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Validation of Cefazolin as Initial Antibiotic for First Upper Urinary Tract Infection in Children

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Abstract

To validate the policy of administering cefazolin (CEZ) as a first-line antibiotic to children who are hospitalized with their first febrile urinary tract infection (UTI), we evaluated microbial susceptibility to CEZ and the efficacy of CEZ. The 75 enrolled children with febrile UTI were initially treated with CEZ. Switching CEZ was not required in 84% of the patients. The median fever duration, prevalence of bacteremia, prevalence of UTI caused by extended-spectrum β-lactamase (ESBL)-producing *Escherichia coli*, and median duration of hospitalization were significantly higher in the CEZ-ineffective group. The risks of vesicoureteral reflux, indication of operation, and renal scarring are not increased, even when CEZ is ineffective as a first-line antibiotic. CEZ is effective in more than 80% of pediatric patients with their first febrile UTI, but it should be switched to appropriate antibiotics considering sepsis or the ESBL-producing Enterobacteriaceae pathogen, when fever does not improve within 72 hours.

Keywords

upper urinary tract infection, antibiotics, cefazolin, validation, children

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Introduction

Urinary tract infection (UTI) is a common disease in children. Early detection and sufficient antibiotic therapy for febrile UTI can prevent progression to urosepsis and meningitis. Hence, it is important to use appropriate antibiotics for the treatment of febrile UTI. However, the antibiotics chosen for the initial treatment of febrile UTI are diverse because of differences in UTI severity, institute policy, and/or clinicians' judgment, and local patterns of susceptibility of coliforms to antibiotics should be considered.[1] On the other hand, it is recommended that third-generation cephalosporins should be considered for empiric treatment of UTI,[1] and UTI caused by pathogens producing extended-spectrum β-lactamase (ESBL) should be treated with carbapenems.[2,3] However, the increase in their use can select carbapenem-resistant pathogens, and the rising rate of resistance of pathogens to antibiotics decreases the number of effective antibiotics.

To consider the balance between the prevention of development of resistance to antibiotics and the limit of antibiotic effectiveness for febrile UTI in children, the efficacy of traditional antibiotics, such as first-generation cephalosporins, should be reevaluated. Preliminarily, we reported the efficacy of cefazolin (CEZ) in children with febrile UTI.[4] The policy in our pediatric department is to administer CEZ as a first-line antibiotic to children who are hospitalized with their first febrile UTI. To validate this policy in this study, we retrospectively evaluated microbial susceptibility to CEZ and the efficacy of CEZ in terms of clinical manifestations and outcomes.

Materials and Methods

Patients

Of the children who were admitted to Showa University Hospital because of febrile UTI during the period from May 2005 to December 2013, 75 who were initially

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treated with CEZ because of a first episode of febrile UTI were enrolled in this study. Febrile UTI was defined as having a fever (≥37.5°C) before admission and urine culture positive for a single pathogenic microorganism; urine samples were obtained by transurethral catheterization (>10^4 colony-forming units/mL). Medical records of those patients were retrospectively reviewed. Patients with anorectal malformation, antenatally diagnosed renal abnormalities, and chromosomal abnormalities were excluded. This study was approved by the ethics committee of Showa University School of Medicine (No. 1696), and the study was performed in accordance with the ethical standards of the 1964 Helsinki Declaration and its later amendments.

Bacterial Isolates

Isolate identification and susceptibility tests were performed using Micro Scan Neg Combo Panel 6.11J in the automated microbiological instrument Microscan Walkaway 96 system (Siemens Healthcare, Bethesda, MD). The obtained minimum inhibitory concentrations (MICs) were interpreted according to the Clinical and Laboratory Standards Institute guidelines.[5] The phenotypes of isolates detected in the initial screening on the basis of the MIC criteria were confirmed by disk diffusion method in the hospital laboratory.

