

Identification and antifungal susceptibility profiles of *Kodamaea ohmeri* based on a seven-year multicenter surveillance study

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Background: *Kodamaea ohmeri* has been a rare fungal pathogen in the past decades but is now becoming more common in various invasive fungal diseases, with high mortality. There are limited data on the occurrence and distribution of *K. ohmeri*.

Methods: Sixty-two *K. ohmeri* isolates collected from 24 hospitals in China over a 7-year period were studied. Performance of three phenotypic methods in the identification of this organism was assessed against a gold standard, 26S rDNA sequencing. Original identification results submitted by the participating local hospitals were reviewed. The Sensititre YeastOne YO10 (SYY) was evaluated in determining the in vitro antifungal susceptibilities using standard broth microdilution method (BMD) as a reference, and essential agreement (EA) was calculated.

Results: Accurate species identification was achieved in 82.3% and 96.8% of the cases by Vitek 2 Compact and Vitek mass spectrometry (MS), respectively. For Bruker MS, 12.9% and 96.8% of the isolates were correctly identified to species level using the direct transfer and protein extraction methods, respectively. Only 29 (46.8%) isolates were initially correctly identified as *K. ohmeri* by the local hospitals. The highest misidentification rate (100%, 16/16) was observed in CHROMagar. According to BMD, the highest MIC₉₀ was seen in fluconazole (8 µg/mL), followed by 1 µg/mL for micafungin, caspofungin, 5-fluorocytosine, and amphotericin B, 0.5 µg/mL for itraconazole, 0.25 µg/mL for posaconazole and voriconazole. Significant differences in EAs for different drugs were observed, ranging from 95.2% for amphotericin B to 22.6% for itraconazole between SYY and BMD.

Conclusion: Our study emphasizes the need for accurate identification of clinical *K. ohmeri* isolates and the importance of validating antifungal susceptibility by standard BMD.

Keywords: *Kodamaea ohmeri*, identification, antifungal susceptibility profiles, invasive fungal disease, surveillance

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Introduction

Invasive fungal disease (IFD) is an important cause of morbidity and mortality in hospitalized patients.¹ The China Hospital Invasive Fungal Surveillance Net (CHIF-NET) program was the first, and currently the largest, national surveillance program established to provide updated information on the epidemiology of invasive fungal infections in mainland China. It was initiated in 2009, and by the seventh surveillance year (2016), as many as 73 hospitals from 30 of the 34 provinces in China had participated, enabling collection of over 8,000 yeast isolates. Although *Candida* species remain the most common fungal pathogens

worldwide, recent reports have highlighted the emergence of infections caused by less-common pathogenic yeasts.^{2,3} One such emerging pathogen is *Kodamaea ohmeri*.

K. ohmeri, previously known as *Pichia ohmeri* and *Yamadazyma ohmeri*, is an ascosporeogenous yeast, and a teleomorph of *Candida guilliermondii* var. *membranaefaciens*, which has been commonly used in the food industry for the fermentation of pickles, rinds, and other fruit.⁴ Now, the genus *Kodamaea* is divided into 5 species (*K. anthropila*, *K. kakaduensis*, *K. laetipori*, *K. nitidularum*, *K. ohmeri*) and only *K. ohmeri* shows pathogenicity in humans.⁴ Since the first case report of sepsis due to *K. ohmeri*,⁵ several case reports of various IFDs, including sepsis or fungemia,^{6,7} catheter-related bloodstream infection,^{8,9} peritonitis,¹⁰ and endocarditis,^{11,12} with high mortality due to *K. ohmeri* have gradually accumulated. Moreover, nosocomial outbreaks of *K. ohmeri* infection in the pediatric ward have also been reported.¹³ All this evidence suggests that *K. ohmeri* should be added to the growing list of opportunistic fungal pathogens in humans, and calls for early recognition and appropriate treatment.

Despite the increasing clinical significance in IFD, there are limited data on the occurrence and distribution of *K. ohmeri* globally. Here, we studied the epidemiology and antifungal susceptibility patterns of *K. ohmeri* clinical isolates based on the multicenter surveillance program-CHIF-NET in China over seven years.

Materials and methods

Ethics

The study was approved by the Human Research Ethics Committee of Peking Union Medical College Hospital (no. S-263). Written informed consent was obtained from patients for the use of the samples in research.

