underscores the important role WGS plays in identifying new mechanisms of antimicrobial resistance.

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607. Scope and Predictive Genetic/Phenotypic Signatures of "Bicarbonate [$NaHCO_3$]-Responsivity" and β-Lactam Sensitization among Methicillin-Resistant *Staphylococcus aureus* (MRSA)

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Background. Selected MRSA strains become susceptible to β-lactams (e.g., oxacillin [OX]; cefazolin [CFZ]) in vitro when tested in a standard medium (cation-adjusted Mueller–Hinton Broth; CA-MHB) supplemented with $NaHCO_3$ ("$NaHCO_3$-responsivity"). In vivo activity of β-lactams was demonstrated for MRSA strains with this phenotype in a rabbit endocarditis model (Ersoy et al Antimicrob Agents Chemother 2019). The current study was designed to: (i) determine the prevalence of the NaHCO3-responsive phenotype in a large collection of clinical MRSA isolates; and (ii) identify genetic and phenotypic predictors of this phenotype. ***Methods.*** 58 recent MRSA bloodstream isolates representing contemporary clonal complex (CC) genotypes were screened for the $NaHCO_3$-responsive phenotype by broth microdilution MICs in CA-MHB, with or without $NaHCO_3$ supplementation (25–44 mM).

Methods. 58 recent MRSA bloodstream isolates representing contemporary clonal complex (CC) genotypes were screened for the NaHCO3-responsive phenotype by broth microdilution MICs in CA-MHB, with or without NaHCO3 supplementation (25–44 mM).

Results. 43/58 (74.1%) and 21/58 (36.2%) were rendered susceptible to CFZ and OX, respectively, in the presence of $NaHCO_3$; 20 of the 21 OX-susceptible strains were also susceptible to CFZ in the presence of $NaHCO_3$. High baseline β-lactam MICs (i.e., MICs in CA-MHB alone ≥64 μg/mL) was not predictive of $NaHCO_3$ responsivity. The CC8 genotype was correlated with $NaHCO_3$ responsivity for OX, but not CFZ ($P < 0.05$).

Conclusion. The $NaHCO_3$-responsive phenotype is relatively common for both OX and especially CFZ among clinical MRSA isolates. Identification of specific genetic factors linked to this phenotype remains ongoing. Confirmation in relevant animal models that this phenotype is predictive of β-lactam efficacy *in vivo* could provide a solid foundation for a paradigm shift in antimicrobial susceptibility testing of MRSA.

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608. Emerging Methicillin Resistance Mechanism in *mec* Gene-Negative Staphylococci not Detected by Reference Methods

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Background. B-lactam resistance in Staphylococci is mediated by *mec* genes usually diagnosed by disc diffusion Cefoxitin test (DDFOX) and PCR testing. Here, we report methicillin-resistant *Staphylococcus lugdunensis* and *Staphylococcus aureus* strains lacking *mec* gene misdiagnosed by reference methods. Since the strains are not B-lactamase hyperproducers we investigated the molecular basis of the methicillin resistance.

Methods. We tested 2 *S. lugdunensis* isolates (SL1, SL2) collected from distinct blood cultures of the same patient and 2 *S. aureus* isolates (SA1, SA2): (i) by DDFOX, (ii) for Oxacillin MIC by agar dilution (AD), (iii) by VITEK®2 (bioMérieux) for Oxacillin MIC (V2 OXA) and Cefoxitin Screen Test (V2 OXSF), (iv) for *mec*A, B, C genes by PCR and (v) by whole-genome sequencing (WGS).

Results. The 4 isolates were methicillin susceptible by DD FOX and *mec* negative. However, all the isolates displayed variable results for V2 OXA MIC (0.5 to ≥4 mg/L) and for V2 OXSF (POSITIVE, NEGATIVE). For SL1 and SL2 isolates, the V2 OXSF growth curve atypical pattern has led to investigating the OXSF wells. The plates inoculated with the broth extracted from the OXSF well showed 2 colony morphotypes (small "P" and regular "G") for both isolates. The small colonies (SL1P, SL2P) were Oxacillin resistant (V2 OXA MIC≥4; AD MIC = 4) and V2 OXSF POSITIVE whereas the regular colonies (SL1G, SL2G) were Oxacillin susceptible (V2 OXA MIC = 2; AD MIC = 0.5) and V2 OXSF NEGATIVE. The 4 morphotypes were cefoxitin susceptible by DDFOX and *mec* negative. Interestingly, WGS revealed a GdpP truncation in the N-terminal domain only found in *S. lugdunensis* small colonies (SL1P, SL2P) phenotypically resistant to Oxacillin. GdpP is a cyclic diadenosine monophosphate phosphodiesterase enzyme which function is the hydrolysis of a signaling nucleotide.

