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In vitro activity of ceftaroline against Gram-positive and Gram-negative pathogens obtained from hospitalised skin infected patients in Germany, 2011–2012

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Introduction and Purpose

Ceftaroline (CPT), the active form of the new parenteral pro-drug CPT fosamil, has shown in vitro activity against Gram-positive and common Gram-negative pathogens, including methicillin-resistant *Staphylococcus aureus* (MRSA) isolates. However, it is not active against extended-spectrum-β-lactamase (ESBL)- and carbapenemase-producing Enterobacteriaceae as well as non-fermenters. CPT fosamil has been approved by the European Medicines Agency for treatment of adults with complicated skin and soft tissue infection (cSSTI) and community-acquired pneumonia in 2012 [1]. In vitro activity of CPT was determined in previous studies [2, 3], but extensive susceptibility data of CPT for German clinical isolates are scarce.

The purpose of this study was to assess the potency of CPT against a German collection of clinical isolates from patients with hospitalised cSSTIs prior to its clinical use.

Methods

Bacterial strains

Between October 2011 and April 2012, 19 laboratories across Germany were requested each to collect 100 non-duplicate Gram-positive and Gram-negative pathogens isolated from blood or relevant wound specimens. Bacterial species and phenotypes tested were methicillin-susceptible *Staphylococcus aureus* (MSSA), MRSA, various streptococcal species and ceftriaxone (CRO)-susceptible isolates of five common members of the Enterobacteriaceae family (*Escherichia coli, Enterobacter cloacae, Klebsiella oxytoca, K. pneumoniae, Proteus mirabilis*).

Susceptibility testing

Organisms were shipped to a coordinating laboratory (Antiinfectives Intelligence) for species confirmation and susceptibility testing. MICs of CPT and comparator drugs were determined by the microdilution method according to the standard ISO 20776-1 [4] and interpreted by EUCAST species-related clinical breakpoints, if available [5]. Test plates (TREK Sensititre GBAZD) for susceptibility testing were purchased from TREK Diagnostic Systems Inc. (Cleveland, Ohio, USA).

Molecular typing of MRSA strains

Clonal lineages of MRSA strains were identified by *spa*-gene sequencing at the Institute for Hygiene and Microbiology, University of Würzburg. *Spa*-typing is a valuable tool for tracking epidemic isolates [6].

Results

A total of 1,959 bacterial strains were analysed. The majority of isolates (n=1,129, 57.6%) were recovered from male patients. One-thousand-six-hundred and thirty-one (83.3%) and 193 (9.9%) isolates were obtained from patients on general wards and intensive care patients, respectively. The source of 135 (6.9%) strains was unknown. The majority of pathogens derived from wound specimens (n=1,618, 82.6%), followed by pus (n=135, 6.9%) and blood samples (n=85, 4.3%). Patients ranged in age from <1 to 102 years (median 62 years).

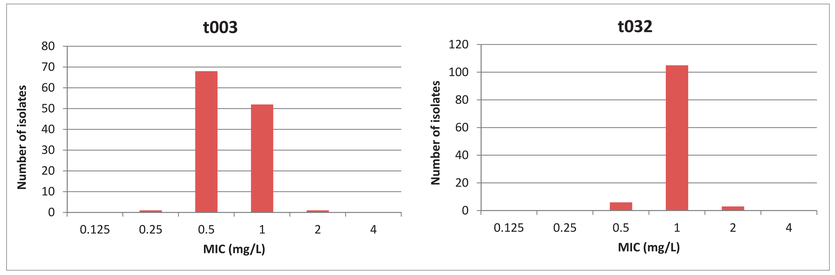
$MIC_{50/90}$ values as well as the rates of susceptible, intermediate and resistant isolates obtained for the antimicrobial agents are presented in the **Table**. All MSSA as well as 356/361 (98.6%) MRSA isolates were susceptible to CPT (MICs ≤1 mg/L). MICs of CPT for the five CPT-resistant strains were 2 mg/L, but turned out to be 1 mg/L (susceptible) in a second test. High resistance rates were found for erythromycin (75.6%) and levofloxacin (93.6%) against MRSA. One MRSA isolate was resistant to daptomycin. All staphylococci were susceptible to linezolid, tigecycline and vancomycin.

