#P0184

28th ECCMID
Madrid, Spain
21-24 April, 2018

Cefiderocol, a Novel Siderophore Cephalosporin: *In Vitro* Activity against Global Isolates of *Stenotrophomonas maltophilia* Isolated Globally

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ABSTRACT

Background: *Stenotrophomonas maltophilia* is a Gram-negative, non-fermentative, environmental bacterium that has emerged as an important cause of health care associated infection. *S. maltophilia* colonizes mucosal surfaces such as the respiratory and urinary track and is associated with implanted central venous catheters. Therapeutic options for *S. maltophilia* infections are scarce, limited to sulfamethoxazole-trimethoprim and colistin in part due to chromosomally mediated resistance to all beta-lactams, Cefiderocol (S-649266) is a novel siderophore cephalosporin for injection. Cefiderocol has potent activity against a broad range of Gram-negative pathogens, including multidrug-resistant strains of *Pseudomonas aeruginosa* and *Acinetobacter baumannii*. In this study, *in vitro* antibacterial activity of cefiderocol was evaluated against global clinical isolates of *S. maltophilia* collected as part of SIDERO-WT-2015 and SIDERO-CR-2014/16 surveillance studies.

Materials and Methods: A global collection of *S. maltophilia* isolates were identified and had susceptibility testing performed centrally at IHMA, Inc. (Schaumburg, USA). In all, 557 strains were tested, with the majority from respiratory tract specimens or blood [sputa (n=167; 30 %), endotracheal aspirates (n=122; 21.9 %), broncho alveolar lavages (n=81; 14.5 %) blood (n=38; 6.8 %)]. Susceptibility was determined by broth microdilution according to the Clinical and Laboratory Standard Institute guidelines. For the MIC determination of cefiderocol, iron-depleted CAMHB was used. Cefepime, ceftazidime-avibactam, ceftolozane-tazobactam, ciprofloxacin, colistin and meropenem were used as reference compounds. Sulfamethoxazole-trimethoprim was not included as a reference compound. Test isolates were collected from global countries in 2015 to 2016 by IHMA.

Results: Cefiderocol showed potent *in vitro* activity against *S. maltophilia*, with MIC_{90} of 0.5 mg/L, and 99.6% of strains were inhibited at ≤4 mg/L. Other β-lactams such as ceftazidime-avibactam, ceftolozane-tazobactam, and meropenem were not effective against *S. maltophilia* (MIC_{50}/MIC_{90}: 16/64, 16/>64, >64/>64 mg/L, respectively). The MIC_{50}/MIC_{90} of colistin was 1/>8 mg/L, and 28% of the isolates showed colistin MIC of >2 mg/L.

Conclusions: Cefiderocol showed potent antimicrobial activity against *S. maltophilia* including colistin resistant isolates. These data suggest that cefiderocol is a promising antibiotic for the treatment of infections caused by this problematic pathogen.

INTRODUCTION

Cefiderocol is a novel parenteral catechol-substituted siderophore cephalosporin that is active against carbapenem-resistant Gram-negative bacteria (1, 2). In this study, we evaluated the *in vitro* activity of cefiderocol and comparators against *Stenotrophomonas maltophilia* clinical isolates collected from a variety of countries in the Americas, Europe and Asia-Pacific regions.

MATERIALS AND METHODS

Test organisms
All *S. maltophilia* isolates (N = 557), which were obtained from either of two surveillance studies (SIDERO-WT-2015 study and SIDERO-CR-2014/2016 study). In SIDERO-WT-2015 study, 340 strains of *S. maltophilia* were among a total of 8954 Gram-negative pathogens isolated in 2015 Nov to 2016 Oct from North America and EU countries. In SIDERO-CR-2014/2016 study, 217 strains of *S. maltophilia* were among a total of 1873 Gram-negative pathogens isolated in 2014 to 2016 from global countries. Tables 1 and2 show the region and body location information of test strains in this study.

Compound
Cefiderocol, cefepime, ceftazidime/avibactam, ceftolozane/tazobactam, ciprofloxacin, colistin and meropenem were used.

MIC determination
Broth microdilution testing was done according to Clinical and Laboratories Standard Institute guidelines (3, 4). To test cefiderocol, the CLSI approved methodology using iron-depleted cation-adjusted Muller-Hinton Broth (ID-CAMHB) was employed. The cefiderocol MIC was read as the first drug well in which the growth was significantly reduced (i.e. a button of < 1 mm or light/faint turbidity) relative to the growth observed in the growth control. The recommended CLSI reference quality control (QC) *Escherichia coli* ATCC 25922 and *Pseudomonas aeruginosa* ATCC 27853 strains were used throughout the testing.

