In vitro Activity of Ceftaroline Against an International Collection of *Kingella kingae* Isolates Recovered From Carriers and Invasive Infections

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Background: Improvements in blood culture techniques and molecular-based diagnostics have led to increased recognition of *Kingella kingae* as an invasive human pathogen causing bacteremia, septic arthritis, osteomyelitis and endocarditis in young children. Serious disease and potentially life-threatening complications of infection due to *K. kingae* necessitate timely identification and appropriate antimicrobial therapy. Ceftaroline is a fifth-generation broad spectrum cephalosporin that possesses activity against Gram-negative and Gram-positive pathogens similar to third-generation cephalosporins, but also includes methicillin-resistant *Staphylococcus aureus*. This study reports the *in vitro* activity of ceftaroline and comparator agents against an international collection of *K. kingae* isolates.

Methods: A collection of 308 *K. kingae* isolates was obtained primarily from children with bacteremia, endocarditis, osteoarticular infections or from asymptomatic pediatric carriers. Isolates were tested for antibiotic susceptibility using Clinical and Laboratory Standard Institute broth microdilution methodology and screened for β-lactamase production using a nitrocefin chromogenic test.

Results: Ceftaroline inhibited all *K. kingae* isolates at ≤0.06 mg/L ($MIC_{50/90}$, 0.015/0.03 mg/L). Ceftaroline MICs were similar to results with ceftriaxone ($MIC_{50/90}$, 0.015/0.015 mg/L), meropenem ($MIC_{50/90}$, 0.015/0.015 mg/L) and ampicillin–sulbactam ($MIC_{50/90}$, 0.06/0.06 mg/L). Ceftaroline MICs were slightly lower than MICs for cefuroxime and amoxicillin/clavulanate ($MIC_{50/90}$, 0.06/0.12 mg/L). MICs were high for clindamycin ($MIC_{50/90}$, 2/4 mg/L) and oxacillin ($MIC_{50/90}$, 4/8 mg/L). Sixteen isolates (5.2%) yielded a positive nitrocefin test indicating production of β-lactamase; ceftaroline demonstrated equivalent MICs against β-lactamase–positive and β-lactamase–negative strains ($MIC_{50/90}$, 0.015/0.3 mg/L).

Conclusions: The potent activity of ceftaroline against this large international collection of *K. kingae* isolates supports further clinical evaluation in children.

Keywords: *Kingella kingae*, ceftaroline, susceptibility

(*Pediatr Infect Dis J* 2022;XX:00–00)

INTRODUCTION

Kingella kingae is a Gram-negative coccobacillus that is a component of the normal oropharyngeal microbiota in children 6–48 months of age.[1–3] Although *K. kingae* is frequently carried asymptomatically, improved detection methods—including inoculating blood culture vials with skeletal system exudates, target polymerase chain reaction assays and universal 16S rDNA amplicon sequencing—have led to increased recognition of this fastidious organism as an invasive human pathogen.[3,4] *K. kingae* has been recently recognized as the most common etiology of joint and bone infections in children 6–48 months of age and is an important cause of bacteremia in young children and bacterial endocarditis in children and adults.[1,3,5] The *K. kingae* disease burden in children is likely to be underestimated based on challenges in diagnosis. The risk of potentially serious disease and life-threatening complications due to *K. kingae* underscores the need for rapid microbiological identification and administration of appropriate antimicrobial therapy.[1,6]

When making decisions about antimicrobial therapy, the pediatric patient population affected by *K. kingae* requires special consideration. In bone and joint infections, causative pathogens beyond *K. kingae* include *Staphylococcus aureus* and *Streptococcus pyogenes* and antimicrobial therapy often consist of intravenous oxacillin, cloxacillin or a second-generation or third-generation cephalosporin.[7] When bone and joint infections are a result of methicillin-resistant *S. aureus* (MRSA), therapeutic options often narrow to vancomycin or clindamycin, which lack activity against *K. kingae*.[8] Importantly, some isolates of *K. kingae* produce a β-lactamase.[9,10] Therefore, the empiric antimicrobial strategy to treat invasive bone and joint infections in children must consider coverage against both Gram-positive and Gram-negative organisms.