The highest MIC observed for CPT among streptococcal isolates was 0.031 mg/L. All streptococci were susceptible to penicillin, daptomycin, linezolid, vancomycin and tigecycline, while susceptibility rates for erythromycin and levofloxacin ranged from 74.9% to 100% and from 93.9% to 100%, respectively. Isolates of *S. intermedius* were susceptible to all antibiotics tested (data not shown).

Among the CRO-susceptible Enterobacteriaceae, all isolates of *E. cloacae* and *P. mirabilis* were susceptible to CPT (MICs ≤0.5 mg/L), while 2.6%, 1.8% and 4.5% of the *E. coli, K. oxytoca* and *K. pneumoniae* isolates, respectively, were resistant. Susceptibility rates of piperacillin-tazobactam were comparable to those of CPT, while resistance to imipenem was not detected, as expected.

Spa-typing of the 361 MRSA isolates revealed two non-typeable strains (0.6%). The remaining strains were associated with 65 different *spa*-types. Predominant *spa*-types were t003 (n=122; 33.8%) and t032 (n=114; 31.6%), also known as EMRSA-3 and EMRSA-15, respectively, and in Germany as Rhine Hesse MRSA and Barnim MRSA, respectively. Isolates belonging to *spa*-type t008 (n=19; 5.3%) were primarily found in the Southwest of Germany. Of interest, MICs of CPT for *spa*-type t003 isolates (peak MIC 0.5 mg/L) tended to be lower than those for *spa*-type t032 isolates (peak MIC 1 mg/L) (**Figure**).

Figure: MIC values of ceftaroline for MRSA isolates with *spa*-types t003 and t032



Conclusions

Based on the results of this surveillance study, CPT was active against pathogens associated with hospitalised cSSTIs in vitro, and CPT fosamil may represent a suitable option for the empiric treatment in clinical situations in which MRSA is suspected.

References

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Table: In vitro activity of ceftaroline und comparators against 1,953* bacterial isolates

