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Review Article

Resistance to ceftaroline - 2018 review

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ABSTRACT

Ceftaroline is a new fifth generation cephalosporin, active mostly against Gram-positive cocci, e.g. *Staphylococcus aureus* (including methicillin-resistant *Staphylococcus aureus*). It is used in treating acute bacterial skin and skin structure infections, community acquired respiratory tract infections and methicillin-resistant *S. aureus* bacteremia. The main resistance mechanisms of bacteria to β-lactam antibiotics, including ceftaroline, are mutations in PBP2a, PBP3 and PBP4. Clinically significant resistance has been noted among both archived and newly-isolated strains in a laboratory test using serial passages. Ceftaroline-resistant strains have also been found in patients suffering from cystic fibrosis, ventilator-associated pneumonia and infectious endocarditis. Irresponsible antibiotic treatment using ceftaroline or other antibiotics (due to a possibility of a cross-resistance) can lead to the spread of ceftaroline resistance and, consequently, its loss of value.

Keywords: Antibiotic; Antibiotic resistance; MRSA; Resistant strains; Ceftaroline-resistant.

1. INTRODUCTION

Ceftaroline, a fifth generation cephalosporin, has been approved by the FDA (Food and Drug Administration) as a therapeutic option for both adult (in 2010) and pediatric (in 2016) patients suffering from acute bacterial skin and skin structure infections (ABSSSI) (including infections caused by MRSA), as well as community-acquired respiratory tract infections (CARTI), including community acquired bacterial pneumonia (CABP).The antibiotic has also been approved for treating patients with methicillin-resistant *S. aureus* bacteremia (MRSAB) and endocarditis. Despite being a new drug, on which many people has pinned their hopes, there are more and more reports of bacterial strains resistant to it.

THE USE OF CEFTAROLINE

Ceftaroline is a broad-spectrum antibiotic [1], active against methicillin-susceptible and methicillin-resistant *Staphylococcus aureus* (MSSA and MRSA), daptomycin-nonsusceptible (DNS) *S. aureus*, vancomycin-intermediate (VISA and hetero-VISA) and vancomycin-resistant (VRSA) *S. aureus*, methicillin-susceptible and methicillin-resistant coagulase-negative streptococci (MSCoNS and MRCoNS), multidrug resistant *Streptococcus pneumoniae*, as well as many genera of Enterobacteriaceae (*Escherichia coli*, *Klebsiella pneumoniae* and *K. oxytoca*, *Enterobacter aerogenes* and *E. cloacae*, *Citrobacter koseri* and *C. freundii*, *Proteus mirabilis*, *Serratia spp.*, *Moraxella*

catarrhalis, Haemophilus influenzae, Morganella morganii) [2-4]. Ceftaroline is ineffective against *Pseudomonas spp., Enterococcus spp., Bacteroides fragilis* and atypical bacteria (*Mycoplasma pneumoniae, Chlamydia pneumoniae* and *Legionella pneumophila*) [2].

In the USA, ceftaroline was put into use in October 2010 and in Europe - two years later. At first, it was used in treating ABSSSI and CARTI [5]. In vitro studies conducted by Gaikwead et al. show high effectiveness of the drug - among 30 MRSA strains sampled from different clinical materials, 2 (6,67%) were resistant to it [6]. Moreover, clinical trials showed that it is well-tolerated by patients [2, 5, 7] (most common side effects were: diarrhea, nausea, headache, pruritus [5]), leaving other antibiotics, with potentially severe side effects, such as nephrotoxicity, ototoxicity [8, 9] (vancomycin) or thrombocytopenia [9] (linezolid), as drugs of last resort [5]. A decreased percentage of patients having to stop therapy due to the side effects was noted - 2,7% compared to 3,7% when treating with ceftriaxone or vancomycin with aztreonam [2]. Another in vitro study showed that when it comes to eradication of MRSA, ceftaroline is as effective as vancomycin, daptomycin and linezolid (when minimal inhibitory concentration for ceftaroline, MIC, $\leq$ 2 mg/l). It doesn't matter then, whether the strain has developed mechanisms of resistance to linezolid or vancomycin [10].

