Clinical Microbiology and Infection 25 (2019) 1429.e1–1429.e4

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Original article

Impact of EUCAST ceftaroline breakpoint change on the susceptibility of methicillin-resistant *Staphylococcus aureus* isolates collected from patients with complicated skin and soft-tissue infections

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ARTICLE INFO

Article history:
Received 16 November 2018
Received in revised form
18 March 2019
Accepted 19 March 2019
Available online 10 April 2019

Editor: F. Allerberger

Keywords:
Breakpoint
Ceftaroline
Complicated skin and soft-tissue infections
EUCAST
Methicillin-resistant *Staphylococcus aureus*

ABSTRACT

Objectives: In 2018, the European Committee on Antimicrobial Susceptibility Testing (EUCAST) introduced an intermediate breakpoint for ceftaroline against *Staphylococcus aureus*. The objective of this study was to compare data on resistance to ceftaroline among methicillin-resistant *S. aureus* (MRSA) isolates using versions 7.1 (March 2017) and 8.0 (January 2018) of the EUCAST breakpoints.

Methods: Participating centers were located in Africa, Asia, Europe, Oceania and South America. Isolates were collected from patients with complicated skin and soft-tissue infections and were cultured from integumentary sources. Methicillin resistance among *S. aureus* was confirmed locally using the oxacillin method. The CLSI broth microdilution method was used to measure ceftaroline MICs at the central laboratory. Versions 7.1 and 8.0 of the EUCAST breakpoints were used to interpret MIC data.

Results: Between 2015 and 2016, 9559 isolates of *S. aureus* were collected, of which 5566 (58.2%) isolates were MRSA. Overall, the lowest rate of MRSA was in Asia (56.5%; 705/1247) and the highest rate was in Oceania (62.7%; 299/477). Using version 7.1 of the EUCAST breakpoints, 4.5% (250/5566) of all MRSA isolates were resistant to ceftaroline and when version 8.0 of the breakpoints was applied, 4.2% (235/5566) of MRSA were in the intermediate category and 0.3% (15/5566) of all isolates were considered resistant.

Conclusions: By applying version 8.0 of the EUCAST breakpoints, the majority of MRSA isolates that were resistant are now in the intermediate category for ceftaroline. Ceftaroline resistance among MRSA now appears rare. **E. Urbán, Clin Microbiol Infect 2019;25:1429.e1–1429.e4**

Introduction

Worldwide, methicillin-resistant *Staphylococcus aureus* (MRSA) is frequently isolated from complicated skin and soft-tissue infections (cSSTI) [1,2], and cases of MRSA are increasing among outpatients [3,4]. Early diagnosis and treatment of cSSTI caused by MRSA can be linked to lower hospital costs, by reducing treatment duration and length of stay [5].

Ceftaroline has antimicrobial activity against MRSA and has been approved for the treatment of cSSTI at a standard dosage of 600 mg every 12 h (given over 60 min) in adults [6]. In 2017, the European Medicines Agency approved a higher dosing regimen of ceftaroline (600 mg every 8 h over 120 min) for cSSTI caused by *S. aureus* with a ceftaroline MIC of 2 or 4 mg/L.

Having two approved dosing regimens (standard and high) is one of the criteria that the European Committee on Antimicrobial Susceptibility Testing (EUCAST) have proposed to use when assigning an intermediate category for an antimicrobial agent [7]. Hence, an intermediate breakpoint of 2 mg/L was introduced for ceftaroline against *S. aureus*, for indications other than pneumonia, in version 8.0 of the EUCAST breakpoints [8]. As a result, the EUCAST resistant breakpoint for ceftaroline against *S. aureus* increased from >1 mg/L in version 7.1 of the breakpoint tables to >2 mg/L in version 8.0 [8,9].

The aim of this study is to present antimicrobial activity data on ceftaroline against a collection of MRSA isolates from cSSTI, and to

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https://doi.org/10.1016/j.cmi.2019.03.023

compare resistance data using EUCAST breakpoints versions 7.1 and 8.0. Isolates were collected between 2015 and 2016 in Africa, Asia, Europe, Oceania and South America for the global AWARE (Assessing Worldwide Antimicrobial Resistance Evaluation) surveillance study (excluding the USA), which now forms part of the ATLAS (Antimicrobial Testing Leadership and Surveillance) database.

