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 to patients with susceptible isolates (OR = 6.8, 93% 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, nonsusceptibility 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 persistently bacteremia. Isolates were initially classified as MRSA/MSSA and MIC testing was performed using the broth microdilution method. All MRSA isolates were confirmed 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 genetic group if they were > 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. A single MIC of 0.5 mg/L was observed in the other five patients. A PFGE dendrogram placing isolates within each patient and within each 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 vrsA, mprF, dltA, clgC, and gdpD genes implicated in resistance to both vancomycin and daptomycin. However, gdpD was not detected in isolated cultures 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 nonsusceptible strains suggests gene upregulation.

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712. Identification of a Novel Tidazolid Resistance Mutation in mprf of Methicillin-Resistant Staphylococcus aureus

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Background. Tidazolid (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 253 rRNA target as well as in the transferable RNA methyltransferase gene mprf, 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 resistant mutants from the first isolate obtained and the last. The presence of cell wall regulation genes between the first isolate obtained and the last. The presence of cell wall regulation genes was confirmed using pulse field gel electrophoresis (PFGE) and placed in the same genetic group if they were > 80% similar by Dice coefficient. Whole genome sequencing (WGS) on isolates and template strain ATCC29213 was done by the Applied Genomics Technology Center.

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 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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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 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 infection 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 (persistance of bacteremia ≥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 (P = 0.012) 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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MIC (mg/L)

| Drug       | N315 | N315-TDZ4 |
|------------|------|-----------|
| Chloramphenicol | 8    | 128       |
| Doxycycline  | 0.125| 0.125     |
| Linezolid   | 2    |           |
| Minocycline | 0.0625| 0.0625   |
| Rifampin    | 1    | 0.001     |
| Tezidol     | 0.25 | 4         |
| Vancomycin  | 0.5  |           |

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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