in each direction and is presented within state boundaries. Facility geocodes were masked from public display for confidentiality. City names were added for orientation. The mapping depicts regional differences, such as 2015 ampicillin susceptibilities ranging 55–64% (Figure 1). The maps provide a preliminary susceptibility prediction in areas where no AMR data were available. Average susceptibilities were compared across 2009, 2013, and 2015 to map areas with the highest rates of AMR change.

**Conclusion.** The described mapping provides a novel visualization of AMR across Wisconsin. The maps created will be utilized in continued efforts to improve the functionality of AMR data in clinical practice to optimize antimicrobial choice.

### Figure 1: Interpolated Wisconsin *Escherichia coli* susceptibility to ampicillin

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

### 696. Mechanism of Cefiderocol high MIC mutants obtained in non-clinical FoR studies

Akinobu Ino, PhD; Toru Nishikawa, PhD; Ryuta Ishii, MS; Miho Kuroda, PhD; Yoshino Ishioka, MS; Naoko Kurihara, MS; Ikeue Sakikiwa, PhD; Takeshi Ota, PhD; Masatomo Rokushima, PhD; Masatsugu Tsuji, PhD; Takafumi Sato, PhD; and Yoshiyuki Yamano, PhD. Drug Discovery and Disease Research Laboratory, Shionogi & Co., Ltd., Osaka, Japan; Shionogi & Co., Ltd., Toyonaka, Japan; Shionogi & Co., Ltd., Osaka, Japan.

**Session:** 67. Resistance Mechanisms: Gram-Negative

**Thursday, October 4, 2018: 12:30 PM**

**Background.** Cefiderocol (S-649266, CFDC) is a novel siderophore cephalosporin with activity across a wide variety of Gram-negative bacteria including carbapenem-resistant strains. We previously reported that CFDC is efficiently transported into *Pseudomonas aeruginosa* via iron transporter PiuA. In this study, we examined frequency of resistance of *P. aeruginosa* to CFDC, and investigated the resistance mechanisms of appeared colonies.

**Methods.** Frequency of resistance (FoR) was determined by plating an overnight culture of *P. aeruginosapAO1 on Mueller-Hinton Agar containing 4 or 10 MIC of CFDC or ceftazidime (CAZ). Appeared colonies were analyzed by whole-genome sequencing (WGS) to identify genomic mutations. The mRNA expression was determined by real-time RT-PCR, and pyoverdine production was determined by MALDI-TOF/MS and by immunoblotting and ELISA, respectively. The crystal structure of anti-P.slv and PerV fragment complex-crystals was solved at 2.8 Å resolution.

**Results.** Whole-genome sequencing revealed intact perV and pol genetic elements in 99% and 94% of isolates, respectively. We identified 46 variants of CFDC that were all bound by the anti-PcrV moiety of MED3902 and confirmed through crystal structure analysis that antibody-antigen contact residues were preserved in all variants. Similarly, anti-Psl binding was confirmed for selected isolates containing the complete Psl operon and strains lacking non-essential psl genes. Importantly, 99.9% of isolates contained the full complement of either genetic element. Consistent with these results, we observed potent MED3902 activity against diverse strain types, including strains that expressed only a single target.

**Conclusion.** Our results indicate PerV and Pol are highly prevalent in recent clinical isolates from around the world, suggesting that MED3902 can mediate broad coverage against Pol.

**Disclosures.** D. E. Tabor. Astra Zeneca: employee, Salary.

### 697. *Pseudomonas aeruginosa* PerV and Pol, the Molecular Targets of Bispecific Monoclonal Antibody MED3902, Are Conserved Among Diverse Hospital Isolates Collected From an International Surveillance Study

David E. Tabor, PhD; Microbial Sciences, MedImmune, Mountain View, California

**Session:** 67. Resistance Mechanisms: Gram-Negative

**Thursday, October 4, 2018: 12:30 PM**

**Background.** *Pseudomonas aeruginosa* is a frequent cause of life-threatening infections in mechanically ventilated patients and is associated with high mortality rates. Bispecific monoclonal antibody MED3902 targeting Per type-3-secretion system (PerV) and the Pol exopolysaccharide is currently under phase 2b development for the prevention of pneumonia in mechanically ventilated subjects with Pol colonization in the lower respiratory tract. In this study, we sought to survey a vast collection of global Pol clinical isolates for presence of perV and pol loci and MED3902 epitope conservation to evaluate the magnitude of Pol strain coverage by MED3902.