ESBL-producing *Escherichia coli* isolates were initially identified by routine methods in our hospital and screened by polymerase chain reaction (PCR) analysis using specific primers for $bla_{\text{CTX-M}}$ detection. Bacterial total DNA was extracted from the colonies grown on agar plates with Luria-Bertani medium. PCR was performed as follows: 10 ng of template DNA, 50 pmol each of forward and reverse primers, and 400 nmol of NTP were mixed in buffer (10 mM Tris-HCl, 50 mM KCl, 2.5 mM $MgCl_2$; pH 8.3) to a final volume of 25 μL. The mixture was incubated at 95°C for 5 minutes, followed by 30 cycles at 95°C for 30 seconds, 60°C for 30 seconds, 72°C for 1 minute, and then 72°C for 7 minutes for final extension. The PCR primers used to detect CTX-M genes were as follows: forward, tttgcgatgtgcagtaccagtaa; and reverse, ctccgctgccggttttatc. PCR products (520 bp) were electrophoresed on a 5% polyacrylamide gel and stained with SYBR Green (TaKaRa Bio Inc, Shiga, Japan). To determine the sequences of the PCR products, they were electrophoresed on a 1% agarose gel, and the expected size band was then cut out from the gel and purified with the GenElute column (Sigma-Aldrich, St Louis, MO). A portion of the purified DNA (0.5 μg) was used in DNA sequencing using the forward or reverse PCR primers. Sequencing reactions were performed using a BigDye Terminators ver. 1.1 Cycle Sequencing kit (Applied Biosystems, Carlsbad, CA). The products were sequenced on an ABI PRISM 310 genetic analyzer (Life Technologies, Carlsbad, CA).

The susceptibility to the following 14 antimicrobial agents was investigated: ampicillin (ABPC), cefazolin (CEZ), cefotiam (CTM), cefotaxime (CTX), ceftazidime (CAZ), cefaclor (CCL), cefmetazole (CMZ), flomoxef (FMOX), imipenem/cilastatin (IPM/CS), cefcapene pivoxil (CFPN-PI), gentamicin (GM), levofloxacin (LVFX), sulfamethoxazole/trimethoprim (ST), and fosfomycin (FOM).

CEZ Therapy

CEZ (50 mg/kg body weight/day), which was divided into 3 doses daily, was intravenously administered. Switching of CEZ to an alternative antibiotic was indicated when early treatment failure was observed. The decision to switch to another antibiotic was made by the attending physicians of the patients. For patients with fever on admission, the effectiveness of CEZ was defined as alleviation of fever within 3 days after the start of CEZ administration.

Diagnostic Methods for Renal Abnormalities

Renal ultrasonography was performed after the clinical diagnosis of UTI to examine for abnormalities in the kidney morphology or any grade of dilation of the collecting system (renal pelvis, calyces, or distal ureters). In accordance with recommendation of the American Academy of Pediatrics,[6] voiding cystourethrography (VCUG) was performed to detect vesicoureteral reflux (VUR) at the earliest convenient time. At the same time, urine culture was repeated to confirm the absence of pathogenic microorganisms, since transurethral catheterization was required to perform VCUG. The severity of VUR was graded in accordance with the international reflux grading system.[7] Renal parenchyma radionuclide scanning with technetium-99-m-DMSA (^{99}Tc DMSA) was performed after the diagnosis of UTI. Focal and diffuse areas of reduced radionuclide uptake noted with preservation of the normal outline of the kidney were considered to be abnormal acute lesions. To investigate renal scarring 1 year after UTI, ^{99}Tc DMSA scanning was performed again on patients who had acute photon defects in the initial scanning.

Differences in Characteristics Between CEZ-Effective and CEZ-Ineffective Groups

To investigate the clinical efficacy of CEZ as a first-line antibiotic and to identify the differences in the following 12 characteristics between the CEZ-effective and CEZ-ineffective groups, the outcomes were evaluated

regarding the use of antibiotics before admission, white blood cell (WBC) count, C-reactive protein (CRP) level, average fever duration, prevalence of bacteremia, prevalence of UTI caused by ESBL-producing *E coli*, duration of hospitalization, UTI recurrence, detection of VUR, indication of operation, photon defects in acute DMSA scans, and renal scarring detected by DMSA 1 year after UTI.

Statistical Analyses

Fisher's exact probably test and Mann-Whitney *U* test were used for statistical analyses using Prism (GraphPad, San Diego, CA). A *P* value less than .05 was considered statistically significant.