Isolates

A total of 62 *K. ohmeri* clinical isolates collected from 24 different hospitals in 14 provinces, as part of the CHIF-NET study, from August 2009 to July 2016, were studied. The study inclusion criteria were as follows: for each surveillance year, all non-repetitive yeast isolates from eligible patients with IFDs were forwarded to the central laboratory, the Department of Clinical Laboratory, Peking Union Medical College Hospital (PUMCH), for species confirmative identification and antifungal susceptibility testing.

DNA extraction and identification

DNA extraction and amplification of the 26S ribosomal DNA were performed with primer pairs NL1/NL4, as previously described.¹⁴ The PCR products were sent to Riobiotech (Beijing, China) for sequencing. Identification was carried out by querying the sequences against GenBank database with nucleotide Basic Local Alignment Search Tool (BLASTn, <http://blast.ncbi.nlm.nih.gov>).

We also evaluated the performance of the Vitek-2 Compact (bioMérieux, France) and two MALDI-TOF MS systems, including the Vitek MS system (IVD Knowledgebase version 3.0; bioMérieux) and the Bruker Autoflex Speed TOF/TOF MS system (Biotyper version 3.1 software; Bruker Daltonics, USA) in the identification of *K. ohmeri* isolates. The Vitek-2 Compact Yeast card was used, and the final profile results were analyzed further as per the database specifications. For Vitek MS system, the results were scored in one of three ways as per the manufacturer's recommendations.¹⁵ For Bruker MS, both direct transfer and the ethanol-formic acid protein extraction methods, as recommended by the manufacturer,¹⁶ were used for sample preparation. Identification was determined according to manufacturer-determined criteria: a score of <1.7 was interpreted as "no" identification, a score of 1.7–2.0 as identification to genus level, and a score of ≥ 2.0 as identification to species level.¹⁷

Antifungal susceptibility testing

In vitro susceptibilities of the isolates to eight antifungal drugs including amphotericin B, 5-flucytosine, fluconazole, itraconazole, voriconazole, posaconazole, micafungin, and caspofungin, were determined by broth microdilution method (BMD) as per Clinical and Laboratory Standards Institute (CLSI) guidelines (document M27-A3).¹⁸ Furthermore, we evaluated the performance of Sensititre YeastOne YO10 (SYY) (Thermo Scientific, USA) in antifungal susceptibility testing of *K. ohmeri* isolates as per the manufacturer's instructions. For both methods, minimum inhibition concentrations (MIC) were read after 24 hrs incubation. Since there is neither clinical breakpoint (CBP) nor epidemiological cut-off values (ECVs) available for *K. ohmeri*, only essential agreement (EA) [percentage of MICs detected by SYY within a single doubling dilution of the corresponding BMD result] for each drug¹⁹ was calculated compared to BMD results (EA for anidulafungin was not calculated due to its inaccessibility in China). *Candida parapsilosis* ATCC 22019 and *Candida krusei* ATCC 6258

were used as the quality control strains for identification and antifungal susceptibility testing.

Results

Detailed information of the study isolates is summarized in Table 1. The 62 isolates were collected from 62 patients at

Table 1 Distribution of the 62 *Kodamaea ohmeri* isolates by department and specimen type

Gender	Male (N=33, 53.2%)	
	Female (N=29, 46.8%)	
Age	59±19.3	
Department	No.	%
Surgery	24	38.7
Medical	20	32.3
Intensive care unit	9	14.5
Pediatrics	4	6.5
Emergency	2	3.2
Organ transplantation	1	1.6
Dermatology	1	1.6
Rehabilitation	1	1.6
Total	62	100
Specimen type	No.	%
Blood	34	54.8
Catheter	10	16.1
Wound	5	8.1
Ascitic fluid	5	8.1
Drainage fluid	4	6.5
Bronchoalveolar lavage fluid	2	3.2
Pleural effusion	1	1.6
Cerebrospinal fluid	1	1.6
Total	62	100

24 hospitals located in 14 provinces across China over seven years. Thirty-four (34/62, 54.8%) of the strains were isolated in CHIF-NET year 2016, ten of which were isolated from one single hospital (Figure 1). The majority of the isolates were from patients admitted to surgical department (38.7%), medical department (32.3%), and intensive care unit (ICU) (14.5%), followed by pediatrics (6.5%), emergency (3.2%), organ transplantation (1.6%), dermatology (1.6%), and rehabilitation (1.6%). Among various specimen types, more than half of the isolates (54.8%) were recovered from blood, followed by catheter (16.1%), wound (8.1%), ascitic fluid (8.1%), drainage fluid (6.5%), broncho-alveolar lavage fluid (3.2%), pleural effusion (1.6%), and cerebrospinal fluid (1.6%) (Table 1).