Ceftaroline fosamil—a *N*-phosphoamino water soluble prodrug cephalosporin—contains the active metabolite ceftaroline.[11,12] This fifth-generation broad spectrum cephalosporin possesses activity against common Gram-positive pathogens found in bacterial skin and skin structure infections and community-acquired pneumonia, including MRSA.[13,14] Additionally, ceftaroline demonstrates activity against respiratory tract Gram-negative pathogens, including *Moraxella catarrhalis*, *Haemophilus parainfluenzae* and *H. influenzae*, along with other enteric bacilli.[15] Efficacy against β-lactam–resistant *S. aureus* can be explained by the high affinity of ceftaroline for staphylococcal PBPs 1, 2 and 3 and MRSA PBP2a.[16,17] Although the literature describes the potent activity of ceftaroline compared with its earlier generation cephalosporin predecessors, the activity of ceftaroline against *K. kingae* isolates remains unknown. This study reports the *in vitro* activity of ceftaroline and comparator agents against an international collection of *K. kingae* isolates.

MATERIALS AND METHODS

Bacterial Isolates

A collection of 308 international *K. kingae* isolates was obtained from Israel, New Zealand, Europe (France, Iceland, Spain and Switzerland), and North America (Canada and USA) from patients with invasive infections or from asymptomatic carriers

Accepted for publication November 18, 2022
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Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (www.pidj.com).

ISSN: 0891-3668/22/XXXX-0000
DOI: 10.1097/INF.0000000000003799

TABLE 1. Antimicrobial activity of ceftaroline and comparator agents tested against an international collection of 308 *Kingella kingae* isolates

Organism/organism group (no. isolates)	No. and cumulative % of isolates inhibited at MIC (mg/L)																	
	≤0.002	0.004	0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	>[†]	MIC_{50}	MIC_{90}	% S[‡]
***Kingella kingae* (308)**																		
Ceftaroline		0	34	217	51	6										0.015	0.03	
		0.0	11.0	81.5	98.1	100.0												
Amoxicillin-clavulanic acid			2	7	35	121	142	1								0.06	0.12	100.0%
			0.6	2.9	14.3	53.6	99.7	100.0										
Ampicillin			16	31	131	114	1	5	6	1	2	1				0.03	0.06	99.0%
			5.2	15.3	57.8	94.8	95.1	96.8	98.7	99.0	99.7	100.0						
Ampicillin-sulbactam			14	36	90	151	12	5								0.06	0.06	100.0%
			4.5	16.2	45.5	94.5	98.4	100.0										
Azithromycin					248	55	4	1								≤0.03	0.06	100.0%
					80.5	98.4	99.7	100.0										
Cefazolin							110	175	23							0.25	0.25	
							35.7	92.5	100.0									
Ceftriaxone			75	204	28	1										0.015	0.015	100.0%
			24.4	90.6	99.7	100.0												
Cefuroxime				0	41	198	67	2								0.06	0.12	
				0.0	13.3	77.6	99.4	100.0										
Cephalexin							0	10	157	123	17	1				0.5	1	
							0.0	3.2	54.2	94.2	99.7	100.0						
Clindamycin							0	1	7	53	175	61			11	2	4	
							0.0	0.3	2.6	19.8	76.6	96.4			100.0			
Gentamicin					0	1	5	89	213							0.5	0.5	
					0.0	0.3	1.9	30.8	100.0									
Levofloxacin				105	178	22	2	1								0.03	0.03	100.0%
				34.1	91.9	99.0	99.7	100.0										
Meropenem	31	29	70	175	3											0.015	0.015	100.0%
	10.1	19.5	42.2	99.0	100.0													
Oxacillin							1	1	1	18	120	121	38	3	5	4	8	
							0.3	0.6	1.0	6.8	45.8	85.1	97.4	98.4	100.0			
Tigecycline			29	119	118	37	5									0.03	0.06	
			9.4	48.1	86.4	98.4	100.0											
Trimethoprim–sulfamethoxazole						220	17	6	6	3	24	4	14		14	≤0.06	4	80.8%
						71.4	76.9	78.9	80.8	81.8	89.6	90.9	95.5		100.0			
β-lactamase negative (292)																		
Ceftaroline		0	34	209	44	5										0.015	0.03	
		0.0	11.6	83.2	98.3	100.0												
Amoxicillin–clavulanic acid			2	7	35	120	128									0.06	0.12	100.0%
			0.7	3.1	15.1	56.2	100.0											
Ampicillin			16	31	131	113	1									0.03	0.06	100.0%
			5.5	16.1	61.0	99.7	100.0											
Ampicillin–sulbactam			14	36	90	150	2									0.06	0.06	100.0%
			4.8	17.1	47.9	99.3	100.0											
Azithromycin					234	53	4	1								≤0.03	0.06	100.0%
					80.1	98.3	99.7	100.0										
Cefazolin							107	163	22							0.25	0.25	
							36.6	92.5	100.0									
Ceftriaxone			74	192	25	1										0.015	0.015	100.0%
			25.3	91.1	99.7	100.0												
Cefuroxime				0	40	186	64	2								0.06	0.12	
				0.0	13.7	77.4	99.3	100.0										
Cephalexin							0	10	149	116	16	1				0.5	1	
							0.0	3.4	54.5	94.2	99.7	100.0						