Table 1. Body site distribution of tested isolates

Body Location		Number of test strain	Ratio (%)	Total (%)
Respiratory	Sputum	167	30.0	72.7
	Endotracheal aspirate	122	21.9	
	Bronchoalveolar lavage	81	14.5	
	Bronchial brushing	25	4.5	
	Other	10	1.8	
Skin	Wound	21	3.8	7.0
	Other	18	3.2	
Blood		38	6.8	6.8
Gastrointestinal	Gall Bladder	19	3.4	5.7
	Other	13	2.3	
Body fluids	Peritoneal	14	2.5	3.9
	Other	8	1.4	
Urinary	Urine	18	3.2	3.6
	Other	2	0.4	
Other	Unknown	1	0.2	0.2
Total		**557**	**100**	**100**

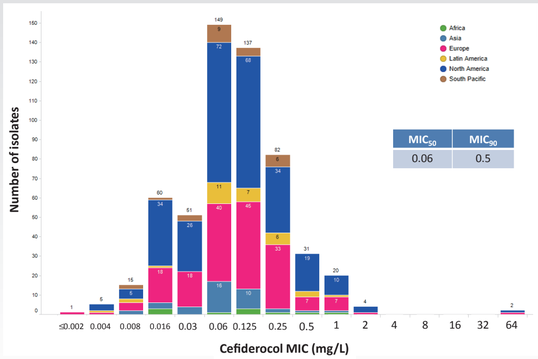
S. maltophilia were isolated: 72.7 % from respiratory, 7.0 % from skin, and 6.8 % from blood.

Table 2. Distribution of isolates tested be region

Region	Number of test strains	% of Total
Europe	176	31.6
North America	275	49.4
Latin America	32	5.7
Asia	39	7.0
South Pacific	25	4.5
Africa	10	1.8
Total	**557**	**100**

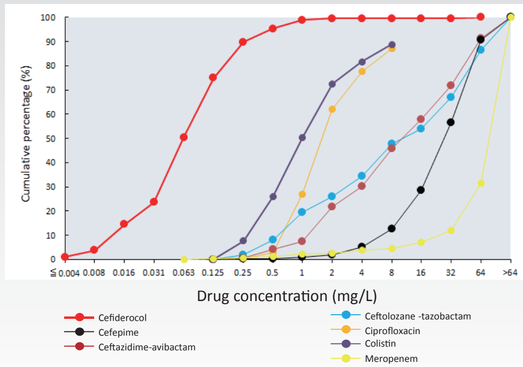
RESULTS

Figure 1. Cefiderocol MIC distribution against 557 *S. maltophilia*



99.6% of *S. maltophilia* isolates had cefiderocol MIC values of ≤4 mg/L.

Figure 2. Cumulative percentage of cefiderocol MIC against 557 *S. maltophilia* from global countries.



- Cefiderocol MIC_{90} values were 0.5 mg/L for *S. malthophilia.*
- The *in vitro* activity of cefiderocol was more active than those of comparator tested.

Table 3. Summary of susceptibility percentage of cefiderocol

Organism	MIC_{50}/MIC_{90}	MIC range	Ratio (%)		
			Cefiderocol MIC : ≤4 mg/L	Colistin % S MIC ≤2 mg/L	Ciprofloxacin % S MIC ≤0.5 mg/L
All *S. maltophilia* (N=557)	0.06/0.5	0.002-64	99.6	72.5	2.9
S. maltophilia (EU) (N=176)	0.06/0.25	0.002-64	99.4	77.3	3.4
S. maltophilia (US) (N=194)	0.06/0.5	0.002-64	99.5	73.7	4.1
Ciprofloxacin-NS *S. maltophilia* #1 (N=541)	0.06/0.5	0.002-64	99.6	71.7	0
Colistin-NS *S. maltophilia* #2 (N=153)	0.12/0.5	0.002-64	98.7	0	0

#1: Ciprofloxacin non-susceptible *S. malthophilia* was defined strains had an MIC value of ≥1 mg/L for the ciprofloxacin.
#2: Colistin non-susceptible *S. malthophilia* was defined strains had an MIC value of ≥4mg/L for the colistin.
#1 , #2: Selection criteria was used by applying EUCAST breakpoint for *P. aeruginosa.*

- Even against ciprofloxacin non-susceptible and colistin non-susceptible *S. maltophilia*, cefiderocol showed activity against 99.6 and 98.7 % of the isolates at MIC of ≤ 4 mg/L, respectively.

CONCLUSIONS

- Cefiderocol showed potent *in vitro* activity against global isolates of *S. maltophilia*.
- Cefiderocol displayed a potent activity against colistin-and/or ciprofloxacin-resistant *S. maltophilia*.

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