**Results.** We set out to determine the effectiveness of meropenem-nacubactam against diverse strain types, including strains that expressed only a single target.

**Conclusion.** Our results indicate PerV and Pol are highly prevalent in recent clinical isolates from around the world, suggesting that MED3902 can mediate broad coverage against Pol.

**Disclosures.** D. E. Tabor. Astra Zeneca: employee, Salary.

### 698. Nacubactam Inhibits Class A β-lactamases

Melissa D. Barnes, PhD; Caryn E. Good, MA/MPH; Saralee Rajakoszubatz, MS1; Margaret A. Taracela, MS1; David Van Duin, MD, PhD; Barry N. Kreiswirth, MD; Michael R. Jacobs, MD/PhD; Kristvincia M. Papp-Wallace, PhD1; and Robert A. Bonomo, MD2. Research, Louis Stokes Cleveland Veteran’s Affairs Medical Center, Cleveland, Ohio; 1Medicine, Case Western Reserve University, Cleveland, Ohio; 2Pathology, Case Western Reserve University, University Hospitals Cleveland Medical Center, Cleveland, Ohio; 3Microbiology, University Hospitals Cleveland Medical Center, Cleveland, Ohio; 4Pathology, Case Western Reserve University, Cleveland, Ohio; 5Medicine, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina; 6Health Research Institute, Rutgers New Jersey Medical School, Newark, New Jersey

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**Background.** Nacubactam, formerly RG6080 and OP5958 (Figure 1A), is a bridged diazabicyclooctasystem (DBO) that inactivates class A and class C β-lactamases. Unlike avibactam, the DBO that is approved for use in combination with ceftazidime, nacubactam also inhibits penicillin binding proteins (i.e., PBZβ) in Enterobacteriaceae. We set out to determine the effectiveness of meropenem-nacubactam against *Klebsiella pneumoniae* clinical strains and to elucidate the structure–function relationships.

**Methods.** Minimal inhibitory concentration (MIC) measurements using broth microdilution according to Clinical and Laboratory Standards Institute for meropenem (MERO) and nacubactam (nac) at a fixed ratio of 4 mg/L: 1 mg/L. The effectiveness of meropenem-nacubactam against *Klebsiella pneumoniae* clinical strains and to elucidate the structure–function relationships.

**Results.** Minimal inhibitory concentration (MIC) measurements using broth microdilution according to Clinical and Laboratory Standards Institute for meropenem (MERO) and nacubactam (nac) at a fixed ratio of 4 mg/L: 1 mg/L. The effectiveness of meropenem-nacubactam against *Klebsiella pneumoniae* clinical strains and to elucidate the structure–function relationships.

**Conclusion.** The MIC increase of CFDC against *P. aeruginosa* occurred due to the mutation of iron transporter-related genes. The resistance acquisition risks should be low as the frequency of resistance to CFDC was lower and the MIC increase of CFDC against the mutants was smaller than that of CAZ. In addition, no cross-resistance between CFDC and CAZ was observed.

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combinations based on the breakpoint of MERO. The strains harboring K73R, S130G, and K234R had slightly elevated MERO-nucobactam MICs relative to wild type but did not have corresponding increases in MERO MICs. Strains with pBCKK-KPC2, K73R or S130G had 0.015 mg/L MERO MICs. The pBRR2-K234R strain had a twofold lower MERO MIC than pBRR2-KPC2 (Figure 1C). The ICSo of cell extracts containing the K234R variant was 741 µM, which is 12-fold higher than that for KPC-2 (66 µM) (Figure 1C). Extracts containing the S130G variant were not inhibited by nacubactam (ICSo > 2.6 mM).

Conclusion. Meropenem-nucobactam is an effective β-lactam-β-lactamase inhibitor combination for Enterobacteriaceae with KPC or OXA-48 β-lactamases. The single amino acid substitutions K73R, S130G, and K234R in KPC-2 affect the inactivation mechanism.