Clindamycin							0	1	6	51	164	59			11	2	4	
							0.0	0.3	2.4	19.9	76.0	96.2			100.0			
Gentamicin						0	5	84	203							0.5	0.5	
						0.0	1.7	30.5	100.0									
Levofloxacin				99	168	22	2	1								0.03	0.03	100.0%
				33.9	91.4	99.0	99.7	100.0										
Meropenem	30	28	67	164	3											0.015	0.015	100.0%
	10.3	19.9	42.8	99.0	100.0													
Oxacillin							1	1	1	18	120	119	27	0	5	4	8	
							0.3	0.7	1.0	7.2	48.3	89.0	98.3	98.3	100.0			
Tigecycline			27	110	113	37	5									0.03	0.06	
			9.2	46.9	85.6	98.3	100.0											
Trimethoprim–sulfamethoxazole						219	17	6	6	3	23	3	6		9	≤0.06	2	84.9%
						75.0	80.8	82.9	84.9	86.0	93.8	94.9	96.9		100.0			
β-lactamase positive (16)																		
Ceftaroline			0	8	7	1										0.015	0.03	
			0.0	50.0	93.8	100.0												
Amoxicillin–clavulanic acid					0	1	14	1								0.12	0.12	100.0%
					0.0	6.2	93.8	100.0										
Ampicillin					0	1	0	5	6	1	2	1				0.5	2	81.2%
					0.0	6.2	6.2	37.5	75.0	81.2	93.8	100.0						
Ampicillin–sulbactam					0	1	10	5								0.12	0.25	100.0%
					0.0	6.2	68.8	100.0										
Azithromycin					14	2										≤0.03	0.06	100.0%
					87.5	100.0												
Cefazolin							3	12	1							0.25	0.25	
							18.8	93.8	100.0									
Ceftriaxone			1	12	3											0.015	0.03	100.0%
			6.2	81.2	100.0													
Cefuroxime				0	1	12	3									0.06	0.12	
				0.0	6.2	81.2	100.0											
Cephalexin								0	8	7	1					0.5	1	
								0.0	50.0	93.8	100.0							
Clindamycin								0	1	2	11	2				2	4	
								0.0	6.2	18.8	87.5	100.0						
Gentamicin					0	1	0	5	10							0.5	0.5	
					0.0	6.2	6.2	37.5	100.0									
Levofloxacin				6	10											0.03	0.03	100.0%
				37.5	100.0													
Meropenem	1	1	3	11												0.015	0.015	100.0%
	6.2	12.5	31.2	100.0														
Oxacillin											0	2	11	3		8	16	
											0.0	12.5	81.2	100.0				
Tigecycline			2	9	5											0.015	0.03	
			12.5	68.8	100.0													
Trimethoprim–sulfamethoxazole						1	0	0	0	0	1	1	8		5	8	>8	6.2%
						6.2	6.2	6.2	6.2	6.2	12.5	18.8	68.8		100.0			

