Background. Relebactam (REL), formerly MK-7655, is a β-lactamase inhibitor of class A and C β-lactamases that is in clinical development in combination with imipenem (IMI). In this study, we evaluated the activity of IMI/REL against Gram-negative bacilli and resistant phenotypes collected in the United States as part of the SMART surveillance program from patients with lower respiratory tract infections (RTIs) in ICUs, where antimicrobial resistance is typically higher than in non-ICU wards.

Methods. In 2015–2017, 26 hospitals in the United States each collected up to 100 consecutive Gram-negative pathogens from RTI per year. Antimicrobial susceptibility was determined for 1,288 non-Proteus Enterobacteriaceae (NPE) and 638 P. aeruginosa isolates collected in ICUs, using broth microdilution and breakpoints; for comparison purposes, the IMI susceptible breakpoint was applied to IMI/REL. Protease were excluded due to intrinsic nonsusceptibility to IMI. Susceptibility was calculated for the 4 United States census regions and overall.

Results. Susceptibility of NPE was lowest in the Midwest to ceftazidime (81%) and cefepime (87%) and highest in the Northeast (88% and 94%, respectively); susceptibility to imipenem (89–93%) and piperacillin–tazobactam (86–90%) showed less variability across regions. Susceptibility of P. aeruginosa to the four agents was lowest in the West (57–65%) and highest in the Northeast (68–76%). Susceptibilities to IMI/REL of NPE and P. aeruginosa as well as phenotypes nonsusceptible (NS) to β-lactams are shown below.

| Organism/phenotype | Midwest | Northeast | South | West | United States |
|---------------------|---------|-----------|-------|------|--------------|
| NPE                 | 95.6 (47) | 95.3 (14) | 95.4 (7) | 97.5 (42) | 97.2 (235) |
| Cefazeime-NS         | 98.4 (41) | 7 (10)    | 97.1 (25) | 98.5 (50) | 98.0 (135) |
| Cefazidine-NS        | 98.5 (48) | 100 (14)  | 97.6 (48) | 98.6 (70) | 98.6 (218) |
| Imipenem-NS          | 48.6 (35) | 83.1 (12) | 71.0 (31) | 78.9 (39) | 67.5 (117) |
| PIPERACILLIN-TEZOBACTAM-NS | 98.8 (97) | 100 (13) | 96.4 (38) | 96.0 (51) | 98.1 (158) |
| P. aeruginosa         | 94.6 (224) | 93.7 (63) | 106.1 (190) | 95.2 (62) | 95.2 (255) |
| Cefazeime-NS         | 82.3 (58) | 81.3 (16) | 73.9 (45) | 75.8 (66) | 77.8 (165) |
| Cefazidine-NS         | 87.2 (67) | 95.7 (13) | 79.4 (49) | 79.1 (67) | 82.4 (100) |
| Imipenem-NS          | 82.6 (69) | 79.0 (19) | 74.1 (58) | 74.0 (73) | 77.2 (219) |
| PIPERACILLIN-TEZOBACTAM-NS | 83.6 (73) | 85.0 (29) | 77.4 (53) | 78.1 (82) | 80.3 (238) |

Disclosures. The 28 laboratories submitted some variability in activity against pathogens from RTI patients in ICUs across census regions, whereas IMI/REL maintained activity in all regions against NPE (96%) and P. aeruginosa (90–95%). IMI/REL remained active against ≥98% of resistant phenotypes of NPE, except the imipenem–NS subset (67.5%, susceptible), which was composed mainly of Serratia spp., and remained active against 77–82% of resistant phenotypes of P. aeruginosa, including 77.2% of imipenem–NS isolates. IMI/REL may provide a valuable therapeutic option for the treatment of ICU patients with respiratory tract infections caused by organisms resistant to commonly used β-lactam.

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710. Increased Clinical Failure Rates Associated with Reduced Metronidazole Susceptibility in Clostridioides difficile

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Background. Current national guidelines suggest limiting metronidazole (MTZ) use due to increased treatment failures in patients with Clostridioides difficile infections (CDI). However, the reason for these increased failure rates is unclear. We hypothesized that the increase in the minimum inhibitory concentration (MIC) of MTZ to C. difficile is a contributing factor to these treatment failures and that the reason for these increased failure rates is unclear. In this study, we examined clinical response rates in patients who received MTZ monotherapy vs. other therapies stratified by MTZ susceptibility.