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699. Relationship Between Klebsiella pneumoniae Antimicrobial Resistance and Biofilm Formation

Jaclyn Casamuno, PharmD1–3; Kathryn Daffinee, BS2; Megan Luther, PharmD1,2; Vrishali Lopes, MS1; Aisling Caffrey, PhD, MS1,2,3 and Kerry LaPlante, PharmD, FCPA1,2,3,4; College of Pharmacy, University of Rhode Island, Kingston, Rhode Island, 2Providing Veterans Affairs Medical Center, Providence, Rhode Island, 3Center of Innovation in Long-Term Support Services, Providence Veterans Affairs Medical Center, Providence, Rhode Island, 4Division of Infectious Diseases, Warren Alpert Medical School of Brown University, Providence, Rhode Island

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Background. Klebsiella pneumoniae is a frequently multidrug-resistant organism with a high propensity to form biofilm. K. pneumoniae is the most common carbapenem-resistant Enterobacteriaceae (CRE), and a triggered threat by the CDC. The relationship between K. pneumoniae biofilm formation and specific antimicrobial resistance patterns has not been well defined.

Methods. K. pneumoniae isolates (n = 139) were evaluated for antimicrobial resistance and biofilm formation (CDC, Providence VA Med. Ctr., Rhode Island Hosp., BEl, and ATCC). Susceptibility was based predominantly on 2017 CLSI (Clinical and Laboratory Standards Institute) breakpoints. Isolates were categorized as multidrug-resistant (MDR); resistant to ≥ 1 antimicrobial in ≥ 3 out of 16 antimicrobial categories) or extensively drug-resistant (XDR; resistant to ≥ 2 antimicrobial in all but ≤ 2 of 16 antimicrobial categories) based on expert consensus criteria for Enterobacteriaceae (European CDC (ECDC)/CDC, 2012). We collapsed antimicrobial categories described by the ECDC/CDC consensus group into nine categories: penicillins, cephalosporins, monobactams, carbapenems, protein synthesis inhibitors, fluoroquinolones, folate pathway inhibitors, fosfomycin, and colistin. Biofilm formation was assessed using a modified crystal violet method (OD600) and defined by tetracut point. Antimicrobial resistance was compared for weak (n = 47) vs. strong (n = 46) biofilm formers by chi-square test. Predictors of strong biofilm formation were identified using logistic regression.

Results. MDR isolates were more common among weak (n = 46/47, 97.9%) vs. strong biofilm formers (n = 35/46, 76.1%; P = 0.002), whereas XDR was similar between groups (n = 12/47, 25.5% vs. n = 13/46, 28.3% P = 0.77). Resistance to penicillins, cephalosporins, monobactams, carbapenems, protein synthesis, or fluoroquinolones was more common among weak biofilm formers (P < 0.05). Carbapenem resistance was inversely associated with strong biofilm formation (odds ratio 0.09; 95% confidence interval 0.02–0.33).

Conclusion. Carbapenem-resistant K. pneumoniae was 91% less likely to form strong biofilm. Potential trade-off mechanisms between antimicrobial resistance and biofilm formation require further exploration.

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700. Identification and Whole-Genome Sequencing (WGS) of Meropenem-Vaborbactam (MV) Resistant Klebsiella pneumoniae (MVRKP) Among Patients Without Prior Exposure to MV, Collateral Damage

Mohamad Yasmn, MD1; Liang Chen, PhD2; Steven H. Marshall, MS1; Barry N. Kreiswirth, PhD1; Federico Perez, MD, MS1 and Robert A. Bonomo, MD, MD

1Infectious Diseases, Case Western Reserve University, Cleveland, Ohio, 2Public Health Research Institute, New York Medical School, New York, 3Research Service, Louis Stokes Cleveland Department of Veterans Affairs Medical Center, Cleveland, Ohio, 4Louis Stokes Cleveland VA Medical Center, Cleveland, Ohio, 5Department of Pharmacology, Biochemistry, Proteomics and Bioinformatics, Case Western Reserve University School of Medicine, Cleveland, Ohio

Session: 67. Resistance Mechanisms: Gram-Negative

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Background. MV is a newly approved β-lactam/β-lactamase inhibitor combination (BLIC) for the treatment of complicated urinary tract infections (cUTI). Vaborbactam is a cyclic boronic acid BII that was mainly developed as a potent inhibitor of KPC carbapenemases and other Ambler class A/B enzymes. Vaborbactam is inactive against metallo-β-lactamases (MBL) and certain Class D enzymes (e.g., OXA-2 and OXA-48). We encountered a case of MV-resistant Klebsiella pneumoniae (MVRKP) and sought to explore the various mechanisms of MV resistance within KP.