Sequence-based identification

The 26S rDNA sequences of the study isolates exhibited 99–100% identity with the sequence of standard strain CBS 6722 in the GenBank. The DNA sequences of the representative isolates have been deposited in GenBank with accession numbers MK414609 to MK414670.

Original species identification results by local hospitals

We looked back into the original information submitted by the local hospitals about the isolates and found that among the 62 *K. ohmeri* isolates re-identified by DNA sequencing in the central laboratory, only 29 (46.8%) were initially identified as *K. ohmeri* correctly by the local hospitals. The remaining 33 (53.2%) were misidentified as *Candida albicans* (n=11), *Candida glabrata* (n=9), *Candida tropicalis* (n=4), *Candida guilliermondii* (n=3), *Candida lusitanae* (n=1), *Cryptococcus neoformans* (n=1), *Candida famata*

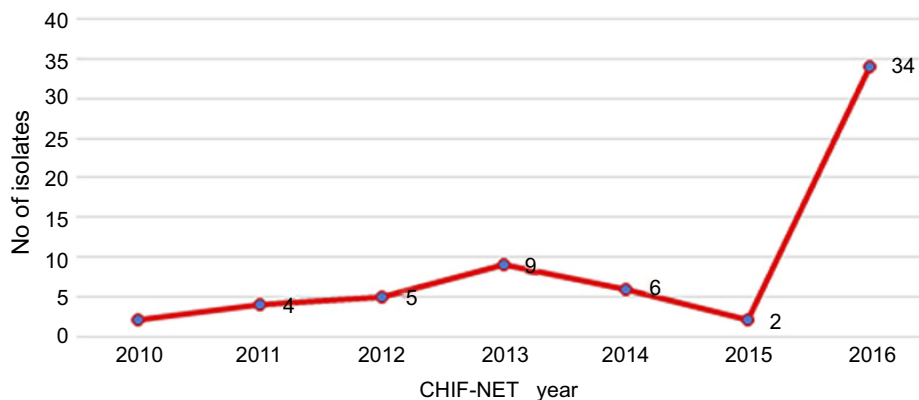


Figure 1 Distribution of 62 *Kodamaea ohmeri* isolated from the seven-year surveillance study.

Abbreviation: CHIF-NET, China Hospital Invasive Fungal Surveillance Net.

(n=2), *Candida pelliculosa* (n=1) and *Candida rugosa* (n=1) by different methods. Vitek MS, Vitek 2 Compact, ATB32 C, and APC 20C correctly identified 100% (2/2), 70% (14/20), 66.7% (4/6), and 56.3% (9/16) of the isolates, respectively. Only one isolate each was identified using BD Phoenix100 and RapID™ YEAST PLUS, and neither of them got the correct result; one misidentified as *C. tropicalis* and the other one as *Cryptococcus neoformans*. Noticeably, the highest misidentification rate (16/16, 100%) was seen in CHROMagar among which nine, four, and three isolates were misidentified as *Candida albicans*, *Candida glabrata*, and *Candida tropicalis*, respectively (Table 2).

Vitek 2 compact and MALDI-TOF MS identification results in the central laboratory

As compared with 26S rDNA sequencing, 82.3% of the isolates were correctly identified by Vitek 2 Compact system while 17.7% of the isolates yielded “no identification” results. Vitek MS system correctly identified 96.8% of the isolates (confidence value, 99.9%) with only one exception of “no identification” result. For the Bruker system, considerable differences were observed in the results of the two sample preparation methods used. According to the manufacturer-determined criteria, 12.9% and 71.0% of the isolates were identified to species and genus level, respectively, while 16.1% yielded “no identification” results using the

direct transfer method. A significant increase in identification accuracy was seen when using the protein extraction method with 96.8% and 3.2% of the isolates correctly identified to species and genus levels, respectively (Table 3).