Methods. Stool samples that tested positive for C. difficile (2017–2018) were collected from two large academic hospital systems in Texas. C. difficile was isolated from stool and visually screened for growth on heme-containing agar plates with MTZ at 2 mg/L (defined as reduced susceptibility). Blinded investigators reviewed electronic medical records to identify the treatment received and determine clinical success or failure for each patient. Treatment failure rates were assessed in patients that received MTZ monotherapy vs. other therapies stratified by MTZ susceptibility. Results were analyzed using multivariate logistic regression analysis.

Results. A total of 172 C. difficile isolates were included of which 55.8% displayed reduced susceptibility to MTZ. Clinical success rates with MTZ varied based on disease severity (mild-moderate: 80.4%; severe/severe-complicated: 64%). Treatment success rates were higher in patients infected with MTZ susceptible isolates (88.4%) vs. non-susceptible isolates (67.5%).
compared with those infected with isolates showing reduced MTZ susceptibility (60.5%; \( P = 0.004 \)). In multivariable logistic regression after controlling for disease severity, patients infected with strains displaying reduced MTZ susceptibility and treated with MTZ were more likely to experience treatment failure compared with patients with susceptible isolates (OR = 6.8, 95% CI:1.6–23.8, \( P = 0.003 \)). In patients given non-MTZ-based therapy, reduced susceptibility to MTZ was not predictive of failure to other treatments.

Conclusion. This is the first report to demonstrate that increased clinical failure rates for MTZ monotherapy are associated with reduced susceptibility to MTZ.

Disclosures. K. Garey, Summit Therapeutics: Collaborator, Research support.

711. Molecular Epidemiology of Daptomycin Non-susceptibility in Methicillin-Resistant Staphylococcus aureus (MRSA) Bacteremia

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Session: 68. Resistance Mechanisms: Gram-Positive
Thursday, October 4, 2018: 12:30 PM

Background. While methicillin resistance in S. aureus strains is prevalent, non-susceptibility to vancomycin and daptomycin, first-line treatments for bacteremia, has emerged as well. Little is known about the molecular epidemiology of daptomycin resistance in S. aureus strains.

Methods. A retrospective study was conducted at an 800-bed hospital in Detroit, Michigan. Blood isolates of S. aureus were obtained over time in patients with persistent bacteremia. Isolates were initially classified as MRSA/ MSSA and MIC testing was conducted in a separate microbiology laboratory. PFGE isolates were recovered from a separate laboratory using Etest strips and microdilution broth testing. Non-susceptibility to daptomycin was defined as an MIC > 1 mg/mL. Isolates from each patient were also assessed for genomic similarity using pulse field gel electrophoresis (PFGE) and placed into the same PFGE group if they were \( \geq 80\% \) similar by Dice coefficient.

Whole genome sequencing (WGS) on isolates and template strain ATCC29213 was done by the Applied Genomics Technology Center.

Results. There were 27 isolates from seven patients in the following distribution: six isolates each from Patients 1 and 2, three isolates each from Patients 3, 4, and 5, five isolates from Patient 6, and one isolate from Patient 7. All isolates from Patients 1 and 3 (n = 9) were classified as MSSA strains and the remainder were MRSA strains. Daptomycin non-susceptible strains were found in the initial isolate on therapy in two patients and MIC increased from first to last isolates in the other five patients. A PFGE dendrogram showing isolates within each patient and within established CDC lineages determined that (1) each patient's first and last isolate remained within the same strain type and (2) the PFGE groups were USA100 (n = 8), USA300 (n = 7), USA900 (n = 6), and USA1000 (n = 3). WGS revealed the presence of vraS, mprF, dluA, clzA, and gdpD. genes implicated in resistance to both vancomycin and daptomycin. However, gdpD was not detected in isolates classified as MSSA.

Conclusion. No genetic modification of strains from each patient was seen between the first isolate obtained and the last. The presence of cell wall regulation genes in both vancomycin susceptible and non-susceptible strains suggests gene upregulation.

Disclosures. M. J. Zervos, Merck: Consultant and Grant Investigator, Grant recipient.

712. Identification of a Novel Tedizolid Resistance Mutation in a Non-susceptible Methicillin-Resistant Staphylococcus aureus

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Session: 68. Resistance Mechanisms: Gram-Positive
Thursday, October 4, 2018: 12:30 PM

Background. Tedizolid (TDZ) is an oxazolidinone antimicrobial with broad-spectrum activity against Gram-positive bacteria including methicillin-resistant S. aureus (MRSA). Resistance to TDZ is uncommon but mutations in the 23S rRNA target as well as in the transferable RNA methyltransferase gene (cfr), which also mediates resistance to linezolid and chloramphenicol have been implicated. The objective of this study was to determine whether other TDZ resistance pathways exist in MRSA.

