Background. MRSA colonization is a common neonatal problem and is associated with invasive infection. Good hand-washing and contact precautions reduce transmission. However, long-term contact isolation, sometimes for months, causes dissatisfaction among neonatal intensive care unit (NICU) care providers and parents. We examined the effectiveness of MRSA decolonization among neonates over 3 years.

Methods. Our NICU patients are routinely screened for MRSA colonization by PCR testing of nasal and rectal swabs upon admission and every 2 weeks. Patients with a history of MRSA infection or colonization became eligible for MRSA eradication upon reaching 2000g. Our protocol included intranasal mupirocin 2% ointment applied to both nares twice daily for 5 days and 2% chlorhexidine wipe bath daily for 7 days. Wipes were used for bathing from the neck down for at least 20 sec per wipe. Two wipes were used for patients < 10 kg with the first wipe being used on the neck, chest, arms, and back, and the second wipe being used on the legs, buttocks, and perineum. Patients were excluded from chlorhexidine bathing if they had a known allergy, were < 27 weeks gestation, < 1 week chronological age, receiving phototherapy, or had severe skin disease, open wounds, or burns. Contact isolation was discontinued if 2 sets of nares and rectal PCR swabs 5 days apart were negative and the patient had not been on antibiotics during the screening period. Surveillance MRSA PCR testing continued. Contact isolation was to be re-initiated if subsequent MRSA screening was positive. Patients were not decolonized a second time.

Results. Among infants admitted to the NICU during from 2016 to 2018 MRSA colonization was identified in 102 patients. Fifty-six were noted to have colonization present on admission and 46 were acquired on or after hospital day 3. The decolonization protocol with follow-up screening was completed in 33 infants. Successful decolonization was achieved for only 5 (15%) of infants. There were no adverse reactions noted among neonates and no MRSA colonized patients reverted to positive by PCR screening while in hospital.

Conclusion. 85% of neonates with MRSA failed decolonization. Using mupirocin intranasally and chlorhexidine bathing to decolonize neonates with MRSA was welcomed by staff and families, but was poorly effective.

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596. Distinct, Segregated Daptomycin-Susceptible and Daptomycin-Non-susceptible Staphylococcus aureus Populations Associated with Tricuspid-Valve Infective Endocarditis

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Session: 65. Mechanisms of Antimicrobial Resistance Thursday, October 3, 2019: 12:15 PM

Background. Loss of daptomycin susceptibility in Staphylococcus aureus is often associated with sequestered foci of infection, driven by selection pressure from both administered antibiotics and host defense peptides. Susceptibility testing of the organism cultured from blood is assumed to parallel that of the infectious foci, such as heart valves. We studied a case of tricuspid valve endocarditis where one leaflet yielded exclusively daptomycin-nonsusceptible S. aureus and another leaflet yielded purely daptomycin-susceptible S. aureus. We examined the responses of the two populations to different anti-staphylococcal therapies to identify regimens effective against both isolates.

Methods. Both isolates were whole-genome sequenced using Illumina technologies. The presence of heterogeneous daptomycin-resistant subpopulations was assessed by dilution plating and population analysis profiling. One compartment pharmacokinetic/pharmacodynamic modeling was used to simulate different potential antistaphylococcal pharmacotherapies against each isolate. Hemolysin activity was evaluated as a correlate for accessory gene regulator function.

Results. The daptomycin-susceptible isolate did not demonstrate heteroresistance while the daptomycin-resistant population was uniformly daptomycin

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non-susceptible. The daptomycin non-susceptible isolate demonstrated regrowth by 72 hours of simulated treatment with vancomycin (2 g Q12H) or daptomycin (10 mg/kg daily). Adding cepafolin (2 g Q8H) to vancomycin or daptomycin prevented regrowth at 72 hours. The daptomycin-resistant isolate was deficient in hemolysin production suggesting agr dysfunction. Comparative sequencing identified daptomycin-resistant isolate mutations in msrF, msrP, and agrA.

Conclusion. This case underscores the complex dynamics of the emergence of S. aureus resistance to daptomycin in vivo. Our pharmacokinetic modeling supports combination therapy in the treatment of endovascular MRSA infection. Reduced hemolysin activity supports the hypothesis that agr modulation is associated with persistent infection and/or treatment failure. Ongoing studies will identify features of distinct bacterial populations that promote ecological succession during infection at a sequenced anatomical site.