Conclusion. We described *mec* negative *S. lugdunensis* and *S. aureus* strains expressing heterogeneous methicillin resistance detected by the VITEK2 OXSF test. *S. lugdunensis* subpopulation of small colonies resistant to oxacillin is associated with a truncation of GdpP protein previously described in *S. aureus*. Interestingly GdpP loss of function in Staphylococci is associated with a reduced growth and may arise as a result of the selective pressure of exposure to B Lactams.

Disclosures. **All authors:** No reported disclosures.

609. Differing Genotypic Contexts Between *E. coli* and *A. baumannii* Modulate the Role of blaADC-7 in the Development of Antibiotic Collateral Sensitivity

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Background. Antibiotic resistance is a global health crisis. While persistent drug discovery of novel antibiotics has previously been relied upon to thwart resistance, evolution inevitably perseveres. While genes conferring antibiotic resistance have previously been characterized, it is unclear how varying genetic contexts can change the antibiotic resistance phenotype a given gene confers.

Methods. The DH10B strain of *E. coli* was transformed with a bla_{ADC-7} plasmid. In 12 evolutionary replicates, the modified *E. coli* strain and a clinical strain of *A. baumannii* containing the same resistance gene were passaged daily for 10 days on cefepime gradient agar plates with gradually increasing concentrations of cefepime. MICs of cefepime and a diverse set of 15 other drugs were determined for the parental strains and after the final passage passage. MIC of cefepime after intermediary passages were determined for select replicates. Lastly the bla_{ADC-7} gene after the final passage was sequenced.

Results. At the end of 10 passages, collateral sensitivity in *A. baumannii* was observed to tigecycline and fosfomycin in 5 and 6 replicates respectively, out of 12 total. 4 out of 12 *E. coli* replicates displayed collateral sensitivity to minocycline (Figure 1). In the third *E. coli* replicate, Sanger sequencing revealed a novel S286R mutation in bla_{ADC-7} appearing in passage seven which preceded a several log fold increase in the MIC of cefepime (Figures 2 and 3). No additional mutations were found in the other evolutionary replicates.

Conclusion. Patterns of resistance varied among antibiotics of the same class, (e.g., tetracyclines, fourth-generation cephalosporins) in both *E. coli* and *A. baumannii*; however, *A. baumannii* expressed less widespread collateral resistance than *E. coli*. A previously undiscovered S286R mutation in bla_{ADC-7} coincided with a pronounced increased in resistance to cefepime. Further studies are required to determine whether this mutation gives rise to a structural change in the protein product. Given that no other mutations were found, resistance to cefepime and subsequent collateral resistance to other antibiotics may have developed due to epigenetic changes or mutations outside the bla_{ADC-7} genes. Indeed, future experiments with whole-genome sequencing may reveal such changes.

