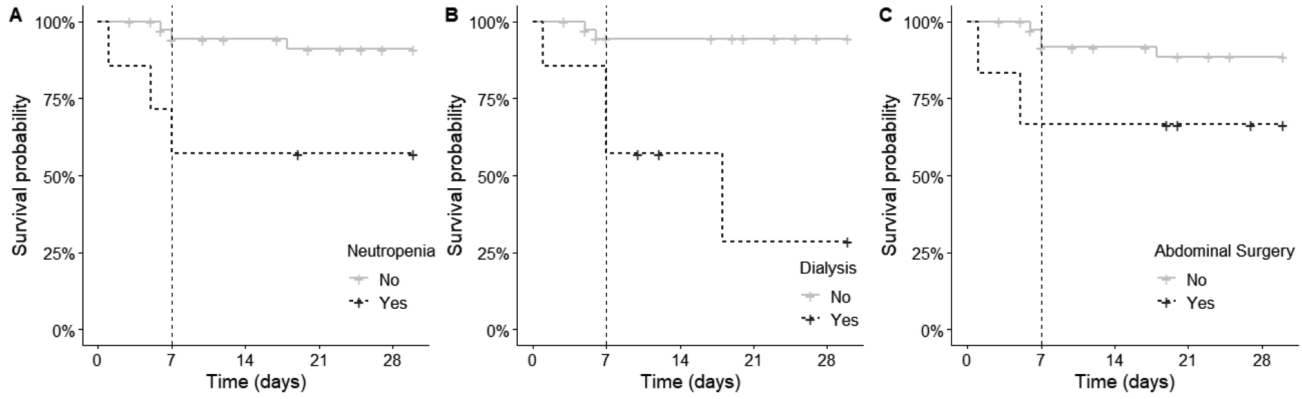

Figure 1. Kaplan-Meier survival curves of the neutropenia, dialysis, and abdominal surgery. Mean survival times for 7-day mortality were lower for the patients with neutropenia, dialysis, and abdominal surgery when compared to patients who had not

disease, neutropenia, prematurity, transplantation, parenteral nutrition, surgery (especially gastrointestinal surgery), bacterial infections, malignancy, colonization with *Candida* spp., broad-spectrum antibiotics, corticosteroids and chemotherapeutic agents, CVCs, dialysis, endotracheal intubation, and stay in the ICU (10-12). Risk factors for IC in this study were similar to those reported in previous studies, and all patients had an underlying disease. Prematurity, congenital heart disease, and solid organ tumor were the most common underlying diseases. Most of our patients had CVCs and received broad-spectrum antibiotic treatment. Particularly, candidemia was catheter-related in 97% of patients with CVC. Also, 41 of 45 IC episodes (91.1%) were considered nosocomial. The high incidence of catheter-related infections and nosocomial candidiasis emphasized the importance of infection control measures and careful care.

Candida species are reported to have differences in clinical features and outcomes. Celebi et al. (12) reported that neutropenia and pre-infection hospitalization were more frequent in non-*albicans* candidemia. Mortality and disseminated candidiasis were higher in patients with *C. albicans*. Similarly, in a study with pediatric 248 candidiasis cases, the mortality rate for *C. albicans* was 34.1% contrast to a rate of 22.4% with non-*albicans* species (13). Dotis et al. (14) showed that using a mechanical ventilator in the two days before *Candida* infection is a significant risk factor for *C. parapsilosis* infection. In a retrospective case-control study at Texas Children's Hospital in 276 episodes of candidemia, there was no difference between *C. albicans* and non-*albicans* candidemia in terms of demographics, underlying diagnosis, risk factors, clinical features, dissemination, or 30-day mortality (15). There was no difference between the invasive infections due to *C. albicans* versus non-*albicans Candida* species and *C. parapsilosis* versus non-*parapsilosis*, in our study. Our sample size might be not enough to determine a small difference.

With the increase of infections caused by non-*albicans Candida* spp., there are problems in the choice of empirical treatment of patients with IC. Studies show that antifungal resistance to non-*albicans Candida* species is higher (9). The sensitivity of *Candida* spp. to antifungal agents can usually be predicted if the species of infectious isolation are known.