Methods

In this study, 9559 isolates of *S. aureus* were collected from patients with cSSTI between 2015 and 2016 for the global AWARE surveillance study (excluding the USA). Isolates were submitted from 132 study centers in the following regions: Africa ($n = 11$), Asia ($n = 18$), Europe ($n = 72$), Oceania ($n = 7$) and South America ($n = 24$). Each center was required to collect 70–95 isolates of *S. aureus*. Demographic information recorded for each isolate included specimen source, and patient age, sex and location in the hospital. To be included in the study, isolates had to be considered the likely causative pathogen of infection and, to be included in this analysis, must have been cultured from integumentary specimens, such as abscesses, burns, impetiginous lesions or wounds. Isolates were excluded if they came from *in situ* drains or drainage bottles, were environmental samples or were duplicate isolates (the same species from the same or different body site isolated at the same time or at any subsequent time from the same patient).

All isolates were identified locally and shipped to the central laboratory (International Health Management Associates, Inc., Schaumburg, IL, USA) for susceptibility testing. The methicillin-resistance status of each *S. aureus* isolate was determined using the oxacillin method (an oxacillin MIC of ≥4 mg/L confirmed methicillin resistance), in accordance with the CLSI definitions [10]. Ceftaroline MICs were determined using broth microdilution methodology according to CLSI guidelines [11]. The testing range for ceftaroline was 0.015–32 mg/L. Ceftaroline MIC values were interpreted using versions 7.1 (susceptible, ≤1 mg/L and resistant, >1 mg/L) and 8.0 (susceptible, ≤1 mg/L; intermediate, 2 mg/L and resistant, >2 mg/L) of the EUCAST breakpoints for indications other than pneumonia [8,9].

Results

In this study, a total of 5566 (58.2%) isolates of MRSA were identified from 9559 isolates of *S. aureus*. The majority of MRSA isolates were collected from inpatients (82.0%; 4562/5566), 58.0% (3227/5566) of isolates were collected from male patients, and 52.4% (2916/5566) of isolates were from patients aged between 18 and 64 years. Most isolates were collected from wounds (52.8%; 2940/5566) and abscesses (23.0%; 1282/5566). The remaining isolates were collected from burns, carbuncles, cellulitis/erysipelas, decubitus, furuncles, impetiginous lesions, skin, skin ulcers or other sources.

The rates of MRSA, by region and year, are presented in Table 1. The overall rate of MRSA collected in all regions over the study period was 58.2% (5566/9559). By region, the lowest rate of MRSA was in Asia (56.5%; 705/1247) and the highest rate was in Oceania (62.7%; 299/477). By year, in each region except Asia, there was a small decrease in rates of MRSA between 2015 and 2016. In Asia, the rates of MRSA in 2015 and 2016 were similar (56.4%; 375/665, and 56.7%; 330/582, respectively).

Table 1
Rates of MRSA collected from patients with cSSTI (2015–2016)

Region	2015 *n* (%)	2016 *n* (%)	2015–2016 *n* (%)
Africa	298 (61.4)	284 (58.7)	582 (60.1)
Asia	375 (56.4)	330 (56.7)	705 (56.5)
Europe	1436 (60.0)	1492 (56.9)	2928 (58.4)
Oceania	127 (65.1)	172 (61.0)	299 (62.7)
South America	621 (57.8)	431 (55.7)	1052 (56.9)
All regions	2857 (59.3)	2709 (57.1)	5566 (58.2)

Abbreviations: cSSTI, complicated skin and soft-tissue infections; MRSA, methicillin-resistant *Staphylococcus aureus*.