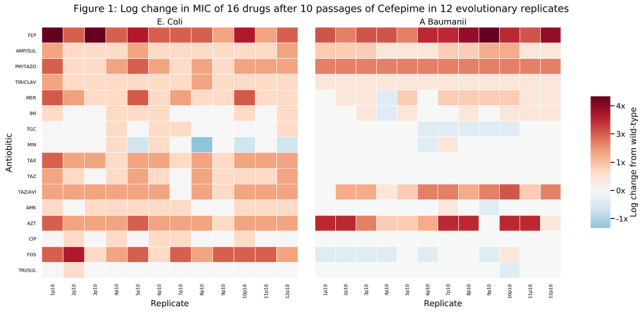


Figure 2: MIC of cefepime for *E. coli* replicate 3

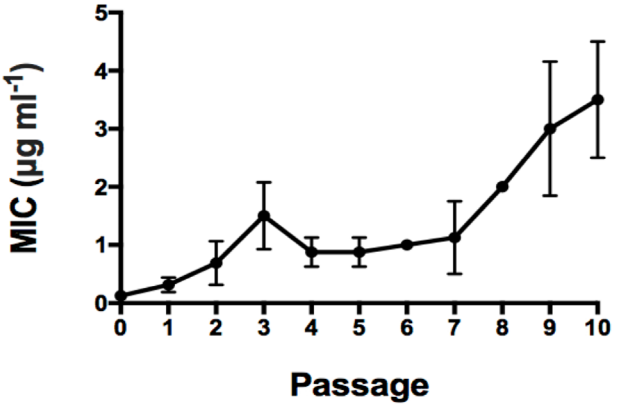
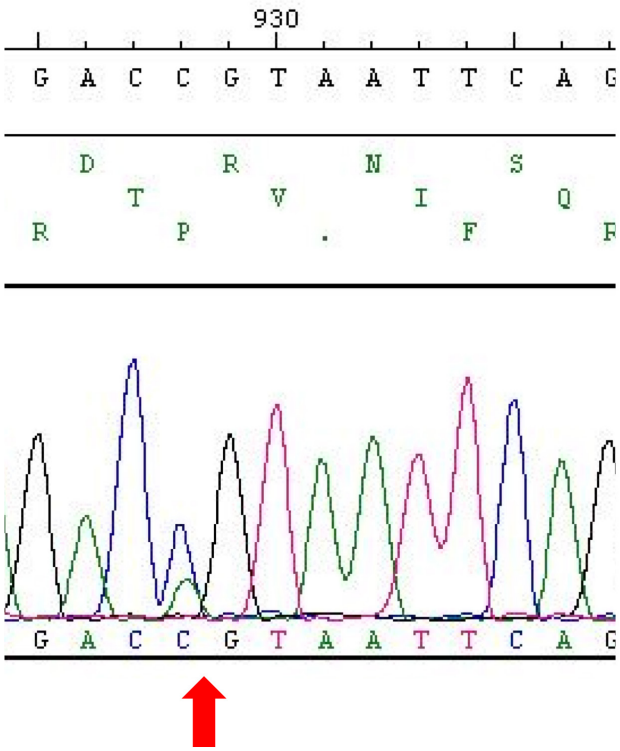


Figure 3: Sanger sequencing of *E. coli* 3p7



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610. Meropenem-vaborbactam (MV) *In Vitro* Activity Against Carbapenem-Resistant *Klebsiella pneumoniae* (CRKP) Isolates with Outer Membrane Porin Gene Mutations

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Background. Vaborbactam is a cyclic boronic acid β-lactamase inhibitor (BLI) developed to potently inhibit Ambler class A&C enzymes, including KPC carbapenemases. Metallo-β-lactamases (MBL) and some Class D oxacillinases (OXA) are not inactivated by vaborbactam. Meropenem-vaborbactam (MV) was recently approved for the treatment of carbapenem-resistant Enterobacteriaceae complicated urinary tract infections. Recent studies have identified outer membrane porin (Ompk35 and -36) mutations in *Klebsiella pneumoniae* (KP) as a mechanism of decreased susceptibility to MV. We evaluated the activity of MV against a historical cohort of *KP* clinical isolates with these porin gene mutations.

Methods. WGS of carbapenem-resistant *KP* clinical isolates was performed and those harboring mutations in Ompk35 or Ompk36 were selected for testing. Strain *KP* ATCC BAA-1705 was used as a positive control. Meropenem and MV minimum inhibitory concentrations (MIC) were determined by broth microdilution (BMD) in custom 96-well plates (ThermoFisher Scientific) with a constant 8 μg/mL vaborbactam concentration. The MIC of ceftazidime–avibactam (CZA) was determined by standard BMD reference methods and interpreted according to CLSI criteria.

Results. A total of 105 *KP* isolates with either partial or complete mutations in outer membrane porin genes were included in the analysis. All isolates were resistant to Meropenem. The median MV MIC was 0.03 μg/mL (range, 0.015 to >16 μg/mL). Eleven isolates (10.4%) were resistant to MV. Sixteen additional isolates (16.1%) demonstrated higher than expected MV MICs ranging from 1 to 4 μg/mL. Only 1/11 resistant isolates harbored a gene for MBL production. Gene mutations in bla_{KPC} were not detected. See Table 1 for characteristics of resistant isolates.