Among adults with CABP, ceftaroline treatment was more effective than a ceftriaxone one [7, 11, 12]. Moreover, the difference between therapeutic effect of both drugs was less significant if in 96 hours prior to their usage no other antimicrobial drug had been used [11].

Ceftaroline is the first intravenous antibiotic used among children over two months old to be approved by the FDA in over a decade [13]. Between 2012-2014 Pfaller et al. analyzed 3141 samples (1681 associated with ABSSSI, 1460 with CARTI) coming from pediatric patients from 29 different centers. The strains of *S. aureus, S. pneumoniae, H. influenzae, P. aeruginosa,* beta-hemolytic streptococci, Enterobacteriaceae (including *E. coli* and *Klebsiella spp.*) and others were isolated. 99-100% of the Gram-positive bacteria, as well as *H. influenzae* strains, were ceftaroline-susceptible. Also, the antibiotic was active against MRSA strains associated with ABSSSI and ceftriaxone-resistant *S pneumoniae* associated with CARTI [14]. The percentage of cured complicated ABSSSI and CABP in population of patients aged 2 months to 17 years old was high [7].

There's also a known case of a ten year old girl who had had an accident and developed a MRSA sepsis (the bacteria were previously isolated from many of her wounds), which was fought off with relatively low dose of ceftaroline (2 x 9 mg/kg/d) - even though MIC of 1,5-4 mg/l suggested decreased susceptibility to it [15].

A therapeutic success in treating MRSAB was also stated among adults in a study conducted by Zasowski et al. [16]. White et al. proved that ceftaroline is effective at treating patients with MRSAB who haven't responded to other drugs [17]. There are also reports stating that ceftaroline combined with daptomycin can be effective in treating daptomycin-resistant or vancomycin-intermediate resistant MRSA infectious endocarditis (IE) [18-20].

RESISTANCE MECHANISMS

Microorganisms for which the MIC value for ceftaroline is equal or less than 1 mg/l (1 μg/ml) are considered susceptible to this antibiotic. When the MIC ranges from 1 to 8 mg/l the microorganism is considered nonsusceptible and when the MIC exceeds 32 mg/l, the microorganism is resistant to ceftaroline [21-24].

Mechanisms of microbial resistance to ceftaroline are based on mutations within the penicillin binding protein (PBP) group, and are primarily observed in *S. aureus* [20-31]. Among the mutations present in PBP proteins, mutations were observed predominantly within the PBP2a protein [25] both inside the penicillin-binding domain (PBD) and outside the penicillin-binding domain (nPBD) [21, 29]. Mutations in PBD seem to correlate more frequently with nonsusceptibility, and mutations in nPBD with resistance to ceftaroline. PBP3 and PBP4 were other mutated PBP to be proved to correlate with ceftaroline resistance. This type of resistance has been overcome by the combination of ceftaroline with very low methicillin or meropenem doses [24, 26].

The PBP2a is a mutated variant of the PBP2

responsible for bacterial cell wall biosynthesis, providing microbial resistance to β-lactam antibiotics. Changes in the staphylococcal *mecA* gene result in conformational changes of the finished PBP2, which reduces its affinity to all β-lactam antibiotics [27]. It can be suspected that further mutations induced by environmental factors (ceftaroline therapy) within or outside the SCCmecA gene (Staphylococcal Cassette Chromosome mec) may result in resistance to fifth generation of cephalosporins [25, 28], which seemed to be completely effective in the treatment of MRSA infections so far. However, studies conducted by Kelley WL et al. show that during the introduction of ceftaroline to use, variants of the PBP2a providing ceftaroline resistance to hospital-acquired MRSA (HA-MRSA) have already existed (Table 1) [29].