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597. Cross-Resistance of Cefotaxime–Tazobactam and Imipenem–Relebactam Against Clinical P. aeruginosa Isolates: SMART United States 2016–2018
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Session: 65. Mechanisms of Antimicrobial Resistance
Thursday, October 3, 2019: 12:15 PM

Background. Cefotaxime–tazobactam (CT) is an antipseudomonal cephalosporin combined with a β-lactamase inhibitor. The combination was cleared by FDA and EMA and is approved in the United States and over 60 countries worldwide. Relebactam (REL) is an inhibitor of class A and C β-lactamases that is in clinical development in combination with imipenem (IMI). Using clinical isolates collected in the United States as part of the global SMART surveillance program, we compared the activity of CT and IMI/REL against P. aeruginosa (PA) isolates.

Methods. In 2016–2018, 29 clinical laboratories from the United States collected up to 250 consecutive, aerobic or facultatively anaerobic, gram-negative pathogens (GNP) that were identified and isolated as potentially causative agents. Minocycline (MIC > 250 µg/mL) was tested against all CT susceptible (S) isolates. Activities of CT, IMI, and REL were determined by the agar dilution method on Mueller–Hinton agar plates using the test cocktails (acquired from Huray Laboratories) and the test incubated for 24 hours. The zone diameters were determined by the AUC method.

Results. A total of 14,606 GNP were collected, of which 2,774 were PA. MICs were determined for IMI/REL–susceptible P. aeruginosa (PA) clinical isolates. CT and IMI/REL were susceptible (S) to 87.3% of isolates. CT and IMI/REL were susceptible to the other, especially among isolates from patients in ICUs. Among all CT-susceptible (CT-NS) isolates (all patient locations, n = 132), 61.4% were IMI/REL–susceptible and 29.6% were IMI/REL–resistant. Of the three CT-NS subsets, 74.0% of isolates were susceptible to both CT and IMI/REL, 15.3% were susceptible only to IMI/REL, and 10.7% were susceptible only to CT. The distribution of C/T and IMI/REL–susceptible and resistant CT-NS isolates is summarized in Table 1.

Conclusion. Resistance to C/T or IMI/REL was not common among recent clinical isolates of PA collected in the United States, and both agents promise to be important treatment options. A significant proportion of isolates nonsusceptible to one agent was susceptible to the other, especially among isolates from patients in ICUs. The data suggest that susceptibility to both agents should be tested at hospitals.

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598. In Vitro Activity of Aztreonam in Combination with Ceftazidime–Avibactam, Amoxicillin–Clavulanate, and Piperacillin–Tazobactam vs. NDM-Producing Escherichia coli and Klebsiella pneumoniae Clinical Isolates
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Session: 65. Mechanisms of Antimicrobial Resistance
Thursday, October 3, 2019: 12:15 PM

Background. There are limited options available for the treatment of infections caused by Enterobacteriaceae that produce an NDM metallo-β-lactamase. The purpose of this study was to compare the in vitro activity of aztreonam in combination with three different β-lactam–β-lactamase inhibitors (ceftazidime–avibactam, amoxicillin–clavulanate, piperacillin–tazobactam) vs. NDM-positive Enterobacteriaceae clinical isolates.

Methods. Seven Escherichia coli and three Klebsiella pneumoniae clinical isolates (all NDM-positive by PCR) were included in this study. The in vitro activities of ceftaziidine–avibactam, amoxicillin–clavulanate, piperacillin–tazobactam, and aztreonam were determined by disk diffusion as described by CLSI. For synergy testing, disks containing a β-lactamase inhibitor (ceftazidime–avibactam, amoxicillin–clavulanate, piperacillin–tazobactam) were applied to Mueller–Hinton agar plates inoculated with the test organisms, and the plates were incubated for 1 hour. The disks were then removed and aztreonam disks were dropped on the previous disk sites. The plates were then incubated as per standard CLSI recommendations for disk diffusion.