Antifungal susceptibility profiles

The antifungal susceptibilities of the study isolates by BMD and SYY are shown in Table 4. Significant differences in EAs for different drugs were observed, ranging from 22.6% for itraconazole to 95.2% for amphotericin B. MIC₅₀s and MIC₉₀s detected by BMD were generally higher (up to four-fold) than those detected by SYY. Due to such a great inconsistency between BMD and SYY, which has been reported with high agreement in yeasts, we repeated the antifungal susceptibility testing by both methods to exclude experimental errors, and the previous results were confirmed. According to BMD, highest MIC₉₀ was seen in fluconazole (8 µg/mL), followed by 1 µg/mL for micafungin, caspofungin, 5-fluorocytosine, and amphotericin B, 0.5 µg/mL for itraconazole, and 0.25 µg/mL for posaconazole and voriconazole.

Discussion

For decades, *K. ohmeri* has been recognized as a fungal contaminant but not as a human pathogen. Systemic infections due to *K. ohmeri* have generally been considered to be rare. Consequently, little attention has been paid to this

Table 2 Original identification results of the 62 *Kodamaea ohmeri* isolates submitted by local hospitals using different phenotypic methods

Identification Results	API 20C	ATB32C	BD Phoenix 100	CHROMagar	RapID™ YEAST PLUS	Vitek 2 Compact	Vitek MS
Correct ID (n=29, 46.8%) <i>Kodamaea ohmeri</i>	9	4				14	2
Incorrect ID (n=33, 53.2%) <i>Candida glabrata</i>	4	1		4			
<i>Candida lusitanae</i>	1						
<i>Candida albicans</i>	1	1		9			
<i>Candida guilliermondii</i>	1					2	
<i>Candida tropicalis</i>			1	3			
<i>Cryptococcus neoformans</i>					1		
<i>Candida famata</i>						2	
<i>Candida pelliculosa</i>						1	
<i>Candida rugosa</i>						1	
Percentage of correct ID	56.25	66.7	0.0	0.0	0.0	70.0	100.0
Percentage of incorrect ID	43.75	33.3	100.0	100.0	100.0	30.0	0.0

Table 3 Performance of Vitek 2 compact system, Vitek MS, and Bruker Biotyper MS compared with 26S rDNA gene sequencing for the identification of 62 *Kodamaea ohmeri* isolates

Identification system	Correct identification to species level		Correct identification to genus level		No identification (invalid result)		Misidentification	
	No.	%	No.	%	No.	%	No.	%
Vitek 2 Compact	51	82.3	0	0	11	17.7	0	0
Vitek MS system	61	98.4	0	0.0	1	1.6	0	0
Bruker Biotyper MS system								
Direct transfer	8	12.9	44	71.0	10	16.1	0	0
Protein extraction	60	96.8	2	3.2	0	0.0	0	0

Table 4 Comparison of in-vitro antifungal susceptibility data (MIC, µg/mL) of the 62 *Kodamaea ohmeri* isolates against nine antifungal agents between BMD and SY Y

Antibiotic	AST method	Number	MIC ₅₀	Fold	MIC ₉₀	Fold	MIC Range	Geom.Mean	EA
Anidulafungin	SY Y	62	0.125	-	0.5	-	0.03–2	0.192	-
Micafungin	BMD	62	0.5	4	1	4	0.12–1	0.473	43.5%
	SY Y	62	0.125		0.25		0.03–1	0.136	
Caspofungin	BMD	62	0.5	2	1	1	0.25–2	0.691	50.0%
	SY Y	62	0.25		1		0.015–2	0.24	
5-Fluorocytosine	BMD	62	0.032	1	1	0.5	0.03–1	0.087	88.7%
	SY Y	62	0.032		2		0.03–2	0.1	
Posaconazole	BMD	62	0.125	4	0.25	2	<0.015–0.5	0.136	40.3%
	SY Y	62	0.032		0.125		0.015–0.25	0.042	
Voriconazole	BMD	62	0.064	2	0.25	4	<0.015–2	0.075	74.2%
	SY Y	62	0.032		0.064		0.004–0.5	0.038	
Itraconazole	BMD	62	0.5	4	0.5	4	0.06–1	0.399	22.6%
	SY Y	62	0.125		0.125		0.008–0.5	0.091	
Fluconazole	BMD	62	4	1	8	1	1–>256	5.115	91.9%
	SY Y	62	4		8		0.5–64	5.058	
Amphotericin B	BMD	62	0.5	1	1	2	0.5–1	0.598	95.2%
	SY Y	62	0.5		0.5		0.06–0.5	0.409	