Other factors leading to the increase of total resistance level in bacteria, include genes taking part in cell wall precursor formation and turnover, such as *femA* and *femB* genes, encoding proteins that take part in forming correct peptidoglycan pentaglycine interpeptide bridge, as well as *fmhA*, *fmhB* and *fmhC* genes, which encode proteins participating in forming peptidoglycan pentaglycine interpeptide. It was also noted that genes engaged in glutamine's and glucosamine's metabolism, such as *femC* and *femD*, can also cause the increase of bacterial resistance [32, 33].

Greninger A et al. suggested that mutations within genes such as *clpX* endopeptidase, *pp2c* protein phosphatase and transcription terminator *rho* can influence resistance to ceftaroline of MRSA in mechanisms different than the one involving *mecA* [34].

Chan LC et al. noted the significance of *gdpP* mutation, often identified within MRSA strains resistant to both ceftaroline and ceftobiprole. However, it's role is yet to be discovered [26, 31].

Table 1. HA-MRSA strains isolated from University Hospital of Geneva's patients' blood between 1998-2003, showing primary resistance to ceftaroline (MIC > 1mg/l) [29].

Strain (GenBank no.)	Molecular type	SCCmec	Mutations	Year	MIC (broth) (mg/l)
12	ST228	I	E239K	1998	2
14	ST228	I	E239K	1998	2
13	ST247	I	N146K, E150K, G246E	1998	4
16	ST247	I	N146K, E150K, G246E	1998	4
56	ST228	I	N146K	1999	2
17	ST228	I	N146K	1999	2
21	ST228	I	N146K	1999	2
57	ST228	I	N146K	2000	2
25	ST228	I	N146K	2000	2
28	ST228	I	N146K	2000	2
30	ST228	I	N146K	2000	4
42	ST228	I	N146K	2002	2
48	ST228	I	N146K	2003	2
52	ST228	I	N146K	2003	2

Chan LC et al. used the method of serial passages and the method of plasmid transduction to estimate the possibility of emergence of ceftaroline resistance and the potential consequences of its transmission in two strains of ceftaroline-passaged mutants: SF8300 and COL. In this way, mutants with MIC greater than 32 mg/l were obtained [26]. Lahiri SD et al. proved, using the method of serial

passages, that induction of ceftaroline-resistance (MIC ranging from 2 to 64 mg/l) is possible among strains ATCC 29213 (MIC: 0.25-4 mg/l), USA300 (MIC: 1-8 mg/l) and ARC3824 (MIC: 8-64 mg/l).

Clinical strains of MRSA, investigated by Lahiri SD et al., have also shown the ability to rapid resistance development (manifesting itself as significant increase of MIC), as presented in Table 2 [30]. It is a discovery of great importance, since passing bacteria imitates the situation in human organism when, due to incorrect dosage, too long therapy or insufficient penetration of the antibiotic to the tissue, in vivo MIC has not been achieved. Besides the mutation within PBP2A, strains with point mutation within PBP4, providing them ceftaroline-resistance, were observed (strains TRN5426 and TRN5549) [25].

Table 2. Clinical MRSA strains with significantly increased (compared to parental strains) MIC due to serial passages. Descendant strains are marked by adding (after the dash) following letters of the alphabet to the name of a parental strain [30].

Strain	Molecular type	SCC mec	Mutations of parental strain	Additional mutations after passage	Year	Country	MIC (broth) of parental strain (mg/l)	MIC (broth) after passage (mg/l)
ARC3824	ST228	I	E239K, E447K		2010	Spain	8	
ARC3824-A	ST228	I	E239K, E447K	Y446N	2010	Spain	8	64
ARC3824-B	ST228	I	E239K, E447K	A601S	2010	Spain	8	16
ARC3824-C	ST228	I	E239K, E447K	A601S	2010	Spain	8	16
ARC3827	ST228	I	E239K		2010	Thailand	2	
ARC3827-A	ST228	I	E239K	-	2010	Thailand	2	4
ARC3827-B	ST228	I	E239K	-	2010	Thailand	2	4
TRN5426	ST22	IV	WT		2012	Portugal	2	
TRN5426-A	ST22	IV	WT	-	2012	Portugal	2	8
TRN5467	ST5	II	N146K, L357I, I563T		2012	South Korea	4	
TRN5467-A	ST5	II	N146K, L357I, I563T	Y446N	2012	South Korea	4	32
TRN5467-B	ST5	II	N146K, L357I, I563T	Y446N	2012	South Korea	4	32
TRN5549	ST22	IV	E150K		2012	Portugal	2	
TRN5549-A	ST22	IV	E150K	-	2012	Portugal	2	8

