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
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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 using the CLSI methodology. All laboratory microbiology isolates were reclassified 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 clonal 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 and MIC increased from first to last isolates in 10 patients. A PFGE dendrogram clusters isolates within each patient and with previously 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 mvaSR, mvaF, dAlA, cIc2, 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 nonsusceptible strains suggests gene upregulation.

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

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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 25S 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-resistant S. aureus N315 by serial passage in escalating concentrations of TDZ in Mueller Hinton broth. After the MIC of 4 mg/L, WGS revealed a single nucleotide variant (A1345G) in the mvoB 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       | 0.125              |
| N315TDZ    | 128                |
| Chloramphenicol       | 8                  |
| Doxycycline           | 0.125              |
| Linezolid          | 2                  |
| Minocycline        | 0.0625             |
| Rifampin            | 0.001              |
| Tedizolid          | 0.25               |
| Vancomycin         | 0.5                |

Conclusion. We have identified a novel mutation in the RNA polymerase gene, mvoB, that mediates oxazolidinone and chloramphenicol resistance. This variant lies outside of the rifampin resistance determinant clusters of mvoB 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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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 isolates shown by WGS to be heteroresistant were included. 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 ≥2 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 CoNS isolates shown by WGS to be hVISA. 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 the 40 CLABSI episodes, heteroresistant isolates had a higher cumulative incidence of poor response to and treatment failure (death or relapse of infection or poor response to vancomycin therapy) than susceptible isolates (P = 0.003 and P = 0.006, 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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Background. Respiratory syncytial virus (RSV) is the most important cause of pneumonia in children <5 years worldwide and may cause severe disease in elderly and high-risk adults. Multiple RSV strains co-circulate and evolve over seasons. We seek to describe the evolution of RSV over five seasons in Seattle, WA, USA with two seasons reported here.

Methods. From 2014 to 2016, subjects 6 months and older seeking outpatient care for acute respiratory illness at Kaiser Permanente Washington were enrolled in the Influenza Vaccine Efficacy Network (Flu VE Network) and a respiratory swab was collected. Real-time polymerase chain reaction (RT-PCR) was performed to test and quantify RSV and subtype positive samples. A subset of RSV samples with cycle threshold (CT) value <30 will be sequenced using a metagenomic next-generation sequencing (NGS) approach. Specific RSV genotypes will be associated with severe disease, defined as requiring emergency department care or hospitalization, or chest radiographic findings.

Results. A total of 8,750 patients were enrolled in the Flu VE Network and PCR testing of seasons 2014/2015 and 2015/2016 resulted in 562 of 4,137 (13.6%) RSV-positive specimens. Of patients with RSV-positive specimens, 204 (36.5%) were adults 18–64 years and 112 (20.0%) were 65+ years. RSV-B predominated in the 2014/2015 season (n = 298; 83.7%), whereas RSV-A was more common in the 2015/2016 season (n = 154; 79.8%) (Figure 1). The median (IQR) CT value for RSV-A specimens was 26.7 (23.3–29.9) compared with 27.9 (25.2–31.3) for RSV-B.

Conclusion. One RSV subtype predominated within each season. Similar RSV subtype distributions were seen across age categories. With multiple RSV vaccine candidates in development, understanding the genetic diversity and circulation of RSV various viruses within a population is important for analyzing the effects of a vaccine on the evolution of RSV.