Methods. A 65-year-old nursing home resident with multiple prior hospitalizations and recent exposure to antibiotics (Timeline) developed sepsis secondary to carbapenem-resistant Klebsiella pneumoniae (CRKP) cUTI. WGS of the patient’s isolate was performed. This was followed by random screening for MV resistance and WGS of other isolates from a historical database.

Results. Results of WGS are seen in the table below. Sequencing of our patient’s isolate revealed strain ST258 with a premature stop in aas9 of OmpK35 as well as insertions at Gly134 and Asp135 (i.e., the GD repeat) of OmpK36. Furthermore, the KPC plasmid’s copy number was approximately five times higher than the chromosome. No mutations encoding efflux system AcrAB-TolC were found.

Conclusion. Resistance to MV in KP was found in isolates that predate the drug’s availability. Notably, resistance occurred in the absence of MBLs and OXAs. The mechanism seems to involve outer membrane porin mutations in OmpK35 and OmpK36. WGS is a useful tool in identifying the mechanism of resistance especially for newer agents.

Table: Characterization of MVRKP by WGS

| Strain | Date | MV/MIC (mg/mL) | MSLT β-Lactamase | Multidrug Transporters and Regulators | OmpK35 | OmpK36 | Notes |
|--------|------|----------------|------------------|--------------------------------------|--------|--------|-------|
| 1      | 2-1-12 | 16          | ST258           | KPC-2 & SHV-160                       | Emr, memb, oqxAB, smaD | FS | 121iso6G | S to CZA and TGC |
| 2      | 4-3-12 | 16          | ST258           | KPC-2 & SHV-160                       | Emr, memb, oqxAB, smaD | FS | 121iso6G | S to CZA and TGC |
| 3      | 2013 | 4          | ST258           | KPC-2 & SHV-160                       | Emr, memb, oqxAB, smaD | FS | 121iso6G | S to CZA and TGC |
| 4      | 2017 | 32          | ST258           | KPC-2 & SHV-160                       | Emr, memb, oqxAB, smaD | FS | 121iso6G | S to CZA and TGC |

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701. Rapid Detection of Antimicrobial Resistance Determinants with the BioFire System

Stefanie Marxreiter, MS1; Eric Lo, BS2; Cody Oswald, BS1; Aubrie Hopper, MLS, ASCP; Becky Barr, MLS, ASCP3; Judy A. Daly, PhD1,2, Kimberly F. Hanson, MD, MHS1, Christine C. Ginochio, PhD MTT1,2; Robert Crisp, PhD1,2 and Andrew Hemmert, PhD1,2; BioFire Diagnostics, LLC, Salt Lake City, Utah, Utah; Primary Children’s Hospital, Salt Lake City, Utah, 3University of Utah, Salt Lake City, Utah, 4UCLA Health, Los Angeles, California, 5University of Maryland, Baltimore, Maryland, 6Cleveland Clinic Foundation, Cleveland, Ohio, 7Ohio State University, Columbus, Ohio, 8University of Utah, Salt Lake City, Utah, 9Brown University, Providence, Rhode Island

Session: 67. Resistance Mechanisms: Gram-Negative

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Background. The rapid and accurate identification of antimicrobial resistance (AMR) in healthcare acquired infections is critical to the proper and timely treatment of these patients. The BioFire® GeneXpert® System is a commercial rapid molecular diagnostic for the detection of key AMR determinants and drug resistance phenotypes. The BioFire system is a commercially available fully automated system, developed using a high-throughput multiplex polymerase chain reaction (PCR) format and able to detect up to 40 pathogens, including multi-drug resistant (MDR) pathogens, in less than 1 hour.

Methods. The aim of the study is to evaluate the performance of the BioFire® GeneXpert® System in detecting resistance mechanisms against the most common MDR pathogens on the market for respiratory infections. This study will be conducted at 17 sites within the United States and at 5 sites in Canada. A total of 2000 samples will be collected from patients presenting for respiratory infections. The samples will be genotypically analyzed for the presence of 32 AMR genes and resistance mechanisms using the GeneXpert® System. The data obtained from the GeneXpert® System will be compared to the results obtained from traditional clinical microbiology methods. The sensitivity, specificity, and accuracy of the GeneXpert® System for detecting AMR determinants will be calculated.

Results. The results of the study will provide important information regarding the performance of the GeneXpert® System for detecting AMR determinants in respiratory infections. This information will be used to improve diagnostic testing and patient care.

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