Moreover, there are more and more reports from all over the world, describing isolating from different clinical samples another MRSA strains capable of developing mechanisms of resistance to ceftaroline (Table 3).

Laboratory results are also confirmed by reported clinical cases. This problem is seen (among others) in patients with cystic fibrosis (CF),

probably due to the multitude of therapeutic cycles using the same antibiotic - in this case - ceftaroline. Such cases, as presented in Table 4, prove that increasing resistance to antibiotics observed in microbiological laboratories while passing bacteria, is also reflected in clinical environment. In these patients, resistance to ceftaroline and its limited clinical effectiveness were observed [22, 31]. The case of ceftaroline resistance was also reported for a strain isolated from the blood of a patient suffering from IE, as well as from the broncho-alveolar lavage fluid (BALF) of a patient suffering from ventilation associated pneumonia (VAP) [35]. Molecular studies conducted on isolated MRSA strains revealed mutations in PBP2a [22, 30, 31].

Table 3. MRSA strains with potential of clinical resistance to ceftaroline [25, 30].

Strain	Molecular type	SCCmec	Mutations	Country	MIC (broth) (mg/l)
TRN5420	ST239	III	E239K	Hungary	2
TRN5427	ST36	II	WT	Greece	2
TRN5428	ST239	III	N146K, E150K, N204K, G246E	Greece	4
TRN5433	ST5	II	K290Q	Japan	4
TRN5444	ST5	II	K281R	China	2
TRN5454	ST5	II	WT	Japan	2
TRN5458	ST239	III	N146K	Philippines	2
TRN5471	ST228	I	N146K, I563T	Italy	4
TRN5474	ST5	II	N236K	Taiwan	2
TRN5475	ST239	III	E239K	China	2
TRN0478	ST228	I	N146K	Hungary	2
TRN5507	ST239	III	N146K	Russia	4
TRN5521	ST228	I	E239K, E447K	Thailand	8
TRN5536	ST239	III	WT	Turkey	2
TRN5539	ST5	II	E170K, N236K	Taiwan	2
TRN5552	ST239	III	N146K, N204K, G246E	South Africa	2
TRN5562	ST22	IV	E239K, G246E	France	2
TRN5563	ST239 with tpi-107	III	N204K, T235I	France	2
TRN5572	ST5	II	WT	Italy	2
ARC3824	ST228	I	E239K, E447K	Spain	8
ARC3828	ST228	I	E239K, E447K	Thailand	8
ARC3830	ST228	I	E239K, E447K	Thailand	8
TRN5474	ST228	I	N236K	Taiwan	2
TRN5472	ST228	I	WT	Italy	2
TRN5545	ST239	III	N146K	Turkey	2
TRN5418	ST5	I	M122I, E150K	Chile	2
TRN5350	ST8	II	N236K	USA	2

Table 4. Summary of clinical cases [22, 30, 31].

