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Session: P-66. Resistance Mechanisms

Background. Cefiderocol (CFDC) is a novel siderophore cephalosporin with efficacy against Gram-negative (GN) bacteria, including carbapenem-resistant Enterobacterales and non-glucose-fermenters such as *Pseudomonas aeruginosa and Acinetobacter baumannii*. In consecutive multinational surveillance (SIDERO-WT) studies (2014–2017), CFDC demonstrated activity with minimum inhibitory concentrations (MICs) of ≤4 mg/mL against 99.4% of 28,629 GN clinical isolates. We conducted molecular characterization of 161 isolates with CFDC MICs >4 mg/mL from the SIDERO-WT studies.

Methods. A total of 161 isolates underwent whole genome sequencing by Illumina Hiseq. Analyses were done using the CLC genomics workbench (Qiagen) for possible resistance-related genes (e.g. β-lactamases, porin channels or penicillin-binding protein genes) and some TonB-dependent siderophore uptake receptor genes (*fiu*, *cir*, *piu*, *pir*). Fiu and Cir in *Escherichia coli* and Piu in *P. aeruginosa* are the iron transporters involved in CFDC transport.

Results. Of 161 isolates with CFDC MIC >4 mg/mL, 128 were *A. baumannii*, 22 Enterobacterales, 7 *Burkholderia multivorans*, 2 *P. aeruginosa,* and 2 *Stenotrophomonas maltophilia*. Genes encoding PER/VEB extended-spectrum β-lactamases and NDM-type metallo-β-lactamases were detected in some isolates, but other β-lactamase genes (*bla*) were not shown to be linked to high CFDC MICs. bla_{PER}/bla_{VEB} were found only in *A. baumannii* and bla_{NDM} was found in *A. baumannii* and *Klebsiella pneumoniae*. In 128 *A. baumannii* isolates, 103 harbored PER or VEB, including PER positive isolates from Russia (n=87) and Turkey (n=6) and 4 VEB positive isolates from USA. Nine NDM-positive isolates (7 *K. pneumoniae*, 2 *A. baumannii*) were found. Disruption of iron transport genes was also detected in some isolates, including *piuA* (11 *A. baumannii*, 1 *P. aeruginosa*), *pirA* (2 *A. baumannii*), and *fiuA* (4 *B. multivorans*, 1 *Proteus mirabilis*). No *cir* homologs were found in 2 *B. multivorans*.

Conclusion. PER and NDM could reduce susceptibility to CFDC, as such isolates have been seen in some countries. Iron transporter disruption was also observed in some isolates with high CFDC MICs; the contribution of these deficiencies in *A. baumannii* and *B. multivorans* requires further study.

Disclosures. Yoshinori Yamano, PhD, Shionogi & Co., Ltd. (Employee) Miki Takemura, MSc, Shionogi & Co., Ltd. (Employee) Krystyna Kazmierczak, PhD, Shionogi & Co., Ltd. (Independent Contractor) Mark G G. Wise, PhD, Shionogi & Co., Ltd. (Independent Contractor) Daniel F. Sahm, PhD, IHMA (Employee)Pfizer, Inc. (Consultant)Shionogi & Co., Ltd. (Independent Contractor) Roger Echols, MD, Shionogi Inc. (Consultant)

1453. PBP2, PBP2a and PBP4 Clone-specific Polymorphisms are not Associated to Ceftaroline (CPT) Susceptibility in Chilean Clinical Isolates of Methicillin-Resistant *Staphylococcus aureus* (MRSA)

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Background. CPT is a last-generation cephalosporin active against MRSA due to its affinity for PBP2a. CPT-resistance (CPT-R) is well-described, with mutations in the active transpeptidase domain of PBP2a associated to high-level resistance. The accumulation of changes in the non-penicillin-binding domain of PBP2a has been linked to elevations of the minimal inhibitory concentration (MIC) to CPT to levels around 2-4ug/mL. PBP4 and PBP2 have also been implicated as potentially relevant *mecA*-independent mechanisms of CPT-R. We recently reported high rates of CPT-non-susceptibility in clinical MRSA strains from Chile. However, the mutational landscape of PBPs in clinical MRSA isolates from Chile and its relation to CPT susceptibility has not been assessed.

Methods. We analyzed 180 MRSA isolates collected from 2000-2018 in Santiago, Chile. Identification was confirmed by MALDI-TOF and methicillin resistance with cefoxitin disk-diffusion. CPT susceptibility was performed by BMD following CLSI-2019 guidance. Whole-genome sequencing was performed for all isolates; the mutational profile of PBPs was determined using reference sequences for PBP2 (AGY89563.1), PBP2a (NG_047938.1) and PBP4 (X91786.1).