Results

The median age was 3 months (range = 1-55 months; 74 [98.7%] were aged ≤24 months). Of the 75 children, 52 (69.3%) were males. Laboratory tests on admission revealed the following: WBC count = 15926.7 ± 5862.5/μL; CRP level = 4.5 ± 3.9 mg/dL; blood urea nitrogen level = 7.5 ± 2.3 mg/dL; creatinine level = 0.2 ± 0.1 mg/dL; aspartate transaminase level = 38.8 ± 17.8 IU/L; and alanine transaminase level = 27.1 ± 16.2 IU/L. The duration of hospitalization was 11.7 ± 2.9 days (7-25 days).

As shown in Figure 1, CEZ was clinically effective in 64 patients. In one of these patients, CEZ was effective for fever alleviation, but it was switched to FOM because the pathogen was identified to be ESBL-producing *E coli*. Although all patients had fever before admission, 23 were afebrile on admission. Regarding fever alleviation after admission, CEZ was effective in 41 of 52 patients (78.8%). In these 41 patients, the median duration of fever was 1 day (range = 0-2 days). In the remaining 11 patients, CEZ was ineffective and was thus switched to other antibiotics. In one of these patients, CEZ was switched to ABPC because of liver dysfunction. Sixty-three (84%) of the enrolled patients did not require the switching of CEZ to other antibiotics for further treatment.

The pathogens isolated from urine were *E coli* (72 patients, 96.0%), *Enterococcus faecalis* (2 patients, 2.7%), and *Klebsiella pneumoniae* (1 patient, 1.3%). Of all the patients, 3 had bacteremia due to *E coli* (4.0%). The antibiotic susceptibilities of these isolates are shown in Table 1. Of all the pathogenic isolates from urine, 61 (81.3%) were susceptible to CEZ. Of the 72 patients whose urine cultures showed *E coli* isolates, 7 (9.7%) showed ESBL-producing *E coli* isolates. All the isolates were susceptible to CMZ, FMOX, and IPM/CS (Table 2), while 6 of those 7 isolates were susceptible to FOM.

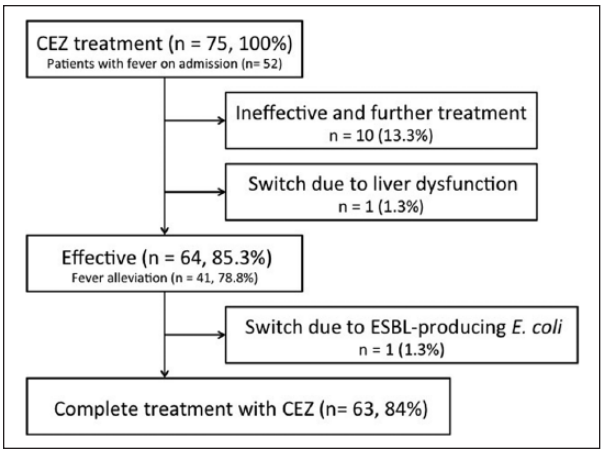

Figure 1. Treatment outcomes in all patients.

Regarding $bla_{CTX\text{-}M}$, CTX-M14 was detected in 6 patients and CTX-M3 in 1 patient.

After antibiotic treatment, it was confirmed that urine cultures were negative for pathogens in 71 of 75 patients. Four patients did not have urine culture after the initial therapy, but all of them had no recurrent UTI.

To identify abnormalities in the urinary tract, urinary tract ultrasonography were performed in 70 patients, VCUG in 74 patients, and renal cortical scintigraphy in 73 patients. In these patients, the initial renal cortical scintigraphy was performed 10 days (median value; range = 6-23 days) after admission. The rates of detection of abnormalities by these examinations are shown in Table 3.

Of the 12 characteristics investigated, 4 (average fever duration, prevalence of bacteremia, prevalence of UTI caused by ESBL-producing *E coli*, and duration of hospitalization) were significantly higher in the CEZ-ineffective group (Table 4).

Discussion

In this study, the major pathogen was found to be *E coli*, and CEZ was effective for 84% of patients with first febrile UTI as the first-line antibiotic. Compared with the CEZ-effective group, the average fever duration, prevalence of bacteremia, and prevalence of UTI caused by ESBL-producing *E coli* were significantly higher in the CEZ-ineffective group. However, renal scarring was not aggravated, even when CEZ switching to other antibiotics was required.