Strain	Disease	Sample	Mutation	MIC (mg/l)
THMS-4519	Cystic fibrosis	Sputum	Y446N	1,5
THMS-3125	Cystic fibrosis	Sputum	Y446N, E447K	>32
THMS-5007	Cystic fibrosis	Sputum	E239K, Y446N, E447K	>32
THMS-5006	Cystic fibrosis	Blood	E239K, Y446N, E447K	>32
USA100	Infectious endocarditis	Blood	E447K	4
USA100	Ventilation associated pneumonia	BALF	E447K	6

Pfaller MA et al. observed ceftaroline resistance in one multi-drug resistant *S pneumoniae* strain. Molecular analysis revealed 31 altered aminoacids within the MurM relative to the standard R6 strain. Changes in PBPs, mainly PBP2x, were also detected [36].

EPIDEMIOLOGY

Despite being put into use only a few years ago, ceftaroline-resistant strains are detected in more and more countries. Moreover, it was proved that resistant strains have been existing for at least over a dozen years prior to introducing ceftaroline. In 2015 Kelley et al. published the results of a study concerning 60 archival MRSA strains (collected between 1994-2003 in Geneva, Switzerland), 40 out of which (66%), dated 1998-2003, turned out to be ceftaroline-resistant [29]. In 2016, in the same center, another study was conducted - this time on MRSA strains collected in 2013 and 2014. 23 out of 96 strains (24%) were ceftaroline-resistant [37].

The AWARE report from 2012 informed that among 2583 *S. aureus* strains collected in Europe, Russia and Turkey, 2 (0.08%) were ceftaroline-resistant (MIC, ≥4 mg/l) and 114 (4.4%) were ceftaroline-intermediate (MIC, 2 mg/l). Given EUCAST (European Committee on Antimicrobial Susceptibility Testing) criteria, 116 strains (4.5%) were ceftaroline-resistant (MIC, >1 mg/l), 94 (81%) out of which came from Russia, Turkey, Italy and Hungary [38]. In the USA the first ceftaroline-resistant MRSA strain was described in 2014 by Long et al. and it was isolated from a twenty-year-old CF patient treated with ceftaroline due to recurring respiratory tract infections caused by multi-drug resistant bacteria (including MRSA) [23].

In 2015 in China, Zhang et al. examined 251 hospital acquired MRSA strains from ABSSSI patients. None of the analyzed strains showed resistance to ceftaroline, but 84 of them (33.5%) showed intermediate resistance (MIC, 2 mg/l) [39]. In the same year, Abbott et al. tested 421 MRSA strains collected in Australia (270 from 2017, the rest from 2013). 71 (16.9%) out of them were nonsusceptible to ceftaroline (MIC, >1.0 mg/l) and most of them had MDR phenotype [40]. In Africa, 37 MRSA strains colonizing patients and 23 infectious MRSA strains were collected. 10 (16.7%) out of them were resistant to ceftaroline [28].

CONCLUSIONS

Ceftaroline as a new antibiotic, in most cases allows to reach therapeutic effect provided in the Summary of Product Characteristics (SPC). However, it is very disturbing that in the moment of being introduced to market, there have already been existing ceftaroline-resistant strains, which may indicate that there's a possibility of obtaining cross-resistance to ceftaroline while using other β-lactam antibiotics in insufficient doses (which can be verified by testing archived MRSA strains). Laboratory tests prove that resistance to ceftaroline may be induced by selecting strains by increasing doses of the antibiotic. It shows rather clearly that bacteria can survive therapeutic concentration of ceftaroline if they have previously been exposed to it. Moreover, ceftaroline-resistant strains are isolated from patients with clinical symptoms of infections.

Thus, ceftaroline, just like any other antibiotic, may lose its clinical value if it's overused, its dosage is incorrect or the rest of β-lactams are

overused or dosed incorrectly. Reasonable antibiotic therapy is probably the only hope for effective use of ceftaroline in the future. However, it is impossible to estimate how fast will the resistance-gaining process progress or what percentage of bacteria will it concern.

AUTHORS' CONTRIBUTIONS

ABo: Paper conception and design. RŚ, ABi, ABo, MB: Acquisition of literature, Analysis and interpretation of literature, Drefting of manuscript. MB, ABo: Drafting of tables. ABi, RŚ: Translation of manuscript. ABo: Adaptation to editorial guidelines. All authors read and approved the final manuscript.