Abbreviations: BMD, broth microdilution method; SY Y, Sensititre YeastOne YO10; EA, essential agreement; MIC, minimuminhibition concentrations.

insignificant yeast until 1998 when the first case of fungemia caused by *K. ohmeri* was described.⁵ Most published studies to date on *K. ohmeri* infections are sporadic cases commonly seen in Asian countries like Korea,^{20,21} Japan,^{8,22} and India.^{23–26} The infections were reported more often in children than in adults, and almost all patients had one or more underlying conditions alongside immunodeficiency.⁸ Mortality rates due to *K. ohmeri* invasive infections have been reported to be as high as 50%.^{13,20} The largest cluster of *K. ohmeri* infection reported was set in a single hospital in North India, presenting as 38

fungemia cases, 78.9% of which were isolated from neonates in intensive care units.²⁶ Several surveillance studies in Spain, Malaysia, and Tunisia have also reported the isolation of *K. ohmeri* but with limited numbers.^{27–29} So far, our study presents as the first, largest, and multicenter epidemiological study of *K. ohmeri* clinical isolates causing IFDs in China.

During the 7-year surveillance, a total of 62 *K. ohmeri* isolates from cases of IFDs were collected and re-identified by 26S rDNA sequencing at the Central hospital, PUMCH. However, according to the original results submitted by the

participating local hospitals, less than half of the isolates were correctly identified as *K. ohmeri* using different methods. The CHROMagar Candida chromogenic growth medium, which was developed based on the characteristic color change of the colonies, is an extremely useful tool in the clinical lab to assist in routine identification of common *Candida* species. However, this medium failed to correctly identify all the 16 *K. ohmeri* isolates reported by local hospitals in this study. It is known that *K. ohmeri* colonies can undergo a unique color change from pink to blue when grown on CHROMagar medium, and this phenomenon takes at least 2–3 days to form pink-blue colonies. Moreover, a full week may be required to obtain complete blue color colony development.²⁰ Thus it is not surprising to note that 9, 4, and 3 isolates amongst the 16 misidentified isolates were incorrectly identified as *C. albicans*, *C. glabrata*, and *C. tropicalis*, respectively, which may be a result of determining the color of the isolates either too early or too late by lab staff. This identification confusion has been previously reported.²⁶ Actually, this is how the largest cluster of *K. ohmeri* infection was discovered, in which 38 (25.7%) of 148 previously identified *C. tropicalis* isolates were re-identified as *K. ohmeri* by genotypic characterisation.²⁶ Therefore, while CHROMagar is a useful and simple identification tool, careful and patient observation is necessary for correct identification of *K. ohmeri*.

Several other fungal identification methods with various levels of accuracy for specific organisms are used by many local hospitals in China. Among 16 isolates identified by API 20C system, seven (43.8%) were misidentified as *C. glabrata* (n=4), *C. lusitanae* (n=1), *C. albicans* (n=1), and *C. guilliermondii* (n=1). The Vitek 2 Compact system correctly identified 70% (14/20) of isolates, with two misidentified as *C. guilliermondii*, two as *C. famata*, and one of each as *C. pelliculosa* and *C. rugosa*. Both the API 20C and Vitek 2 Compact systems have been shown to yield false-positive results, identifying *C. haemulonii* or *C. parapsilosis* as *K. ohmeri*.^{20,30} It is also known that *C. auris* and *C. haemulonii* are closely related and cannot be distinguished with conventional identification methods.³¹ Due to the emerging role of *C. auris* as a multidrug-resistant fungal pathogen with high morbidity and mortality, early accurate identification of this organism is crucial for patient management.³² In this case, the use of the faster molecular diagnostic tools for the proper identification of fungal pathogens is strongly recommended. The other four methods including ATB32C, BD Phoenix100,

RapID™ YEAST PLUS, and Vitek MS, which were used for fungal identification by a small number of hospitals, yielded a wide variety of results which were difficult to generalize.