The *in vitro* antimicrobial activity of ceftaroline against MRSA isolates collected in this study is presented in Table 2. The overall ceftaroline MIC_{50} and MIC_{90} values in all regions over the study period were 0.5 and 1 mg/L, respectively, and the same MIC_{50} and MIC_{90} values were observed over the study period in each region. By year, the ceftaroline MIC_{50} was also 0.5 mg/L in each region, and the MIC_{90} was 1 mg/L in all years except 2015 in Asia (MIC_{90} 2 mg/L) and 2016 in Oceania (MIC_{90} 0.5 mg/L).

According to version 7.1 of the EUCAST breakpoints, the overall percentage of MRSA isolates that were resistant to ceftaroline in all regions over the study period was 4.5% (250/5566; Table 2). When version 8.0 of the breakpoints was applied, 0.3% (15/5566) of all isolates collected were in the resistant category and 4.2% (235/5566) were in the intermediate category. By region, when version 7.1 of the EUCAST breakpoints was used, the rates of ceftaroline resistance ranged from 1.0% (3/299; Oceania) to 7.8% (55/705; Asia). Applying version 8.0 of the breakpoints for each region, Oceania had both the lowest rate of ceftaroline-resistant MRSA isolates and the lowest rate of ceftaroline-intermediate isolates (0.0%; 0/299, and 1.0%; 3/299, respectively). The highest rate of ceftaroline-resistant MRSA was collected in Asia (1.8%; 13/705), and the highest rate of ceftaroline-intermediate isolates was collected in South America (7.5%; 79/1052).

Applying version 7.1 of the EUCAST breakpoints, there was a decrease in ceftaroline resistance between 2015 and 2016 in each region except South America, where rates were 7.1% (44/621) and 8.4% (36/431), respectively (Table 2). Using the version 8.0 breakpoints, there were similar rates of ceftaroline resistance among MRSA in each region in 2015 and 2016 (0.0%–0.2%) except in Asia, where ceftaroline resistance decreased from 2.9% (11/375) in 2015 to 0.6% (2/330) in 2016. Between study years, there was a decrease in the proportion of ceftaroline-intermediate MRSA isolates between 2015 and 2016 in all regions except South America.

Discussion

The focus of this study was the revision of the EUCAST breakpoints for ceftaroline against *S. aureus* and the effects on the susceptibility to ceftaroline among a collection of MRSA isolates from cSSTI. In version 8.0 of the EUCAST breakpoints, an intermediate category was introduced for ceftaroline against *S. aureus*, for indications other than pneumonia, and the resistant breakpoint increased to >2 mg/L [8,9].

Applying version 7.1 of the EUCAST breakpoints for ceftaroline and *S. aureus*, the overall rate of ceftaroline resistance among MRSA isolates in the current study was 4.5%. With version 8.0 of the breakpoints, previously resistant isolates according to version 7.1 became largely assigned to the intermediate category for ceftaroline, and the overall rate of ceftaroline resistance decreased to 0.3%. By region, with version 8.0, rates of ceftaroline-resistant MRSA decreased to 0.0%–0.1% in Africa, Europe, Oceania and South America, and decreased to 1.8% in Asia. This change reflects a low occurrence of MRSA isolates from cSSTI with a ceftaroline MIC value of > 2 mg/L in the regions presented here.

Ceftaroline can therefore be considered a treatment option for cSSTI caused by MRSA, provided that steps are taken to quantify the *in vitro* susceptibility of MRSA to ceftaroline to ensure that the correct dosing regimen is administered. Although *S. aureus* isolates with ceftaroline MICs of 4 mg/L are rare [12,13], there is evidence to

Table 2
In vitro activity of ceftaroline against a collection of MRSA isolates from patients with cSSTI (2015–2016)