TRANSPARENCY DECLARATION

Authors have declared that no competing interests exist.

REFERENCES

1. Lim L, Sutton E, Brown J. Ceftaroline: a new broad-spectrum cephalosporin. Am J Heal Pharm. 2011; 68: 491-498.
2. Ghamrawi RJ, Neuner E, rehm SJ. Ceftaroline fosamil: A super-cephalosporin? Cleve Clin J Med. 2015; 82: 437-444.
3. Cercenado E, Morosini MI. Espectro antimicrobiano de ceftarolina. Actividad in vitro frente a estafilococos resistentes a la meticilina. Enferm Infecc Microbiol Clin. 2014; 32: 8-14.
4. Rolston KVI, Jamal MA, Nesher L, Shelburne SA, Raad I, Prince RA. In vitro activity of ceftaroline and comparator agents against Gram-positive and Gram-negative clinical isolates from cancer patients. Int J Antimicrob Agents. 2017; 49: 416-421.
5. Shirley D-AT, Heil EL, Johnson JK. Ceftaroline fosamil: a brief clinical review. Infect Dis Ther. 2013; 2: 95-110.
6. Gaikwad V, Gohel T, Panickar S, Chincholkar V, Mangalkar S. In vitro activity of ceftaroline: a novel antibiotic against methicillin-resistant *Staphylococcus aureus.* Indian J Pathol Microbiol. 2016; 59: 496.
7. Scott LJ. Ceftaroline fosamil: a review in complicated skin and soft tissue infections and community-acquired pneumonia. Drugs. 2016; 76: 1659-1674.
8. Cheung RP, DiPiro JT. Vancomycin: an update. Pharmacotherapy. 1986; 6: 153-169.
9. Pigrau C. [Oxazolidinones and glycopeptides]. Enferm Infecc Microbiol Clin. 2003; 21: 157-164; quiz 165, 169.
10. Mélard A, Garcia LG, Das D, Rozenberg R, Tulkens PM, Van Bambeke F, et al. Activity of ceftaroline against extracellular (broth) and intracellular (THP-1 monocytes) forms of methicillin-resistant *Staphylococcus aureus*: comparison with vancomycin, linezolid and daptomycin. J Antimicrob Chemother. 2013; 68: 648-658.
11. Taboada M, Melnick D, Iaconis JP, Sun F, Zhong NS, File TM, et al. Ceftaroline fosamil versus ceftriaxone for the treatment of community-acquired pneumonia: individual patient data meta-analysis of randomized controlled trials. J Antimicrob Chemother. 2016; 71: 862-870.
12. Livermore DM, Warner M, Mushtaq S. Methodological agreement on the in vitro activity of ceftaroline against cefotaxime-susceptible and -resistant pneumococci. Int J Antimicrob Agents. 2014; 43: 131-134.
13. Allergan Receives FDA Approval of TEFLARO® (ceftaroline fosamil) for Pediatric Patients - Allergan n.d. https://www.allergan.com/news/news/thomson-reuters/allergan-receives-fda-approval-of-teflaro-ceftaro (accessed April 14, 2018).
14. Pfaller MA, Mendes RE, Castanheira M, Flamm RK, Jones RN, Sader HS. Ceftaroline activity tested against bacterial isolates causing community-acquired respiratory tract infections and skin and skin structure infections in pediatric patients from United States hospitals. Pediatr Infect Dis J. 2017; 36: 486-491.
15. Borgmann S, Rieß B, von Wernitz-Keibel T, Matthias Buehler M, Strommenger B, Layer F. Recovery of a 10-year-old girl from methicillin-resistant *Staphylococcus aureus* sepsis in response to low-dose ceftaroline treatment. Ther Clin Risk Manag. 2016; 12: 749.
16. Zasowski EJ, Trinh TD, Claeys KC, Casapao AM, Sabagha N, Lagnf AM, et al. A multicenter observational study of ceftaroline fosamil for methicillin-resistant *Staphylococcus aureus* bloodstream infections. Antimicrob Agents Chemother. 2016; 61: AAC.02015-16.
17. White BP, Barber KE, Stover KR. Ceftaroline for the treatment of methicillin-resistant *Staphylococcus aureus* bacteremia. Am J Heal Pharm. 2017; 74: 201-208.
18. Werth BJ, Barber KE, Ireland CE, Rybak MJ.