Our findings are consistent with those of some previous studies, which showed that *E coli* was the most commonly isolated pathogen from urine.[8-12] To assess the efficacy of antibiotics for UTI in children, MIC was used as an indicator of the efficacy of antibiotics in many

Table 1. Antibiotic Susceptibility of Strains Obtained From Urine Samples[a].

	MIC (μg/mL)													
	≤0.25	0.5	≤1	>1	≤2	>2	≤4	>4	≤8	>8	≤16	>16	>32	NA
ABPC					2[b]		45					28[c] (7)		
CEZ							61		2[b,c]		1	11[b] (7)		
CTM									64[c]			11[b] (7)		
CTX									66[c]				7 (7)	2[b]
CAZ			66[c] (2)						4 (3)		2 (1)	1 (1)		2[b]
CCL									62[c]			11 (7)		2[b]
CMZ							70[c] (6)		2 (1)		1			2[b]
FMOX			2[b]						72[c] (7)				1	
IPM/CS			75[b,c] (7)											
CFPN-PI	30[c]	25	5	9 (7)										6[b]
GM			49[c] (1)		16 (2)		1			9[b] (4)				
LVFX			66[b,c] (1)					9 (6)						
ST			1[b]		63[b,c] (4)	10 (3)								1
FOM							69[c] (6)				5[b]	1 (1)		

Abbreviations: MIC, minimum inhibitory concentration; ABPC, ampicillin; CEZ, cefazolin; CTM, cefotiam; CTX, cefotaxime; CCL, cefaclor; CMZ, cefmetazole; FMOX, flomoxef; IPM/CS, imipenem/cilastatin; CFPN-PI, cefcapene pivoxil; GM, gentamicin; LVFX, levofloxacin; ST, sulfamethoxazole-trimethoprim; FOM, fosfomycin; NA, not applicable; ESBL, extended-spectrum β-lactamase.
[a]Values in parentheses indicate the number of ESBL strains included.
[b]Including strains of *Enterococcus faecalis*.
[c]Including a strain of *Klebsiella oxytoca*.

Table 2. Characteristics and Antibiotic Susceptibility in Patients With UTI Due to ESBL-Producing *Escherichia coli* Strains.

	Patient 1		Patient 2		Patient 3		Patient 4		Patient 5		Patient 6		Patient 7	
Case	MIC (μg/mL)	Susceptibility	MIC (μg/mL)	Susceptibility	MIC (μg/mL)	Susceptibility	MIC (μg/mL)	Susceptibility	MIC (μg/mL)	Susceptibility	MIC (μg/mL)	Susceptibility	MIC (μg/mL)	Susceptibility
Age (months)	3		2		5		6		1		2		7	
Gender	Female		Male		Male		Female		Male		Male		Male	
Past history	—		—		Bacteremia		—		—		—		—	
CEZ effectiveness	Ineffective		Ineffective		Ineffective		Effective		Effective		Effective		Ineffective	
bla$_{CTX-M}$	M3		M14		M14		M14		M14		M14		M14	
ABPC	>16	R	>16	R	>16	R	>16	R	>16	R	>16	R	>16	R
CEZ	>16	R	>16	R	>16	R	>16	R	>16	R	>16	R	>16	R
CTM	>16	R	>16	R	>16	R	>16	R	>16	R	>16	R	>16	R
CTX	>32	R	>32	R	>32	R	>32	R	>32	R	>32	R	>32	R
CAZ	16	R	>16	R	<1	R	<1	R	8	R	8	R	8	R
CCL	>16	R	>16	R	>16	R	>16	R	>16	R	>16	R	>16	R
CMZ	<4	S	8	S	<4	S	<4	S	≤4	S	≤4	S	≤4	S
FMOX	<8	S	<8	S	<8	S	<8	S	≤8	S	≤8	S	≤8	S
IPM/CS	<1	S	<1	S	<1	S	<1	S	≤1	S	≤1	S	≤1	S
CFPN-PI	>1	R	>1	R	>1	R	>1	R	>1	R	>1	R	>1	R
GM	2	S	>8	R	>8	R	<1	S	2	R	>8	R	>8	R
LVFX	>4	R	>4	R	>4	R	<1	S	>4	R	>4	R	>4	R
ST	>2	R	>2	R	<2	S	<2	S	>2	R	≤2	S	≤2	S
FOM	<4	S	<4	S	>16	R	<4	S	≤4	S	≤4	S	≤4	S

Abbreviations: UTI, urinary tract infection; ESBL, extended-spectrum β-lactamase; MIC, minimum inhibitory concentration; ABPC, ampicillin; CEZ, cefazolin; CTM, cefotiam; CTX, cefotaxime; CCL, cefaclor; CMZ, cefmetazole; FMOX, flomoxef; IPM/CS, imipenem/cilastatin; CFPN-PI, cefcapene pivoxil; GM, gentamicin; LVFX, levofloxacin; ST, sulfamethoxazole-trimethoprim; FOM, fosfomycin; S, susceptible; R, resistant.