Conclusion. Resistance and decreased susceptibility to MV is demonstrated in a historical cohort of *KP* clinical isolates dating back to 2013. WGS reliably identifies porin variants secondary to gene mutations in Ompk35 and Ompk36 as the underlying mechanism of decreased susceptibility. CZA appears to retain activity against these isolates. Caution should be exercised regarding the empiric use of MV against increasingly resistant *KP* as a result of non-β-lactamase-mediated mechanisms.

Table 1. Whole genome sequencing and MICs of MV resistant isolates

		MIC (μg/ml)			Typing	Enzymes	Outer membrane porin variant	
Strain	Date	MV	MEM	CZA	MLST	β-lactamase	OmpK35	OmpK36
1	2012	>16/8	>8	2/4	ST-258	KPC-2; SHV-160	FS 121insG	ins Gly134-Asp135
2	2015	>16/8	>8	2/4	ST-258	KPC-2; SHV-160	FS 121insG	WT
3	2017	>16/8	>8	>64	ST-147	NDM-5; OXA-181; CTXM-15; SHV-11	Partial FS	ins Asp135, Thr136
4	2014	16/8	>8	1/4	ST258	KPC-2; SHV-160	FS 121insG	ins Gly134-Asp135
5	2013	16/8	>8	1/4	ST-258	KPC-2, SHV-160	FS 121insG	ins Gly134-Asp135
6	2014	4/8	>8	1/4	ST-258	KPC-2; SHV-160	FS 121insG	ins Gly134-Asp135
7	2013	16/8	>8	1/4	ST-258	KPC-2, SHV-11	FS 121insG	ins Gly134-Asp135
8	2013	>16/8	>8	0.5/4	ST-258	KPC-2; SHV-160	FS 121insG	WT
9	2013	8/8	>8	1/4	ST-258	KPC-2, SHV-160	FS 121insG	ins Gly134-Asp135
10	2013	8/8	>8	4/4	ST-258	KPC-2; SHV-160	FS 121insG	ins Gly134-Asp135
11	2017	>16/8	>8	8/4	ST-258	KPC-2; SHV-11; SHV-12	FS stop aa89	ins Gly134-Asp135

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611. Fosfomycin Resistance of Multidrug-Resistant *Escherichia coli* and Mechanisms of Fosfomycin Resistance

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Background. Fosfomycin is one of the antibiotics that may be a candidate for the next-generation antimicrobial agents againt multidrug-resistant bacteria. To date, it is known that the resistance rate is not high for *Escherichia coli*. However, it is necessary to update the fosfomycin resistance rates in *E. coli* according to the studies that extended spectrum β-lactamase (ESBL) producing *E. coli* strains are highly resistance to fosfomycin. We evaluated the resistance rate of fosfomycin, the resistant mechanism of fosfomycin in *E. coli*, and the activity of fosfomycin against susceptible and resistant strains of *E. coli*.

Methods. A total of 283 clinical isolates was collected from patients with *Escherichia coli* species during the period of January 2018 to June 2018, in three tertiary hospitals of Republic of Korea. *In vitro* antimicrobial susceptibility tests were performed in all E. coli isolates using the broth microdilution method according to the Clinical and Laboratory Standard Institute (CLSI). Multilocus sequence typing (MLST) of the Oxford scheme was conducted to determine the genotypes of *E. coli* isolated. Fosfomycin genes were investigated for all fosfomycin-resistant *E. coli* strains.

Results. The overall resistance rate to fosfomycin was 10.2%, compared with 53.4%, 46.3%, 41.3%, 31.1%, 10.6%, 2.5%, and 2.1% for ciprofloxacin, cefixime, cefepime, piperacillin/tazobactam, colistin, ertapenem, and amikacin, respectively. The 29 fosfomycin-resistant isolates did not show a clonal pattern on the phylogenetic tree. *MurA* and *glp* genes were identified in all strains. *FosA3* were identified in two strains and *uhp* gene were identified in 4 strains. In time-kill curve studies, fosfomycin was more bactericidal than cefixime against all sensitive *E. coli* strain. Morever, fosfomycin was more bactericidal than piperacillin/tazobactam against ESBL-producing *E. coli* strain.

Conclusion. The resistant rate of fosfomycin to *E. coli* is still low. Fosfomycin was active against *E. coli* including ESBL producing strains.

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612. Molecular Mechanisms Leading to Ceftolozane–Tazobactam Resistance in Clinical Isolates of *Pseudomonas aeruginosa* from Five Latin American Countries

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