Region, year	Isolates (*n*)	MIC (mg/L)			EUCAST version 7.1[a] (%)			EUCAST version 8.0[b] (%)		
		MIC_{50}	MIC_{90}	Range	S	I	R	S	I	R
Africa										
2015	298	0.5	1	0.25–2	94.0	—	6.0	94.0	6.0	0.0
2016	284	0.5	1	0.25–2	98.6	—	1.4	98.6	1.4	0.0
2015–2016	582	0.5	1	0.25–2	96.2	—	3.8	96.2	3.8	0.0
Asia										
2015	375	0.5	2	0.12–4	89.3	—	10.7	89.3	7.7	2.9
2016	330	0.5	1	0.12–4	95.5	—	4.5	95.5	3.9	0.6
2015–2016	705	0.5	1	0.12–4	92.2	—	7.8	92.2	6.0	1.8
Europe										
2015	1436	0.5	1	0.03–4	96.8	—	3.2	96.8	3.1	0.1
2016	1492	0.5	1	0.06–2	97.1	—	2.9	97.1	2.9	0.0
2015–2016	2928	0.5	1	0.03–4	96.9	—	3.1	96.9	3.0	<0.05
Oceania										
2015	127	0.5	1	0.25–2	97.6	—	2.4	97.6	2.4	0.0
2016	172	0.5	0.5	0.25–1	100	—	0.0	100	0.0	0.0
2015–2016	299	0.5	1	0.25–2	99.0	—	1.0	99.0	1.0	0.0
South America										
2015	621	0.5	1	0.25–4	92.9	—	7.1	92.9	6.9	0.2
2016	431	0.5	1	0.12–2	91.6	—	8.4	91.6	8.4	0.0
2015–2016	1052	0.5	1	0.12–4	92.4	—	7.6	92.4	7.5	0.1
All regions										
2015	2857	0.5	1	0.03–4	94.7	—	5.3	94.7	4.8	0.5
2016	2709	0.5	1	0.06–4	96.3	—	3.7	96.3	3.6	0.1
2015–2016	5566	0.5	1	0.03–4	95.5	—	4.5	95.5	4.2	0.3

Abbreviations: cSSTI, complicated skin and soft-tissue infections; MIC, minimum inhibitory concentration; MIC_{50}, MIC required to inhibit growth of 50% of isolates (mg/L); MIC_{90}, MIC required to inhibit growth of 90% of isolates (mg/L); MRSA, methicillin-resistant *Staphylococcus aureus*; I, intermediate; R, resistant; S, susceptible.
–, no breakpoints available.
[a] EUCAST breakpoints version 7.1: S, ≤1 mg/L and R, >1 mg/L [9].
[b] EUCAST breakpoints version 8.0: S, ≤1 mg/L and R, >2 mg/L [8].

suggest that the higher dosing regimen of ceftaroline may still be an effective treatment option [14]. Using a population pharmacokinetic model comprising pharmacokinetic data from 21 clinical studies, a high probability of target attainment (>90%) was predicted for ceftaroline at 600 mg every 8 h against *S. aureus* with ceftaroline MICs of ≤4 mg/L [14].

The revised ceftaroline resistance rate against MRSA reported by this study in Asia (1.8%), using version 8.0 of the EUCAST breakpoints, was higher than in other participating regions. Previous studies have identified a set of MRSA isolates collected in Thailand with ceftaroline MIC values of ≥2 mg/L [12,13,15]. Among the isolates selected for molecular characterization, the majority with ceftaroline MIC values of 2 mg/L had a single amino acid substitution in the non-penicillin-binding domain of penicillin-binding protein 2a (PBP2a), and isolates with ceftaroline MICs of 4 mg/L [13] or 8 mg/L [12,15] all had an additional single amino acid substitution in the penicillin-binding domain of PBP2a.

The data presented in this study show that the rates of MRSA from patients with cSSTI were >50% in each region submitting isolates, and that the rates did not vary greatly from the overall rate of 58.2% for the study period. This reaffirms that MRSA is a common cause of cSSTI globally, and that recent rates seem to be consistent, year-on-year. In surveillance studies of isolates from skin infections, high rates of MRSA have also been reported: Africa and the Middle East, 53.6% (883/1646) in 2012–2014 [16]; Asia-Pacific and South Africa, 31.8% in 2011 [17]; Europe, Russia and Turkey, 56.8% (1467/2583) in 2012 [18]; and Latin America, 56.0% (390/696) in 2012 [19]. The lower rates of MRSA reported by Flamm et al. [17] may indicate that MRSA rates have increased in certain regions since 2011; however, rates of MRSA are also influenced by their contributing study centers and countries, which are likely to differ between studies.