Results. All isolates were phenotypically-confirmed MRSA and harbored *mecA*. The MIC_{50}/MIC_{90} by BMD was 2/2μg/dL; only 71 (39%) isolates were CPT-susceptible (MIC <1μg/mL). Most isolates belonged to ST5/SCC*mec*I (70%,126/180), ST105/SCCmecII (10%,18/180) and ST8/SCC*mec*IV (5%, 9/180). All ST5/SCC*mec*I isolates carried the mutations in PBP2 (Y156D), PBP2a (M122I and E150K), and PBP4 (T189S, L234H, and T409A); CPT-susceptibility among ST5/SCC*mec*I was only 22%. On the other hand, all ST105/SCC*mec*II isolates had mutations in PBP2 (S707L) and PBP4 (T189S, L234H, and T409A) and exhibited a higher CPT-susceptibility rate (67%). All 9 isolates belonging to the ST8/SCC*mec*IV lineage harbored a non-coding mutation in PBP2a (g-6t) and the previously observed L234H change in PBP4. Importantly, no association between specific polymorphisms and MIC to CPT was found.

Table 1. PBPs mutations compared to CPT MICs by MLST and SCCmec

MLST	SCCmec	Mutational profile			MIC					
		PBP2	PBP2a	PBP4	0.125	0.25	0.5	1	2	4
ST 5	SCCmec I	Y156D	M122I/E150K	T189S, L234H, T409A	1		5	22	86	12
ST 5	SCCmec IV	-	g-6t	T189S, L234H, T409A		1				
ST 105	SCCmec II	S707L	-	T189S, L234H, T409A		1	8	3	3	3
ST 225	SCCmec II	S707L	-	T189S, L234H, T409A			1	1		
ST 125	SCCmec IV		g-6t	T189S, T409A			1	1		
ST 72	SCCmec IV	-	g-6t	T25A, T189S, P235S, Q383K, T409A			4		2	
ST 72	SCCmec VI	-	g-6t	T25A, T189S, P235S, Q383K, T409A			3		1	
ST 1472	SCCmec IV	-	g-6t	T25A, L234H, T409A			1			
ST 22	SCCmec IV		g-6t	T25A, D98E, E398A, T409A		1				
ST 2802	SCCmec IV	-	g-6t	P235S			2			
ST 2039	SCCmec III	-	-	P235S				1		
ST 923	SCCmec IV	-	g-6t	P235S		1	1			
ST 8	SCCmec IV	-	g-6t	L234H			8		1	
ST 239	SCCmec III	-	-	L234H				3	1	
ST UN	SCCmec IV	-	g-6t	L234H			1			

Conclusion: Changes in the studied PBPs were frequent among MRSA circulating in Chile and were conserved among different genetic backgrounds. However, these changes were not associated with the level of CPT MIC among these isolates.

Disclosures. **Cesar A. Arias, MD, MSc, PhD, FIDSA**, **Entasis Therapeutics** (Scientific Research Study Investigator)**MeMed** (Scientific Research Study Investigator)**Merck** (Grant/Research Support)

1454. Plazomicin Activity against *Enterobacterales* Isolates Producing Extended-Spectrum β-Lactamases (ESBLs), Carbapenemases, and Aminoglycoside-Modifying Enzymes (AMEs) from United States (US) Hospitals

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Session: P-66. Resistance Mechanisms

Background. Limited therapeutic options are available for the treatment of multidrug resistant (MDR) organisms. Plazomicin (PLZ) is an aminoglycoside developed to overcome common aminoglycoside-resistance mechanisms. We evaluated the activity of PLZ and comparators against *Enterobacterales* isolates collected in 2018-2019 carrying genes encoding ESBLs, carbapenemases, and AMEs.

Methods. Among 3,899 *Enterobacterales* isolates from US hospitals susceptibility (S) tested using reference broth microdilution method, 619 isolates from selected species displaying elevated MIC values for cephalosporins, carbapenems and/or resistance (CLSI criteria) to amikacin (AMK), gentamicin (GEN) and tobramycin (TOB) were submitted to whole genome sequencing for detection of resistance genes.

Results. Most isolates producing ESBLs (n= 418) carried bla_{CTX-M} (n= 386). The activity of PLZ (99.3% susceptible [S]) was comparable to that of colistin and higher than other comparators against ESBL isolates (Figure). AMK inhibited 96.4% of the isolates and GEN and TOB inhibited 57.9% and 43.5%, respectively. Only 34 isolates produced carbapenemases, including 19 KPC-2, 10 KPC-3, 1 each with VIM-1, OXA-181, NDM-5 and KPC-2-like plus 1 isolate carrying the genes encoding NDM-1 and OXA-232. These isolates displayed higher resistance rates to comparators and only PLZ, and tigecycline inhibited >90% of these isolates. AMK and GEN inhibited 67.6% and 55.9% of these isolates, respectively. PLZ was active against 97.7% of isolates carrying AME genes (n= 306) that carried *aac(6')-Ib-cr* (n =177), *aac(3)-IIa* (n = 159) and *aac(3)-IId* (n =81), among others. Most of these isolates were resistant to GEN and TOB (only 10.8-14.1% S), but 92.8% were S to AMK. Three *K. pneumoniae* isolates carried 16S rRNA methyltransferases, 1 *armA* (also harboring NDM-1) and 2 *rmtB1*.

Conclusion. The activity of PLZ against *Enterobacteriaceae* isolates carrying AMEs, ESBLs, and carbapenemases was greater than the activity of other aminoglycosides tested and comparable to those of tigecycline and colistin against carbapenemase-producing organisms. Isolates carrying genes encoding ESBLs, AMEs and carbapenemases are usually MDR and PLZ had activity against these organisms collected in the US.