Evaluation of ceftaroline, vancomycin, daptomycin, or ceftaroline plus daptomycin against daptomycin-nonsusceptible methicillin-resistant *Staphylococcus aureus* in an *in vitro* pharmacokinetic/ pharmacodynamic model of simulated endocardial vegetation. Antimicrob Agents Chemother. 2014; 58: 3177-3181.

19. Shafiq I, Bulman ZP, Spitznogle SL, Osorio JE, Reilly IS, Lesse AJ, et al. A combination of ceftaroline and daptomycin has synergistic and bactericidal activity *in vitro* against daptomycin nonsusceptible methicillin-resistant *Staphylococcus aureus* (MRSA). Infect Dis (Auckl). 2017; 49: 410-416.
20. Jongsma K, Joson J, Heidari A. Ceftaroline in the treatment of concomitant methicillin-resistant and daptomycin-non-susceptible *Staphylococcus aureus* infective endocarditis and osteomyelitis: case report. J Antimicrob Chemother. 2013; 68: 1444-1445.
21. Harrison EM, Ba X, Blane B, Ellington MJ, Loeffler A, Hill RLR, et al. PBP2a substitutions linked to ceftaroline resistance in MRSA isolates from the UK. J Antimicrob Chemother. 2016; 71: 268-269.
22. Lahiri SD, McLaughlin RE, Whiteaker JD, Ambler JE, Alm RA. Molecular characterization of MRSA isolates bracketing the current EUCAST ceftaroline-susceptible breakpoint for *Staphylococcus aureus*: the role of PBP2a in the activity of ceftaroline. J Antimicrob Chemother. 2015; 70: 2488-2498.
23. Long SW, Olsen RJ, Mehta SC, Palzkill T, Cernoch PL, Perez KK, et al. PBP2a mutations causing high-level ceftaroline resistance in clinical methicillin-resistant *Staphylococcus aureus* isolates. Antimicrob Agents Chemother. 2014; 58: 6668-6674.
24. Abbott IJ, Jenney AWJ, Jeremiah CJ, Mirčeta M, Kandiah JP, Holt DC, et al. Reduced *in vitro* activity of ceftaroline by etest among clonal complex 239 methicillin-resistant *Staphylococcus aureus* clinical strains from Australia. Antimicrob Agents Chemother. 2015; 59: 7837-7841.
25. Lahiri SD, Alm RA. Identification of non-PBP2a resistance mechanisms in *Staphylococcus aureus* after serial passage with ceftaroline: involvement of other PBPs. J Antimicrob Chemother. 2016; 71: 3050-3057.
26. Chan LC, Basuino L, Diep B, Hamilton S, Chatterjee SS, Chambers HF. Ceftobiprole- and ceftaroline-resistant methicillin-resistant *Staphylococcus aureus*. Antimicrob Agents Chemother. 2015; 59: 2960-2963.
27. Lavanya P, Ramaiah S, Anbarasu A. A molecular docking and dynamics study to screen potent anti-staphylococcal compounds against ceftaroline resistant MRSA. J Cell Biochem. 2016; 117: 542-548.
28. Schaumburg F, Peters G, Alabi A, Becker K, Idelevich EA. Missense mutations of PBP2a are associated with reduced susceptibility to ceftaroline and ceftobiprole in African MRSA. J Antimicrob Chemother. 2016; 71: 41-44.
29. Kelley WL, Jousselin A, Barras C, Lelong E, Renzoni A. Missense mutations in PBP2A affecting ceftaroline susceptibility detected in epidemic hospital-acquired methicillin-resistant *Staphylococcus aureus* clonotypes ST228 and ST247 in Western Switzerland archived since 1998. Antimicrob Agents Chemother. 2015; 59: 1922-1930.
30. Lahiri SD, Alm RA. Potential of *Staphylococcus aureus* isolates carrying different PBP2a alleles to develop resistance to ceftaroline. J Antimicrob Chemother. 2016; 71: 34-40.
31. Cannavino CR, Mendes RE, Sader HS, Farrell DJ, Critchley IA, Biek D, et al. Evolution of ceftaroline-resistant MRSA in a child with cystic fibrosis following repeated antibiotic exposure. Pediatr Infect Dis J. 2016; 35: 813-815.
32. Tschierske M, Mori C, Rohrer S, Ehlert K, Shaw KJ, Berger-Bächi B. Identification of three additional femAB-like open reading frames in *Staphylococcus aureus*. FEMS Microbiol Lett. 1999; 171: 97-102.
33. Rohrer S, Ehlert K, Tschierske M, Labischinski H, Berger-Bächi B. The essential *Staphylococcus aureus* gene fmhB is involved in the first step of peptidoglycan pentaglycine interpeptide formation. Proc Natl Acad Sci USA. 1999; 96: 9351-9356.
34. Greninger AL, Chatterjee SS, Chan LC, Hamilton SM, Chambers HF, Chiu CY. Whole-genome sequencing of methicillin-resistant *Staphylococcus aureus* resistant to fifth-generation cephalosporins reveals potential non-mecA mechanisms of resistance. PLoS One. 2016; 11: e0149541.
35. Nigo M, Diaz L, Carvajal LP, Tran TT, Rios R, Panesso D, et al. Ceftaroline-resistant, daptomycin-tolerant, and heterogeneous vancomycin-intermediate methicillin-resistant *Staphylococcus aureus* causing infective endocarditis. Antimicrob Agents Chemother. 2017; 61: e01235-16.
36. Pfaller MA, Mendes RE, Flamm RK, Jones RN, Sader HS. Ceftaroline activity against multidrug-resistant *Streptococcus pneumoniae* from U.S. Medical Centers (2014) and molecular characterization of a single ceftaroline nonsusceptible