*Greater than the highest concentration tested.
†Susceptible (S) criteria available in the CLSI M45-A3 (2015) document.

between 1960 and 2021.[2,3] Isolate sources were divided into 5 categories: asymptomatic carrier, bacteremia, endocarditis, osteoarticular infection and unknown. Osteoarticular infection included osteomyelitis, septic arthritis, spondylodiscitis and tenosynovitis. Isolates recovered from blood cultures drawn from patients with focal diseases, including septic arthritis and endocarditis, were categorized as osteoarticular infections or endocarditis, respectively. Identification was confirmed using matrix-assisted laser desorption ionization-time of flight mass spectrometry using the MALDI Biotyper (Bruker Daltonics, Billerica, MA) according to manufacturer's instructions. All isolates were tested for production of β-lactamase using a nitrocefin disk test (BD BBL Cefinase, cat. no. 231650).

Susceptibility Testing

Broth microdilution methods was performed according to Clinical and Laboratory Standard Institute (CLSI) guidelines for testing ceftaroline and comparator agents.[18] The β-lactam/β-lactamase inhibitor combinations used a 2:1 ratio for ampicillin–sulbactam and amoxicillin–clavulanate, whereas a 1:19 ratio was applied for trimethoprim–sulfamethoxazole. Frozen-form broth microdilution panels were manufactured by JMI Laboratories containing cation-adjusted Mueller-Hinton broth with 5% lysed horse blood. Quality assurance was performed by concurrently testing CLSI-recommended quality control reference strains, including *Escherichia coli* ATCC 35218 and *S. pneumoniae* ATCC 49619. CLSI susceptibility breakpoints were used to determine susceptibility and resistance rates for comparator agents, where available.[18,19] In addition, susceptibility results were analyzed by β-lactamase production.[20]

RESULTS

The *K. kingae* isolates in this study originated predominantly from patients in Israel (177; 57.5%), Spain (42; 13.6%) and France (34, 11.0%). The remaining isolates (17.9% of the total) came from patients in the USA (28), Canada (12), Iceland (9), Switzerland (2) and New Zealand (4). Overall, 80.2% (247/308) of the isolates originated from invasive infections and 16.2% (50/308) were from carriers. The associated clinical condition (invasive infection or carrier) was unknown for 11 (3.6%) isolates. Of the invasive isolates, 65.6% (n = 162/247) were from osteoarticular infections, 29.6% (n = 73/247) from bacteremia, and 4.9% (n = 12/247) from endocarditis. While the collection primarily contained isolates from children (n = 244), adult isolates were also included (n = 7). Age information was unavailable for most of the invasive isolates from patients in France, Canada and New Zealand; however, it was assumed that most of these isolates were from children because bacteremia and bone and joint infections in which *K. kingae* is the causative agent are extremely rare in adult patients.