Isolates (no. tested)	Drug	MIC_{50} (mg/L)	MIC_{90} (mg/L)	%S	%I	%R
MSSA (435)	Ceftaroline	0.25	0.25	100.0	–	0.0
	Daptomycin	0.5	0.5	100.0	–	0.0
	Erythromycin	0.25	≥8	87.1	0.2	12.6
	Levofloxacin	0.25	1	90.3	0.5	9.2
	Linezolid	1	1	100.0	–	0.0
	Tigecycline	≤0.125	0.25	100.0	–	0.0
	Vancomycin	1	1	100.0	–	0.0
MRSA (361)	Ceftaroline	1	1	98.6	–	1.4**
	Daptomycin	0.5	1	99.4	–	0.6
	Erythromycin	≥8	≥8	24.4	0.0	75.6
	Levofloxacin	≥8	≥8	6.4	0.0	93.6
	Linezolid	1	1	100.0	–	0.0
	Tigecycline	≤0.125	0.25	100.0	–	0.0
	Vancomycin	1	1	100.0	–	0.0
S. anginosus (65)	Ceftaroline	≤0.008	0.016	–	–	–
	Daptomycin	≤0.25	0.5	100.0	–	0.0
	Erythromycin	≤0.125	4	80.0	6.2	13.8
	Levofloxacin	0.5	1	100.0	0.0	0.0
	Penicillin	≤0.031	≤0.031	100.0	–	0.0
	Tigecycline	≤0.125	≤0.125	100.0	0.0	0.0
S. agalactiae (179)	Ceftaroline	≤0.008	0.016	–	–	–
	Daptomycin	≤0.25	0.5	100.0	–	0.0
	Erythromycin	≤0.125	≥8	74.9	0.0	25.1
	Levofloxacin	0.5	1	96.1	2.8	1.1
	Penicillin	≤0.031	0.063	100.0	–	0.0
	Tigecycline	≤0.125	≤0.125	100.0	0.0	0.0
S. constellatus (21)	Ceftaroline	≤0.008	0.016	–	–	–
	Daptomycin	≤0.25	0.5	100.0	–	0.0
	Erythromycin	≤0.125	≤0.125	100.0	0.0	0.0
	Levofloxacin	0.25	1	100.0	0.0	0.0
	Penicillin	≤0.031	≤0.031	100.0	–	0.0
	Tigecycline	≤0.125	≤0.125	100.0	0.0	0.0
S. dysgalactiae (91)	Ceftaroline	≤0.008	≤0.008	–	–	–
	Daptomycin	≤0.25	≤0.25	100.0	–	0.0
	Erythromycin	≤0.125	1	86.8	1.1	12.1
	Levofloxacin	0.5	1	97.8	2.2	0.0
	Penicillin	≤0.031	≤0.031	100.0	–	0.0
	Tigecycline	≤0.125	≤0.125	100.0	0.0	0.0
S. pyogenes (214)	Ceftaroline	≤0.008	≤0.008	–	–	–
	Daptomycin	≤0.25	≤0.25	100.0	–	0.0
	Erythromycin	≤0.125	≤0.125	94.4	0.0	5.6
	Levofloxacin	0.5	1	93.9	6.1	0.0
	Penicillin	≤0.031	≤0.031	100.0	–	0.0
	Tigecycline	≤0.125	≤0.125	100.0	0.0	0.0
E. coli, CRO-susc. (229)	Ceftaroline	0.125	0.5	97.4	–	2.6
	Imipenem	≤0.5	≤0.5	100.0	0.0	0.0
	Piperacillin-tazobactam	2	4	96.5	1.7	1.7
	Levofloxacin	≤0.125	≥8	79.5	1.3	19.2
	Tigecycline	≤0.125	0.5	100.0	0.0	0.0
E. cloacae, CRO-susc. (87)	Ceftaroline	0.125	0.5	100.0	–	0.0
	Imipenem	≤0.5	≤0.5	100.0	0.0	0.0
	Piperacillin-tazobactam	2	4	100.0	0.0	0.0
	Levofloxacin	≤0.125	≤0.125	100.0	0.0	0.0
	Tigecycline	0.25	0.5	100.0	0.0	0.0
K. oxytoca, CRO-susc. (55)	Ceftaroline	0.125	0.5	98.2	–	1.8
	Imipenem	≤0.5	≤0.5	100.0	0.0	0.0
	Piperacillin-tazobactam	2	2	98.2	1.8	0.0
	Levofloxacin	≤0.125	≤0.125	100.0	0.0	0.0
	Tigecycline	0.25	0.25	100.0	0.0	0.0
K. pneumoniae, CRO-susc. (89)	Ceftaroline	0.063	0.5	95.5	–	4.5
	Imipenem	≤0.5	≤0.5	100.0	0.0	0.0
	Piperacillin-tazobactam	2	8	94.4	1.1	4.5
	Levofloxacin	≤0.125	0.5	95.5	0.0	4.5
	Tigecycline	0.25	1	95.5	3.4	1.1
P. mirabilis, CRO-susc. (127)	Ceftaroline	0.063	0.25	100.0	–	0.0
	Imipenem	2	2	96.1	3.9	0.0
	Piperacillin-tazobactam	≤1	≤1	100.0	0.0	0.0
	Levofloxacin	≤0.125	2	89.0	6.3	4.7
	Tigecycline	2	4	33.9	41.7	24.4

Abbreviations: %-S, % susceptible strains; %-I, % intermediate strains; %-R, % resistant strains; CRO-susc., susceptible to ceftriaxone; *Only species comprising at least 20 isolates are listed; **Strains with an MIC of 2 mg/L of ceftaroline were re-tested and then found to be susceptible (1 mg/L).