Nevertheless, the Vitek MS system performed the best among all the methods with 100% accuracy, albeit only two isolates identified using this method. Therefore, we performed a parallel study for identification of all the 62 *K. ohmeri* isolates using three commonly used phenotypic methods in our lab. To the best of our knowledge, this is the first evaluation study on the performance of three phenotypic methods for the identification of *K. ohmeri*. In general, the Vitek 2 Compact system (82.3% vs 70%) and Vitek MS (98.4% vs 100%) showed similar results with those submitted by the local hospitals. The Bruker system demonstrated a difference in the identification accuracy of *K. ohmeri* based on the sample preparation method. The identification accuracy obtained using the protein extraction method (96.8%) was comparable to that of Vitek MS, while the direct transfer method was only comparable to that of Vitek 2 Compact only when the genus identification cut-off value (>1.7) was adopted (83.9%). While MALDI-TOF MS is increasingly being used to identify *Candida* species in clinical laboratories, only one study has previously reported on the use of Bruker system for identification of *K. ohmeri*.⁸ In that study, the protein extraction procedure was used, which yielded a high confidence score although only one isolate was tested.⁸ These data suggest that both Vitek MS and Bruker system with protein extraction method for sample preparation can be used as a fast and accurate tool for *K. ohmeri* identification.

For the first time, we also compared the *in-vitro* susceptibilities of 8 antifungal agents using standard BMD and the commercial SYY against 62 *K. ohmeri* isolates. The commercial SYY system is an adapted microbroth susceptibility testing system based on the M27-A3 standard for yeasts, which has been widely used in antifungal susceptibility testing of yeasts and is now being evaluated in molds.^{33,34} Excellent EAs have been reported in triazoles and echinocandins against *Candida* spp., ranging from 92.3% to 100%.^{35,36} Surprisingly, significant differences in EAs against *K. ohmeri* isolates were observed, especially for itraconazole presenting as 22.6%. We excluded experimental errors by repeating both procedures, and the results were confirmed. We tried to find a possible explanation for this finding, but it proved difficult as there is limited data

reported in literature on this aspect. Most of the published literature concerning *K. ohmeri* infections only used one method, either the commercial SYY or the standard BMD, to determine the MIC values. Only one previous study used BMD to confirm the MIC for micafungin using a colorimetric method for a single *K. ohmeri* isolate causing fungemia and found a 640-fold difference in the MIC value between the two methods.²² Despite the scarce evidence, this should serve as a reminder that validation of the antifungal susceptibility test by standard BMD for rare yeasts like *K. ohmeri* is important as susceptibility results often play an important role in the choice of antifungal agent to administer.

Since no CBP or ECV has been established to date for *K. ohmeri*, we could not compare the susceptibility or resistance patterns of our isolates with those reported in literature. However, based on MIC distribution of susceptibility results by BMD, our findings are in agreement with previous results showing that *K. ohmeri* strains have low MICs to all antifungal agents tested except for fluconazole, with MIC₅₀ and MIC₉₀ as high as 4 and 8 µg/mL, respectively.²⁶ Twenty-four of the tested isolates exhibited MICs of ≥8 µg/mL, one of which had the highest MIC of >256 µg/mL. Compared to the large cluster from India,²⁶ the present isolates had similar MIC_{90s} for amphotericin B, itraconazole and posaconazole, while a two-fold increase in MIC₉₀ was observed for voriconazole and caspofungin, and a four-fold increase for fluconazole. Previous studies concluded that amphotericin B or echinocandin should be considered to be a good antifungal choice for treatment of *K. ohmeri* infections.^{8,37} Considering that antifungal treatment should be adjusted according to susceptibility results of the clinical isolates, based on the MIC results of our isolates, all the eight antifungal agents tested except fluconazole, may be successful in treating most of the *K. ohmeri* infections according to the in vitro susceptibility results.

In conclusion, this is the first systemic study regarding the epidemiology, identification, and antifungal susceptibility profiles of *K. ohmeri* isolates in China. Our study emphasizes the need for accurate identification of clinical *K. ohmeri* isolates as an emerging human pathogen in China and the importance of validation of antifungal susceptibility results by standard BMD.

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Disclosure

All authors report no conflicts of interest in this work.

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