Table 3. Abnormal Findings on Renal Ultrasonography, Voiding Cystourethrography, and Renal Cortical Scintigraphy.

Diagnostic Methods	Subject	Findings		No. of Affected Kidneys	Rate (%)	
Renal ultrasonography	70	Hydronephrosis grade	I	20	25/70	(18.5)[a]
			2	1		
			3	3		
			4	0		
		Hydroureter grade	I	6		
			2	2		
			3	0		
Voiding cystourethrography	74	VUR grade	I	5	31/74	(41.9)[b]
			II	31		
			III	10		
			IV	4		
			V	0		
Renal cortrical scintigraphy	74	Acute photon defect		15	14/74	(18.9)[c]
		Cortical scar		5	5/74	(6.8)[c]

Abbreviations: VUR, vesicoureteral reflux.
[a]One patient had bilateral hydroureter without hydronephrosis, 2 patients had bilateral hydronephrosis, and 3 patients had left hydronephrosis complicated by ipsilateral hydoureter.
[b]Nineteen of 31 patients had bilateral VUR.
[c]One patient had bilateral photon defects.

Table 4. Differences in Characteristics Between CEZ Effective and Ineffective Groups.

Characteristics	CEZ Effective Group (n = 64)	CEZ Ineffective Group (n = 10)	*P* Value
Use of antibiotics before admission (%)	12.5	20	.63
Average WBC count (/μL)	15,938	14,830	.67[a]
Average CRP level (mg/dL)	4.5	3.6	.82[a]
Fever duration after CEZ treatment (days)	1	2.6	<.0001[a]
Bacteremia (%)	0	20	<.05
UTI by ESBL-producing *Escherichia coli* (%)	3.1	40	<.05
Duration of hospitalization (days)	11.3	13.5	<.05[a]
VUR (%)	37.5	60	.55
Indication of operation (%)	4.7	10	.46
UTI recurrence (%)	10.9	10	1.00
Photon defects in acute DMSA scan (%)	14.1	40	.21
DMSA renal scarring (%)	6.3	10	.54

Abbreviations: CEZ, cefazolin; UTI, urinary tract infection; WBC, white blood cell; CRP, C-reactive protein; ESBL, extended-spectrum β-lactamase; VUR, vesicoureteral reflux.
[a]Mann-Whitney *U* test.

in vitro studies, but clinical effects of actually administered antibiotics were not used in in vivo studies.[8-10] In particular, a few reports do not recommend the use of first-generation cephalosporin for empiric therapy.[8,9] MIC is one of the indicators for the choice of antibiotics, but it is based on in vitro assessment. Therefore, clinical efficacy should be assessed after using each antibiotic in vivo. Chen et al investigated the antibiotic susceptibility of pathogens and evaluated the clinical responses of children with UTI to several antibiotics.[11] Regarding CEZ efficacy, the results of the present study are consistent with the conclusion of Chen et al, that is, CEZ and GM may be used as the first-line treatment for children with UTI.[11] They mentioned a few limitations in their study. First, most urine samples were collected by the urine bag technique or by voiding. Second, CEZ and GM combination therapy was administered most often as the first-line treatment, which makes treatment response evaluation difficult because of the high rate of susceptibility to GM in UTI treatment.

To clarify these issues and to simplify urine sampling and analysis, urine samples were obtained by catheterization, and CEZ alone was used for the initial empirical therapy in our present study. Our data showed that CEZ

was effective for more than 80% of patients with their first febrile UTI as a first-line antibiotic. We emphasize here that we do not necessarily recommend CEZ treatment for all pediatric patients with their first febrile UTI. However, our present study indicates that empiric antibiotic therapy using antimicrobial combinations, third-generation cephalosporins, or carbapenems can be reserved for serious cases. Moreover, a first-generation cephalosporin such as CEZ alone is adequate to treat such patients, when serious or critical infections such as infections with sepsis and bacterial meningitis are excluded.