Ceftaroline inhibited all *K. kingae* isolates at ≤0.06 mg/L ($MIC_{50/90}$, 0.015/0.03 mg/L; Table 1). The ceftaroline MIC results were like those of ceftriaxone ($MIC_{50/90}$, 0.015/0.015 mg/L), meropenem ($MIC_{50/90}$, 0.015/0.015 mg/L), ampicillin ($MIC_{50/90}$, 0.03/0.06 mg/L) and ampicillin–sulbactam ($MIC_{50/90}$, 0.06/0.06 mg/L). Other β-lactam agents and β-lactam/β-lactamase inhibitor combinations yielded low MIC values against this collection, including cefuroxime ($MIC_{50/90}$, 0.06/0.12 mg/L) and amoxicillin–clavulanate ($MIC_{50/90}$, 0.06/0.12 mg/L). The isolates exhibited higher MIC values for clindamycin ($MIC_{50/90}$, 2/4 mg/L). The activity of ceftaroline and comparators was similar against carrier and invasive isolates, except for trimethoprim–sulfamethoxazole and ampicillin, which had MIC_{90} values that were 4-fold higher against carrier isolates (8 and 0.25 mg/L, respectively) than against invasive isolates (MIC_{90}, 2 and 0.06 mg/L, respectively).

Of the 308 isolates, 16 (5.2% of collection) yielded a positive nitrocefin test, indicating production of a β-lactamase. Ceftaroline demonstrated equivalent MIC results against β-lactamase–positive ($MIC_{50/90}$, 0.015/0.03 mg/L) and β-lactamase–negative strains ($MIC_{50/90}$, 0.015/0.03mg/L). Oxacillin demonstrated similar MIC values against both β-lactamase–positive ($MIC_{50/90}$, 8/16 mg/L) and β-lactamase–negative ($MIC_{50/90}$, 4/8 mg/L) isolates. Decreased susceptibility was observed for ampicillin ($MIC_{50/90}$, 0.5/2 mg/L), ampicillin–sulbactam ($MIC_{50/90}$, 0.12/0.25 mg/L) and trimethoprim–sulfamethoxazole ($MIC_{50/90}$, 8/>8 mg/L) against β-lactamase–positive isolates compared with their β-lactamase–negative counterparts ($MIC_{50/90}$, 0.03/0.06, 0.06/0.06 and ≤0.06/2 mg/L, respectively). Amoxicillin–clavulanate, ampicillin–sulbactam, azithromycin, ceftriaxone, levofloxacin and meropenem remained active (100% susceptible per CLSI) against all *K. kingae* isolates, whereas ampicillin and trimethoprim–sulfamethoxazole had decreased susceptibility against β-lactamase–positive isolates (81.2% and 6.2% susceptible) compared with β-lactamase–negative isolates (100% and 84.9% susceptible).

DISCUSSION

Bone and joint infections in young children are medical emergencies. If not promptly diagnosed and adequately treated, these infections can result in severe morbidity and devastating functional sequelae.[21] Traditionally, *H. influenzae* type b and Gram-positive bacteria such as *S. aureus*, *S. pyogenes* and *S. pneumoniae* were the most common bone and joint infection pathogens in preschool-age children.[22–25] In recent years, profound changes in the etiology of pediatric osteoarthritis as a result of conjugate vaccine implementation against *H. influenzae* type b[26] and *S. pneumoniae*,[27] increased prevalence of community-associated MRSA (CA-MRSA),[28] and the emergence of *K. kingae* as an important pathogen causing bone and joint infections and tenosynovitis in children aged 6–48 months.[21,29]

Naturally, these etiological changes have significant implications for the empiric antimicrobial therapy of these infections, pending the results of blood cultures, molecular assays and susceptibility testing. In regions where the prevalence of MRSA remains low (<10% of clinical isolates), isoxazolyl penicillins offer appropriate coverage of Gram-positive pathogens; however, *K. kingae* seem to be less susceptible to these penicillins (oxacillin $MIC_{50/90}$, 4/8 mg/L). With this information in mind, it is notable that Kenne et al. described a clinical case of spondylodiscitis treatment failure with high-dose and prolonged administration of flucloxacillin caused by *K. kingae* in a 3-year-old patient.[30] The strain recovered from this patient (18CHL2748T) was sent to our laboratory, which confirmed an elevated oxacillin MIC (8 mg/L) (see Table, Supplemental Digital Content 1, http://links.lww.com/INF/E894, for the susceptibility profile data for this strain), consistent with the distribution of oxacillin MICs in the collection tested here. Accordingly, we conclude that isoxazolyl penicillins such as oxacillin may not possess adequate pharmacokinetic/pharmacodynamic attributes to cover invasive infections caused by *K. kingae*, even when used at a high dosage and for a prolonged period.