Reported rates of MRSA may also depend upon specimen source. The yearly rates of MRSA presented in this study (59.3% in 2015 and 57.1% in 2016), were for integumentary sources from patients with cSSTI. The European Centre for Disease Prevention and Control (ECDC) published notably lower MRSA rates (population-weighted means across 30 European countries) of 16.9% in 2015 and 13.7% in 2016 [4], solely from invasive isolates (blood and cerebrospinal fluid). In their report, they note that invasive isolates may not be representative of isolates of the same bacterial species from other type of infections, and list wound infections as an example. In the present study, the majority of isolates were collected from wounds (52.8%).

In line with the ceftaroline breakpoint revisions by EUCAST based on the higher dosing regimen approved by the European Medicines Agency, the CLSI revised their ceftaroline MIC breakpoints in January 2019. The intermediate and resistant CLSI breakpoints for ceftaroline of 2 and ≥4 mg/L, respectively, have been replaced by a new susceptible-dose-dependent MIC category of 2–4 mg/L and an increased resistant breakpoint of ≥8 mg/L [20].

There are a number of limitations associated with the collection of isolates for surveillance studies such as AWARE that should be borne in mind when considering these results. First, participating study centers are not located in every country of each region, and some regions have more participating centers than others (e.g. 52.6% of all MRSA isolates collected in the current study were obtained from Europe). Therefore, all countries or regions are not equally represented. Second, years of participation can vary for the same center, which may not collect isolates year-on-year. Also, each study center is required to collect a defined number of isolates for each bacterial species (limited to one isolate per species per patient) from a limited number of infection types. Furthermore, this study did not include isolates collected in the USA. Therefore, the data presented here are representative of a collection of isolates, rather than showing the true prevalence of ceftaroline resistance among MRSA isolates from around the world.

Despite these limitations this is the first surveillance study, to date, showing the impact of revised EUCAST breakpoints for ceftaroline on the ceftaroline susceptibility of MRSA isolates from

cSSTI. The findings indicate that for the regions included in this study, MRSA isolates with a ceftaroline MIC value of > 2 mg/L are rare, and most isolates that were previously considered resistant to ceftaroline can now be categorized as intermediate.

Transparency declaration

EU has no conflicts of interest to disclose. GGS is an employee and shareholder of Pfizer Inc.

Funding

This study is funded by Pfizer. Medical writing support was provided by Neera Hobson PhD at Micron Research Ltd, Ely, UK, and was funded by Pfizer. Micron Research Ltd also provided data management services, which were funded by Pfizer.

Access to data

The data sets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Contribution

EU participated in data collection and interpretation, as well as drafting and reviewing the manuscript. GGS was involved in the study design, data interpretation and drafting and review of the manuscript. Medical writing support was provided by Micron Research Ltd, Ely, UK. All authors read and approved the final manuscript.

Acknowledgements

The authors would like to thank all participating investigators and laboratories and would also like to thank the staff at IHMA for their coordination of the study. Some of these data were presented in poster #P2503 at the 28th European Congress of Clinical Microbiology & Infectious Diseases, Madrid, Spain, 24 April 2018.

References

[1] Renteria MI, Biedenbach DJ, Bouchillon SK, Hoban DJ, Raghubir N, Sajben P, et al. *In vitro* activity of tigecycline against isolates collected from complicated skin and skin structure infections and intra-abdominal infections in Africa and Middle East countries: TEST 2007–2012. Diagn Microbiol Infect Dis 2014;79:54–9.

[2] Seaton RA, Gonzalez-Ruiz A, Cleveland KO, Couch KA, Pathan R, Hamed K. Real-world daptomycin use across wide geographical regions: results from a pooled analysis of CORE and EU-CORE. Ann Clin Microbiol Antimicrob 2016;15:18.

[3] Sowash MG, Uhlemann AC. Community-associated methicillin-resistant *Staphylococcus aureus* case studies. Methods Mol Biol 2014;1085:25–69.

