

**Table 1:** \*t-test.

Strain	ST	Isolate Data			qRT-PCR Results					P <sup>†</sup> Value
		CrrB Background	Colistin MIC (E Test) µg/mL	Polymyxin B MIC (BMD) µg/mL	phoP	phoQ	pmrA	pmrC	pmrK	
NR 5083	258	L87V	4.0	>128	3	2.3	0.8	0.8	0.9	
NR 5083 <sup>Δcrrb</sup>	258	160 bp deletion	0.38	1	2.9	2.03	0.83	0.6	0.9	
NR 5337	258	WT	0.125							
NR 5337 <sup>Δcrrb</sup>	258	160 bp deletion	0.125							

**Disclosures.** A. C. Uhlemann, Merck: Investigator, Grant recipient.

**708. Incidence and Relatedness of Carbapenemase-Producing Carbapenem-Resistant Enterobacteriaceae Infections in Previously Colonized or Infected Patients**

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**Session:** 67. Resistance Mechanisms: Gram-Negative  
Thursday, October 4, 2018: 12:30 PM

**Background.** In patients with history of carbapenemase-producing carbapenem-resistant Enterobacteriaceae (CPCRE), the need for CPCRE targeted treatment in subsequent sepsis episodes is unclear. We determine the likelihood of CPCRE infection (CI) in patients previously colonized (PC) or infected (PI) with CPCRE and relatedness of both episodes.

**Methods.** Adult inpatients with CPCRE isolated from any site in June 2012–May 2014 at a tertiary-care hospital were prospectively followed for 2 years to assess for subsequent CI. Bacteria isolates from paired episodes were subjected to Illumina HiSeq2500 and multilocus sequence typing.

**Results.** Six of 25 (24%) PI and 11 of 152 (7%) PC patients had subsequent CI—overall incidence was 9.6%. KP was most commonly implicated. While bacteria species differed in four cases, the carbapenemase type was conserved in all but one. Those with initial bacteremia, intra-abdominal (IA) or lung infection (n = 6) were five times more likely to develop CI. Only 33% of PI vs. 62% of PC patients had subsequent infections of the same clonal group. For PC, KP (OR 9.3) and OXA carbapenemase (OR 12.8) significantly predicted for subsequent CI. In PI, chronic renal failure requiring dialysis (OR 70.2) and KPC enzyme (OR 14) were predisposing factors. In-hospital mortality was observed in six cases.

Initial			Subsequent			Time (Days)
Site	Bacteria	Gene	Site	Bacteria	Gene	
U	KP	OXA-48	B	KP	OXA-48	26
IA	EC	KPC-2	L	KP	OXA-1; KPC-2	17
B	KP	KPC-2; OXA-1	B	KP	KPC-2; OXA-1	8
S	KP	OXA-48	S	KP	OXA-48	146
L	KP	KPC-2	B	KP	KPC-2; OXA-1	91
U	KP	KPC-2	S	KP	KPC-2	45
				ECO	KPC-2	
R	KP	OXA-1	IA	KP	OXA-1	6
L	KP	KPC-2	B	KP	KPC-2	82
L	KP	OXA-1; KPC-2	U	KP	KPC-2	23
R	ECO	KPC-2	IA	ECO	KPC	16
R	KP	NDM-1; OXA-1; OXA-181;	S	KP	NDM-1; OXA-181;	13
S	EC	OXA-1; OXA-48	S	ECO	OXA-1; OXA-181	93
IA	KP	KPC-2	B	ECO	OXA-181	311
R	KP	KPC-2	U	KP	KPC-2; OXA-181	250
R	KP	KPC-2; OXA-1; OXA-9	L	KP	KPC	6
R	KP	OXA-1; OXA-181	B	ECO	OXA-181	5
R	KP	KPC-2; OXA-1	S	KP	KPC	367

B, blood; IA, intra-abdominal; L, lung; R, rectal; S, skin soft tissue; U, urine; EC, *Enterobacter cloacae*; ECO, *Escherichia coli*; KP, *Klebsiella pneumoniae*

**Conclusion.** Incidence of CI in carriers is low. Patients with IA and respiratory CI in the preceding 93 days are candidates for CPCRE treatment; empiric therapy should be active against the carbapenemase identified in the index episode.

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**709. Activity of Key β-Lactam Agents Against Gram-Negative Bacilli From ICU Patients with Lower Respiratory Tract Infections, SMART United States 2015–2017**

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**Session:** 67. Resistance Mechanisms: Gram-Negative  
Thursday, October 4, 2018: 12:30 PM

**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 (RTI) 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 1,298 non-*Proteaceae* Enterobacteriaceae (NPE) and 638 *P. aeruginosa* isolates collected in ICUs, using CLSI broth microdilution and breakpoints; for comparison purposes, the IMI susceptible breakpoint was applied to IMI/REL. *Proteaceae* 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 region (57–65%) and highest in the Northeast (68–76%). Susceptibilities to IMI/REL of NPE and *P. aeruginosa* as well as of phenotypes nonsusceptible (NS) to β-lactams are shown below.