In regions where CA-MRSA prevalence exceeds 10% of isolates causing osteoarthritis, the empiric administration of vancomycin or clindamycin is recommended.[7,31] However, *K. kingae* is intrinsically resistant to these drugs.[3] Thus, empiric therapy with vancomycin or clindamycin, combined with a second-generation or third-generation cephalosporin targeted against non-staphylococcal pathogens, is often used.[8] In this study, ceftaroline showed potent *in vitro* activity against an international collection of *K. kingae*, including against those where β-lactamase production was

detected. In contrast, clindamycin, trimethoprim–sulfamethoxazole and oxacillin had limited activity, specifically against isolates producing β-lactamases. These findings are concerning, as clindamycin, trimethoprim–sulfamethoxazole and oxacillin are often administered to children with bone and joint infections, yet do not have sufficient *in vitro* activity against *K. kingae*. Therefore, ceftaroline, which possesses broad Gram-negative and Gram-positive bacteria activity, including *K. kingae*, could be clinically useful for the empirical single-drug treatment of osteoarticular infections in children. These *in vitro* data support further evaluation of ceftaroline in both animal models and in clinical trials in children in the treatment of *K. kingae* infections causing osteoarticular infections, bacteremia and endocarditis.

ACKNOWLEDGEMENTS

The authors would like to thank the following staff members at JMI Laboratories (North Liberty, Iowa, US): Gina Bartleson, Amy Chen and Michael Janechek for technical support and assistance with manuscript preparation. The authors would also like to thank Tony Walls, Trevor Anderson, and the Canterbury Health Laboratory in Christchurch, New Zealand for providing Kingella kingae isolate 18CHL2748T included in this study.

Available upon reasonable request.

This study was performed by JMI Laboratories and supported by Pfizer. This analysis and article preparation was funded by Pfizer.

J.B. involved in conceptualization; J.M., R.M. and H.H. participated in data curation; J.M. and R.M. involved in formal analysis; R.M. and J.B. involved in funding acquisition; J.M. and R.M. involved in the investigation; J.M., R.M. and H.H. participated in methodology; J.M., R.M. and H.H. participated in project administration; J.M., R.M. and P.Y. participated in resources; J.M. and R.M. participated in software: J.M. and R.M. participated in supervision; J.M. and R.M. participated in validation; R.M., P.Y. and J.B. participated in visualization; H.M. and P.Y. participated in writing—original draft; J.M., R.M., H.H., E.P., J.S.G., P.Y. and J.B. participated in writing—review and editing.