isolate. Microb Drug Resist. 2017; 23: 571-579.

37. Andrey DO, François P, Manzano C, Bonetti EJ, Harbarth S, Schrenzel J, et al. Antimicrobial activity of ceftaroline against methicillin-resistant *Staphylococcus aureus* (MRSA) isolates collected in 2013-2014 at the Geneva University Hospitals. Eur J Clin Microbiol Infect Dis. 2017; 36: 343-350.
38. Karlowsky JA, Biedenbach DJ, Bouchillon SK, Iaconis JP, Reiszner E, Sahm DF. *In vitro* activity of ceftaroline against bacterial pathogens isolated from skin and soft tissue infections in Europe, Russia and Turkey in 2012: results from the Assessing Worldwide Antimicrobial Resistance Evaluation (AWARE) surveillance programme. J Antimicrob Chemother. 2016; 71: 162-169.
39. Zhang H, Xiao M, Kong F, O'Sullivan MVN, Mao L-L, Zhao H-R, et al. A multicentre study of meticillin-resistant *Staphylococcus aureus* in acute bacterial skin and skin-structure infections in China: Susceptibility to ceftaroline and molecular epidemiology. Int J Antimicrob Agents. 2015; 45: 347-350.
40. Abbott IJ, Jenney AWJ, Jeremiah CJ, Mirčeta M, Kandiah JP, Holt DC, et al. Reduced *in vitro* activity of ceftaroline by E-test among clonal complex 239 methicillin-resistant *Staphylococcus aureus* clinical strains from Australia. Antimicrob Agents Chemother. 2015; 59: 7837-7841.