In the present study, 9.3% of all isolates were ESBL-producing *E coli* and CTX-M14 was the most commonly encountered ESBL genotype, which was consistent with the findings of previous studies.[13,14] The prevalence of UTI caused by ESBL-producing *E coli* was higher in the CEZ-ineffective group than in the CEZ-effective group. However, it is noteworthy that those isolates were susceptible to CMZ and/or FOM. The incidence of UTI caused by ESBL-producing pathogens is increasing, and carbapenems are recommended as the antibiotics of last resort for its treatment.[3] However, the increase in carbapenem use results in the emergence of carbapenem-resistant Enterobacteriaceae pathogens.[15] Some reports show the effectiveness of noncarbapenems for UTI caused by ESBL-producing pathogens.[16-18] Regarding CMZ and FOM, their effectiveness is consistent with the findings of some previous studies mainly in adults.[17-19] CEZ was found to be effective for fever alleviation in 3 patients with UTI caused by ESBL-producing *E coli* in our present study. This can be explained by the high concentration of CEZ in urine. In addition, it is reported that UTIs caused by ESBL-producing bacteria in children do not have worse outcomes than UTIs caused by non-ESBL-producing bacteria.[20] Furthermore, it is reported that the infection site strongly affects the efficacy of a therapy for susceptible isolates to decrease the mortality of patients with ESBL-producing Enterobacteriaceae pathogens, and a therapy for nonsusceptible isolates is a risk factor for mortality except for UTIs.[21] These observations indicate that CEZ can be adequate and appropriate for UTI patients, who are not clinically serious or critical, and that third-generation cephalosporins or carbapenems can be reserved for serious cases in order to prevent the development of resistance to antibiotics. Considering the emergence of carbapenem-resistant Enterobacteriaceae pathogens, carbapenems should be limited to patients with severe non-UTIs caused by ESBL-producing Enterobacteriaceae pathogens, as previously reported.[19]

Our study has certain limitations. First, results of this study should be interpreted with caution because this is a retrospective and single-center investigation of a small number of patients. We excluded the patients with UTI caused by multiple pathogens to simplify CEZ efficacy assessment. Hence, we do not necessarily recommend CEZ treatment for all pediatric patients with their first febrile UTI. Decisions in antibiotic therapy modified by the attending physicians, who usually have considerable experience in treating clinically serious or critical patients, should be valued. However, CEZ efficacy should be assessed on the basis of not only MIC but also clinical prognosis, as in our study, which provides clinically relevant information. Second, there is no solid evidence that supports the notion that the use of CEZ instead of high cephalosporin or carbapenem decreases the multidrug resistance rate, whereas high cephalosporin use is a risk factor for the emergence of ESBL-producing Enterobacteriaceae strains.[22] Regarding this point, further investigation is required.

In conclusion, CEZ was effective in about 80% of pediatric patients with their first febrile UTI when they were not clinically serious or critical. The risks of VUR, indication of operation, and renal scarring did not increase, even when CEZ was ineffective as a first-line antibiotic. CEZ should be switched to appropriate antibiotics considering sepsis or the strain of ESBL-producing Enterobacteriaceae, when fever is not alleviated within 72 hours.

Authors' Note

Yoshifusa Abe and Hitomi Wakabayashi contributed equally as first authors.

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Author Contributions

YA: Contributed to conception and design; contributed to acquisition, analysis, and interpretation; drafted the manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

HW: Contributed to acquisition and analysis; drafted the manuscript; gave final approval.

YO: Contributed to acquisition and analysis; gave final approval.

AM: Contributed to acquisition; drafted the manuscript; gave final approval.

ME: Contributed to acquisition; gave final approval.

TT: Contributed to acquisition and analysis; drafted the manuscript; gave final approval.

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KU: Contributed to acquisition, analysis, and interpretation; gave final approval.
KF: Contributed to acquisition, analysis, and interpretation; drafted the manuscript; gave final approval.
KI: Contributed to acquisition; gave final approval.

Declaration of Conflicting Interests

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