Results. All ten isolates demonstrated phenotypic resistance to aztreonam, amoxicillin-clavulanate, and piperacillin–tazobactam, and eight were resistant to ceftazidime–avibactam (CLSI breakpoints). The zone diameter observed for aztreonam in combination with amoxicillin–clavulanate was greater than for either antimicrobial on its own for nine isolates. Seven isolates (70%) had susceptibility to aztreonam restored (zone diameter ≥21 mm) in the presence of avibactam. Aztreonam in combination with amoxicillin–clavulanate demonstrated in increased zone diameter for all isolates relative to the zone for each antimicrobial alone, but only two (20%) had aztreonam susceptibility restored. Aztreonam susceptibility was not restored for any of the isolates in combination with piperacillin–tazobactam.

Conclusion. Of the three β-lactam–β-lactamase inhibitor–aztreonam combinations evaluated, ceftazidime–avibactam plus aztreonam demonstrated the greatest in vitro activity vs. NDM-producing Enterobacteriaceae.

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599. LiaF is an Activator of the LiaR-Mediated Response Against Daptomycin and Antimicrobial Peptides in Multidrug-Resistant Enterococcus faecalis (Efs)
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Session: 65. Mechanisms of Antimicrobial Resistance
Thursday, October 3, 2019: 12:15 PM

Background. Daptomycin (DAP) is a key first-line agent for the treatment of vancomycin-resistant enterococcal infections. Resistance to DAP in enterococci is regulated by the LiaR/F system, a three-component regulatory system that consists of the two-component sensor kinase (LiaS), a response regulator (LiaR) and a transmembrane protein of unknown function (LiaF). Previous studies indicate that deletion of liaS results in increased LiaR expression, suggesting that LiaS modulates LiaR expression.

Methods. We generated three liaF mutants in OG1RF, a DAP-susceptible laboratory strain of Efs (DAP MIC = 2 µg/mL): (i) a non-polar, C-terminal truncation of liaF (OGIRF∆liaF), (ii) a null liaF mutant with a premature stop codon (OGIRFliaFp), and (iii) an isolate LiaF deletion at position 177 (OGIRFliaF177). We generated DAP MICs by Etest and characterized the localization of anionic phospholipids microdomains using 10-methyl-acridine-orange (NAO). The expression of the liaXYZ (the main target of LiaR) and liaFSR clusters were evaluated by qRT-PCR and relative expression ratios (Log2 fold change) were calculated by normalizing to gyrB expression. We assessed activation of LiaSR by evaluating LacZ reporter expression of liaXΔlacZ and liaXYZ reporter expression in a LiaR–/– strain (OG1RFΔliaR) in the presence of N-acetyl-DL-methionine (NAM), a modulator of LiaR activity. We also analyzed expression of LiaS using two different reporter constructs for LiaS expression in the LiaR–/– strain (OG1RFΔliaR) in the presence of NAM.

Results. Full deletion of liaF or the C-terminal truncation of LiaF did not have any effect on DAP MICs, membrane architecture or a significant increase in LiaS surface expression. In contrast, deletion of liaF caused a 7-fold increase in liaS expression and the LiaS mutant had an increase in membrane phospholipid microdomain and LTA content relative to wild type strains. Our findings indicate LiaF is a positive activator of LiaS expression and LiaR activity.

Conclusion. LiaF is likely a key activator of the LiaFSR stress response and the critical regulatory domain appears to be located in a stretch of four isoleucines toward the C-terminal of the protein.

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600. β-Lactam Resistance Mechanisms in Pseudomonas aeruginosa Isolates Analyzed Using Whole-Genome Sequencing (WGS) and Transcriptional Analysis and Their Impact in Resistance to New β-Lactam–β-Lactamase Inhibitors
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Session: 65. Mechanisms of Antimicrobial Resistance
Thursday, October 3, 2019: 12:15 PM

Background. Ceftazidime–avibactam (CAZ–AVI) and cefotaxime–tazobactam (C-T) display excellent antipseudomonal activity, but Pseudomonas aeruginosa (PSA) susceptibility against these agents can be affected by acquired resistance genes and mutations. We evaluated resistance mechanisms against these agents among 109 PSA isolates using WGS and messenger (mRNA)-sequencing.