JMI Laboratories was contracted to perform services in 2021 for AbbVie Inc., Affinity Biosensors, AimMax Therapeutics, Inc., Alterity Therapeutics, Amicrobe, Inc., Arietis Pharma, Armata Pharmaceuticals, Inc., Astrellas Pharma Inc., Basilea Pharmaceutica AG, Becton, Dickinson and Company (BD), bioMérieux, Inc., Boost Biomes, Brass Dome Ventures Ltd., Bravos Biosciences, Bugworks Research Inc., Centers for Disease Control and Prevention, Cerba Research, Cidara Therapeutics, Cipla Ltd., ContraFect Corp., CXC7, DiamondV, Enveda Biosciences, Fedora Pharmaceuticals, Inc., Fimbrion Therapeutics, First Light Diagnostics, Forge Therapeutics, Inc., Fox Chase Cancer Center, GlaxoSmithKline plc (GSK), Harvard University, Institute for Clinical Pharmacodynamics (ICPD), International Health Management Associates (IHMA), Inc., Iterum Therapeutics plc, Janssen Research & Development, Johnson & Johnson, Kaleido Biosciences, Inc., Laboratory Specialists, Inc. (LSI), Meiji Seika Pharma Co., Ltd., Melinta Therapeutics, Menarini Group, Merck & Co., Inc., MicuRx Pharmaceuticals Inc., Mutabilis, Nabriva Therapeutics, National Institutes of Health, Novome Biotechnologies, Omnix Medical Ltd., Paratek Pharma, Pattern Bioscience, Pfizer Inc., Prokaryotics Inc., Pulmocide Ltd., QPEX Biopharma, Inc., Roche Holding AG, Roivant Sciences, SeLux Diagnostics, Inc., Shionogi Inc., Sinovent Pharmaceuticals, Inc., SNIPR Biome ApS, Spero Therapeutics, Summit Therapeutics, Inc., T2 Biosystems, TenNor Therapeutics, Thermo Fisher Scientific, University of Southern California, University of Wisconsin, USCAST, U.S. Food and Drug Administration, Venatorx Pharmaceutics, Inc., Weill Cornell Medicine, and Wockhardt Ltd.

There are no speakers' bureaus or stock options to declare.

JSB has no personal conflicts of interest to declare, but his employer, the Regents of the University of California, has contracts with Pfizer, Inc. The other authors have no conflicts of interest to disclose.

REFERENCES

1. Yagupsky P. *Kingella kingae*: carriage, transmission, and disease. *Clin Microbiol Rev*. 2015;28:54–79.
2. Porsch EA, Starr KF, Yagupsky P, et al. The type a and type b polysaccharide capsules predominate in an international collection of invasive *Kingella kingae* isolates. *mSphere*. 2017;2:e00060–e00067.
3. Matuschek E, Åhman J, Kahlmeter G, et al. Antimicrobial susceptibility testing of *Kingella kingae* with broth microdilution and disk diffusion using EUCAST recommended medium. *Clin Microbiol Infect*. 2017;24:396–401.
4. Chometon S, Benito Y, Chaker M, et al. Specific real-time polymerase chain reaction places *Kingella kingae* as the most common cause of osteoarticular infections in young children. *Pediatr Infect Dis J*. 2007;25:377–381.
5. Yagupsky P, Porsch E, St Geme IJW. *Kingella kingae*: an emerging pathogen in young children. *Pediatrics*. 2011;127:557–565.
6. Foster MA, Walls T. High rates of complications following *kingella kingae* infective endocarditis in children. *Pediatr Infect Dis J*. 2014;33:785–786.
7. Shahrestani S, Evans A, Tekippe EM, et al. *Kingella kingae* septic arthritis in an older-than-expected child. *J Pediatr Infect Dis Soc*. 2018;8:83–86.
8. Saphyakhajon P, Joshi AY, Huskins WC, et al. Empiric antibiotic therapy for acute osteoarticular infections with suspected methicillin-resistant *Staphylococcus aureus* or *Kingella*. *Pediatr Infect Dis J*. 2008;27:765–767.
9. Banerjee A, Kaplan JB, Soherwady A, et al. Characterization of TEM-1 β-Lactamase-Producing *Kingella kingae* clinical isolates. *Antimicro Agents Chemother*. 2013;57:4300–4306.
10. Basmaci R, Bidet P, Berçot B, et al. First identification of a chromosomally located penicillinase gene in *Kingella kingae* species isolated in continental Europe. *Antimicro Agents Chemother*. 2014;58:6258–6259.
11. US FDA. *Teflaro (ceftaroline fosamil) [package insert]*. 2021.
12. Welte T, Kantecki M, Stone GG, et al. Ceftaroline fosamil as a potential treatment option for *Staphylococcus aureus* community-acquired pneumonia in adults. *Int J Antimicrob Agents*. 2019;54:410–422.
13. Zhang H, Xu Y, Jia P, et al. Global trends of antimicrobial susceptibility to ceftaroline and ceftazidime-avibactam: a surveillance study from the ATLAS program (2012-2016). *Antimicro Resist Infect Control*. 2020;9:166.
14. Karki A, Thurm C, Cervellione K. Experience with ceftaroline for treatment of methicillin-resistant *Staphylococcus aureus* pneumonia in a community hospital. *J Community Hosp Intern Med Perspect*. 2017;7:300–302.
15. Flamm RK, Sader HS, Farrell DJ, et al. Summary of ceftaroline activity against pathogens in the United States, 2010: report from the Assessing Worldwide Antimicrobial Resistance Evaluation (AWARE) Surveillance Program. *Antimicrob Agents Chemother*. 2012;56:2933–2940.
16. Laudano J. Ceftaroline fosamil: a new broad-spectrum cephalosporin. *J Antimicrob Chemother*. 2011;66Suppl 3:iii11–iii18.
17. Moisan H, Pruneau M, Malouin F. Binding of ceftaroline to penicillin-binding proteins of *Staphylococcus aureus* and *Streptococcus pneumoniae*. *J Antimicrob Chemother*. 2010;65:713–716.
18. CLSI. M45-A3. *Methods for antimicrobial dilution and disk susceptibility testing of infrequently isolated or fastidious bacteria: third edition*. Clinical and Laboratory Standards Institute; 2015.
19. CLSI. M100Ed32. *Performance standards for antimicrobial susceptibility testing: 32nd informational supplement*. Clinical and Laboratory Standards Institute; 2022.
20. Skov R, Matuschek E, Sjolund-Karlsson M, et al. Development of a pefloxacin disk diffusion method for detection of fluoroquinolone-resistant *Salmonella enterica*. *J Clin Microbiol*. 2015;53:3411–3417.
21. Juchler C, Spyropoulou V, Wagner N, et al. The contemporary bacteriologic epidemiology of osteoarticular infections in children in Switzerland. *J Pediatr*. 2018;194:190–196.e1.
22. Jackson M, Nelson J. Etiology and medical management of acute suppurative bone and joint infections in pediatric patients. *J Pediatr Orthop*. 1983;2:313–323.
23. Luhmann J, Luhmann S. Etiology of septic arthritis in children: an update for the 1990s. *Pediatr Emerg Care*. 1999;15:40–42.
24. Dodwell ER. Osteomyelitis and septic arthritis in children: current concepts. *Curr Opin Pediatr*. 2013;25:58–63.