However, some *Candida* spp. are not in parallel with the general sensitivity pattern similar to our study. We found that 61.8% of all *Candida* isolates were fluconazole sensitive, and 38.2% were fluconazole-resistant. The most prominent feature of our study was high fluconazole resistance in *C. parapsilosis* strains, which was 73.3%. However, fluconazole is the first recommended antifungal agent for *C. parapsilosis* infections (16). A prospective study which includes 1,218 episodes of *Candida* BSI conducted by using species-specific CLSI reference broth microdilution method for the sensitivity of antifungal agents established that 2.9% of *C. parapsilosis* was non-susceptible to fluconazole (17). Devrim et al. (18) reported that fluconazole resistance was 58.4% in 12 pediatric hematology and oncology patients with catheter-associated *C. parapsilosis* blood supply infection. In our country, revised susceptibility of 453 *Candida* strains isolated from adult and pediatric patients, according to CLSI M27-A3 criteria was evaluated. Fluconazole resistance was 1.4% in *C. albicans*, 18.2% in *C. parapsilosis*, 2.6% in *C. tropicalis,* and %14.3 in *C. glabrata*. There were no AmB-resistant isolates in this study. The highest resistance to fluconazole was in *C. parapsilosis* species (19). Therefore, antifungal susceptibility testing is beneficial for effective antifungal therapy. Considering the current dominance of non-*albicans* strains and fluconazole resistance rates in our hospital, the treatment of echinocandin or AmB as initial treatment is seen as a good option.

It is difficult to assess the death attributed to *Candida*, and the published attributable mortality rates vary depending on the type of study. The overall mortality rate in children with candidiasis ranges from 10% to 26% (8,20,21) In most studies, the presence of an arterial catheter, neutropenia, steroid treatment, insufficiency of antifungal

therapy, prolonged antibiotic therapy, immunosuppressive conditions, disseminated candidiasis, use of TPN and mechanical ventilation, intensive care, and *C. albicans* isolation was established to be associated with mortality due to candidemia (12,22). In our study, the overall mortality rate was 13.3%, in *C. albicans* isolated patients 10%, in non-*albicans Candida* spp. isolated 14.2% and in *C. parapsilosis* isolated 15%. This mortality rate was within the ranges reported in the literature. Although there are studies analyzing the risk factors affecting mortality in the first 30 days, there are not enough studies investigating the risk factors affecting mortality in the first 7 days. In our study, dialysis, neutropenia were risk factors that increased mortality on the 7th and 30th days. Additionally, abdominal surgery is also a risk factor in the first 7 days of mortality. So in the first 7 days of follow-up of patients undergoing abdominal surgery, dialysis, and neutropenia with IC, caution should be exercised for IC and may be evaluated for prophylactic antifungal therapy.

The principal limitations of this study are relatively small sample size and it may not be possible to evaluate multivariate analyzes. Another limitation is that our studies are single-centered and cannot be generalized to other centers.

Conclusions

In summary, we found that *C. parapsilosis* and *C. albicans* are seen more frequently. When considering that the fluconazole resistance of *C. parapsilosis* is 73.3%, the most effective treatment seems to be AmB and caspofungin. Dialysis, neutropenia, and abdominal surgery were risk factors that increased mortality. These data will help us to identify patients who are at risk for IC and will guide us in the selection of empirical treatment.

Ethics

Ethics Committee Approval: This study was approved by the Dokuz Eylül University Non-Invasive Research Ethics Committee (decision no: 2016/13-23, date: 12.5.2016).

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Z.G.K., N.B., Concept: Z.G.K., N.B., M.C.E., M.D.D., Design: Z.G.K., N.B., M.C.E., A.N.E., M.D.D., Data Collection or Processing: Z.G.K., N.B., M.C.E., M.D.D., Analysis or Interpretation: Z.G.K., N.B., A.N.E., Literature Search: Z.G.K., N.B., A.N.E., Writing: Z.G.K., N.B., M.C.E., A.N.E., M.D.D.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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