[4] European Centre for Disease Prevention and Control (ECDC). Surveillance of antimicrobial resistance in Europe 2016. In: Annual report of the European Antimicrobial resistance Surveillance Network (EARS-Net). Stockholm: ECDC; 2017. Available at: https://ecdc.europa.eu/sites/portal/files/documents/AMR-surveillance-Europe-2016.pdf. [Accessed 22 August 2018].

[5] Garau J, Blasi F, Medina J, McBride K, Ostermann H, REACH study group. Early response to antibiotic treatment in European patients hospitalized with complicated skin and soft tissue infections: analysis of the REACH study. BMC Infect Dis 2015;15:78.

[6] The European Committee on Antimicrobial Susceptibility Testing (EUCAST). EUCAST addendum to Breakpoint Table v 7.1. 2017. Available at: http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/Addenda/Addendum_2017-07-14.pdf. [Accessed 18 June 2018].

[7] Kahlmeter G, EUCAST Steering Committee. EUCAST proposes to change the definition and usefulness of the susceptibility category 'Intermediate'. Clin Microbiol Infect 2017;23:894–5.

[8] The European Committee on Antimicrobial Susceptibility Testing (EUCAST). Breakpoint tables for interpretation of MICs and zone diameters. Version 8.0. 2018. Available at: http://www.eucast.org. [Accessed 18 June 2018].

[9] The European Committee on Antimicrobial Susceptibility Testing (EUCAST). Breakpoint tables for interpretation of MICs and zone diameters. Version 7.1. 2017. Available at: http://www.eucast.org. [Accessed 18 June 2018].

[10] Clinical and Laboratory Standards Institute (CLSI). Performance standards for antimicrobial susceptibility testing. 27th ed. CLSI supplement M100. Wayne, PA: CLSI; 2017.

[11] Clinical and Laboratory Standards Institute (CLSI). Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically, 10th ed. CLSI standard M07. Wayne, PA: CLSI; 2015.

[12] Alm RA, McLaughlin RE, Kos VN, Sader HS, Iaconis JP, Lahiri SD. Analysis of *Staphylococcus aureus* clinical isolates with reduced susceptibility to ceftaroline: an epidemiological and structural perspective. J Antimicrob Chemother 2014;69:2065–75.

[13] 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;70:2488–98.

[14] Das S, Li J, Iaconis J, Zhou D, Stone GG, Yan JL, et al. Ceftaroline fosamil doses and breakpoints for *Staphylococcus aureus* in complicated skin and soft tissue infections. J Antimicrob Chemother 2019;74:425–31.

[15] Biedenbach DJ, Alm RA, Lahiri SD, Reiszner E, Hoban DJ, Sahm DF, et al. *In vitro* activity of ceftaroline against *Staphylococcus aureus* isolated in 2012 from Asia-Pacific countries as part of the AWARE surveillance program. Antimicrob Agents Chemother 2015;60:343–7.

[16] Karlowsky JA, Biedenbach DJ, Bouchillon SK, Hackel M, Iaconis JP, Sahm DF. In vitro activity of ceftaroline against bacterial pathogens isolated from patients with skin and soft tissue and respiratory tract infections in African and Middle Eastern countries: AWARE global surveillance program 2012–2014. Diagn Microbiol Infect Dis 2016;86:194–9.

[17] Flamm RK, Jones RN, Sader HS. In vitro activity of ceftaroline tested against isolates from the Asia-Pacific region and South Africa (2011). J Glob Antimicrob Resist 2014;2:183–9.

[18] 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;71:162–9.

[19] Hoban D, Biedenbach D, Sahm D, Reiszner E, Iaconis J. Activity of ceftaroline and comparators against pathogens isolated from skin and soft tissue infections in Latin America—results of AWARE surveillance 2012. Braz J Infect Dis 2015;19:596–603.

[20] Clinical and Laboratory Standards Institute (CLSI). Performance standards for antimicrobial susceptibility testing, 29th ed. CLSI supplement M100. Wayne, PA: CLSI; 2019.