25. Welkon C, Long S, Fisher M, et al. Pyogenic arthritis in infants and children: a review of 95 cases. *Pediatr Infect Dis J*. 1986;5:669–676.
26. Howard A, Viskontas D, Sabbagh C. Reduction in osteomyelitis and septic arthritis related to *Haemophilus influenzae* type B vaccination. *J Pediatr Orthop*. 1999;19:705–709.
27. Olarte L, Romero J, Barson W, et al. Osteoarticular infections caused by *Streptococcus pneumoniae* in children in the post-pneumococcal conjugate vaccine era. *Pediatr Infect Dis J*. 2017;36:1201–1204.
28. Vardakas KZ, Kontopidis I, Gkegkes ID, et al. Incidence, characteristics, and outcomes of patients with bone and joint infections due to community-associated methicillin-resistant *Staphylococcus aureus*: a systematic review. *Eur J Clin Microbiol Infect Dis*. 2013;32:711–721.
29. Villani M, Hamilton EC, Klisterman MM, et al. Primary septic arthritis among children 6 to 48 months of age: Implications for PCR acquisition and empiric antimicrobial selection. *J Pediatr Orthop*. 2021;41:190–196.
30. Kenne A, Creighton J, Anderson T, et al. *Kingella kingae* spondylodiscitis: treatment failure with flucloxacillin. *Pediatr Infect Dis J*. 2022;41:48–50.
31. Pääkkönen M, Peltola H. Bone and joint infections. *Pediatr Clin North Am*. 2013;60:425–436.