Organism/phenotype	% IMI/REL-susceptible (total n)				
	Midwest	Northeast	South	West	United States
NPE	96.2 (475)	98.3 (119)	96.4 (279)	97.9 (425)	97.0 (1298)
Cefepime-NS	98.4 (61)	7 of 7*	97.1 (35)	98.0 (50)	98.0 (153)
Ceftazidime-NS	98.9 (88)	100 (14)	97.8 (46)	98.6 (70)	98.6 (218)
Imipenem-NS <sup>‡</sup>	48.6 (35)	83.3 (12)	71.0 (31)	76.9 (39)	67.5 (117)
Piperacillin-tazobactam-NS	98.5 (67)	100 (12)	96.4 (28)	98.0 (51)	98.1 (158)
<i>P. aeruginosa</i>	94.6 (224)	93.7 (63)	90.7 (161)	90.0 (190)	92.2 (638)
Cefepime-NS	82.8 (58)	81.3 (16)	73.3 (45)	75.8 (66)	77.8 (185)
Ceftazidime-NS	87.7 (57)	86.7 (15)	79.6 (49)	79.1 (67)	82.4 (188)
Imipenem-NS	82.6 (69)	79.0 (19)	74.1 (58)	74.0 (73)	77.2 (219)
Piperacillin-tazobactam-NS	83.6 (73)	85.0 (20)	77.4 (53)	78.1 (82)	80.3 (228)

\*% susceptible not shown if n<10

<sup>‡</sup>Includes *Serratia* spp. (72%, 84/117), *Klebsiella* spp. (12%, 14/117), *Enterobacter* spp. (9%, 11/117), other species (7%, 8/117)

**Conclusion.** The studied β-lactams showed 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-lactams.

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

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

**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 an increase in the minimum inhibitory concentration (MIC) of MTZ to *C. difficile* may contribute to these poor response rates. The objective of this study was to examine clinical response rates in patients with CDI 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%)

compared with those infected with isolates showing reduced MTZ susceptibility (60.5%;  $P = 0.004$ .) In multivariate 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:1.96–23.8;  $P = 0.003$ ). In patients given non-MTZ-based therapies, 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.

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### 711. Molecular Epidemiology of Daptomycin Nonsusceptibility 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 done by the clinical microbiology laboratory; MICs were reconfirmed by 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 in the same PFGE group if they were <sup>3</sup> 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 nonsusceptible strains were found in the initial isolate on therapy in two patients and the MIC increased from first to last isolates in the other five patients. A PFGE dendrogram comparing isolates within each patient and with 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 *vraSR*, *mprF*, *dltA*, *cls2*, 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 daptomycin susceptible and nonsusceptible strains suggests gene upregulation.

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### 712. Identification of a Novel Tedizolid Resistance Mutation in *rpoB* of 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 rRNA methyltransferase gene *cfz*, which also mediate 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 0.5x the MIC. Once visible growth was achieved a sample of the broth was diluted 1:1,000 into fresh MHB with twice the previous concentration of TDZ until an isolate with an MIC of  $\geq 4$  mg/mL was recovered. This MIC was selected since it is 1 dilution above the breakpoint for resistance  $\geq 2$  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 *rpoB* 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.

Drug	MIC (mg/L)	
	N315	N315-TDZ4
Chloramphenicol	8	128
Doxycycline	0.125	0.125
Linezolid	2	8
Moxifloxacin	0.0625	0.0625
Rifampin	0.001	0.001
Tedizolid	0.25	4
Vancomycin	0.5	1

**Conclusion.** We have identified a novel mutation in the RNA polymerase gene, *rpoB*, that mediates oxazolidinone and chloramphenicol resistance. This variant lies outside of the rifampin resistance determinant clusters of *rpoB* 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 or clinical significance of heteroresistance. This is a retrospective study to evaluate frequency, risk factors and clinical impact of heteroresistance in CoNS CLABSI in immunocompromised children.

**Methods.** The study was approved by the Institutional Review Board. All patients undergoing treatment for leukemia at St. Jude 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  $\geq 2$  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  $\geq 1$  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 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;  $P = 0.035$ ). In the 40 CLABSI episodes, heteroresistant isolates had a higher cumulative incidence of poor response and of treatment failure ( $P = 0.006$  and  $P = 0.003$ , respectively).

**Conclusion.** Vancomycin heteroresistance is common in CoNS causing CLABSI in children undergoing treatment for leukemia, and is associated with an increased risk of Treatment Failure. 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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**Session:** 69. Respiratory Infections: Viral  
Thursday, October 4, 2018: 12:30 PM