Methods. Using a well-characterized MRSA strain, N315, we selected for TDZ resistance by serial passage in escalating concentrations of TDZ in Mueller Hinton broth (MHB) starting with 0.5× the MIC. Once visible growth was achieved a sample was diluted 1:1,000 into fresh MHB with twice the previous concentration of TDZ until an isolate with an MIC of ≥4 mg/mL was recovered. This MIC was selected since it is above the breakpoint for resistance to 2× mg/L. This isolate was subjected to whole genome sequencing (WGS) and MICs to other antimicrobials were assessed. Homology modeling was performed to evaluate the potential impact of the mutation on target protein function.

Results. After 10 days of serial passage we recovered a stable mutant with a TDZ MIC of 4 mg/L. WGS revealed a single nucleotide variant (A1345G) in the bpdE gene corresponding to an amino acid substitution at D449N. The following table and figure summarize the changes in drug susceptibility between the parent and evolved strain and reveals the location of the amino acid substitution relative to the TDZ binding site.

| MIC (mg/L) | Drug          |
|-----------|---------------|
| N315      | N315-TDZ4     |
| Chloramphenicol | 8  | 128 |
| Doxycycline  | 0.125 | 0.125 |
| Linezolid   | 2       |
| Moxifloxacin| 0.0625 | 0.0625 |
| Rifampin    | 0.001 | 0.001 |
| Tedizolid   | 0.25 | 4 |
| Vancomycin  | 0.5   |

Conclusion. We have identified a novel mutation in the RNA polymerase gene, bpdE, that mediates oxazolidinone and chloramphenicol resistance. This variant lies outside of the rifampin resistance determinant clusters of bpdE that span from 1,384 to 1,464 and 1,543 to 1,590, and as expected did not affect rifampin susceptibility. The underlying molecular mechanism by which this single nucleotide variant confers TDZ resistance remains unclear but may involve transcriptional modulation by altered sigma factor binding.

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713. Vancomycin Heteroresistance in Coagulase Negative Staphylococci (CoNS) Causing Central Line-Associated Bloodstream Infection (CLABSI) in Pediatric Patients with Leukemia

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Session: 68. Resistance Mechanisms: Gram-Positive
Thursday, October 4, 2018: 12:30 PM

Background. Heteroresistance to vancomycin in Staphylococcus aureus may be associated with poor response to therapy. Although CoNS are the most important CLABSI pathogens in children with leukemia, and treatment failure is common, little is known about the frequency and clinical significance of heteroresistance. This is a retrospective study to evaluate frequency, risk factors and clinical impact of heterogeneous CoNS in CLABSI in immunocompromised children.

Methods. The study was approved by the Institutional Review Board. All patients undergoing treatment for leukemia at St. Jude’s Children’s Research Hospital with CoNS isolated from blood between 2010 and 2016 were eligible. The first available isolate from each blood culture episode was obtained from the clinical laboratory and tested for vancomycin heteroresistance by population analysis profiling in comparison to the hVISA strain Mu3. Clinical data were collected from the medical record for up to 9 months after the episode. Episodes with ≥2 positive cultures or a single positive culture from a single lumen CVC were classified as CLABSI. Outcomes of interest included treatment failure (death or relapse of infection) or poor response to vancomycin therapy (persistence of bacteremia ≥21 day after initiation of vancomycin or treatment failure). Logistic regression was used to test associations between heteroresistance and exposures, and cumulative incidence analyses were used to test the effect on outcomes.

Results. A total of 74 CoNS isolates were obtained from 65 participants, 39 with AML and 26 with ALL and 26 with AML; 25/74 (33.8%) of isolates showed heteroresistance. The strongest identified risk factor for infection with a heteroresistant organism was number of days of vancomycin in the preceding 60 days (OR = 1.05/day; \( P = 0.003 \)). In patients given non-MTZ-based therapies, reduced susceptibility to MTZ was not predictive of failure to other treatments (death or relapse of infection) or poor response to vancomycin therapy (persistence of bacteremia ≥21 day after initiation of vancomycin or treatment failure). Logistic regression was used to test associations between heteroresistance and exposures, and cumulative incidence analyses were used to test the effect on outcomes.

Conclusion. Further research should aim to validate this finding in an independent cohort and identify strategies to improve the diagnosis and treatment of these infections.

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714. Predictors of Influenza-Associated Hospitalization and Pneumonia in a Pediatric Population in Bangkok, Thailand

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