had more than one KPC-harbor ing species. KPC-harbor ing isolates displayed ertap enem MICs ranging from 1 to >8 mg/L. Preliminary analyses suggest that blaKPC is contained within a nonclassical Tn4401 structure (lacking the upstream promoter). Mating experiments indicate that blaKPC is carried by a conjugative IncN backbone plasmid. Interestingly, K. pneumoniae isolates were noncolon by PFGE and belonged to multiple STs unrelated to CG258 (ST34, ST36, among others) and different wti types (37, 154, among others).

**Conclusion.** We report a multispecies outbreak of KPC-2 producing CRE in children mainly driven by horizontal dissemination of a promiscuous IncN plasmid. The noncolonial, multispecies nature of this outbreak provides insights into the complex dynamics of KPC dissemination in countries like Chile, where the clonal spread of highly successful clones like CG258 is not the predominant dissemination vehicle, and instead HGT-related spread could be playing a more important role.

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2561. Using Whole Genome Sequencing to Assess the Emergence of Antibiotic Resistance During Treatment of Enterococcus faecium and Enterococcus faecalis Bacteremia at Mount Sinai Hospital

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**Session:** 270. Genomics and Susceptibility of Superbugs Saturday, October 6, 2018: 2:00 PM

**Background.** Multidrug-resistant Enterococci are a major cause of nosocomial infections, yet our understanding of how resistance emerges during antibiotic treatment remains incomplete. We performed whole-genome sequencing of all paired isolates from 11 Enterococcus faecium and 10 Enterococcus faecalis cases that acquired resistance during hospitalization at Mount Sinai Hospital. Comparative and phylogenetic genomic analyses identified novel mechanisms of resistance and heteroresistance.

**Methods.** 2.5 years of electronic health records were analyzed to identify cases of bacteremia that acquired resistance to at least 1 of the 8 antibiotics. Core genome phylogenetic analyses of paired susceptible and resistant isolates was performed to confirm persistent single clone infections. Long read sequencing data, with Illumina error correction, were used to assemble and align complete genomes. Population analysis profile (PAP) assays were performed to assess the prevalence of heteroresistance.

**Results.** Among the 102 persistent enterococcal bacteremia cases, 57 isolates from 21 cases (20.6%) cases experienced a gain in resistance. Phylogenetic analyses confirmed that 80% of cases had single clone blood infections, with maximum of 138 days separating paired isolates. Known genetic determinants were responsible for emerging linezolid (LIN), vancomycin (VAN), and gentamicin synergy resistance in almost all cases. In 2 instances, emerging daptomycin (DAP) resistance was not accounted for by known resistance determinants. Notably, PAP assays revealed that LIN-, VAN-, and DAP-resistant subclones were present in only a subset of bacteria in clinical isolates. Longitudinal pairwise analyses of complete genomes revealed novel candidate SNPs for DAP resistance, both located in genes involving cell wall metabolism and maintenance, as well as plasmid recombination events that led to VAN heteroresistance.

**Conclusion.** Our study demonstrates the high prevalence of emerging antibiotic resistance during treatment. We find previously unreported single and structural genomic events that contribute rapid adaptation to antibiotic treatment.

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2562. Re-Appraisal of Aminoglycoside (AG) Susceptibility Testing Breakpoints Based on the Application of Pharmacokinetics–Pharmacodynamics (PK-PD) and Contemporary Microbiology Surveillance Data

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**Background.** Resistance to AGs and numerous other classes continues to emerge. To ensure that susceptibility is accurately characterized and that clinicians have reliable data to select effective agents, appropriate in vitro susceptibility testing interpretive criteria (susceptible breakpoints [BKPTs]) are crucial to ensure optimal patient care. Recently, USCAST, the USA voice to EUCAST/EMA, evaluated the BKPTs for the 3 most commonly used AGs, gentamicin, tobramycin, and amikacin [Bhavnani et al., IDWeek 2016; P.1977]. As a result of consultation from interested parties, which included evaluating AG dosing regimens provided in the USA-FDA product package inserts and simulated patients with varying creatinine clearance, these BKPTs were reassessed.

**Methods.** Data sources considered included longitudinal US reference MIC distributions using in vitro surveillance data collected over 18 years, QC performance (MIC, disk diffusion), population pharmacokinetics (PK), and in vivo PK-PD models. Using population PK models, PK-PD targets for efficacy and Monte Carlo simulation, percent probabilities of PK-PD target attainment by MIC after administration of traditional and extended interval AG dosing regimens were evaluated among simulated patients. Epidemiological cut-off and PK-PD BKPTs were considered when recommending BKPTs for AG–pathogen pairs.

**Results.** An example of PK-PD target attainment analysis output is provided in Figure 1 and a subset of recommended AG BKPTs for 3 pathogens is shown in Table 1. Updated USCAST BKPTs, which were based on the application of population PK and PK-PD models, simulation techniques, and contemporary MIC distribution statistics, are generally lower than those of EUCAST/EMA, USA-FDA, and CLSI. Adequate PK-PD target attainment was not achieved for some AG-pathogen pairs, even when high-dose AG dosing regimens and PK-PD targets for stasis were evaluated (e.g., gentamicin vs. P. aeruginosa; amikacin vs. S. aureus).

**Conclusion.** These revised AG BKPT recommendations, which will be made freely available to EUCAST, USA-FDA, and CLSI, will be finalized after considering comments from additional interested stakeholders. This process will be followed in an effort to bring harmonization to global BKPTs for AGs.

**Figure 1.** Percent probabilities of PK-PD target attainment by MIC value for tobramycin dosing regimens using total-drug plasma PK-PD targets for Enterobacteriaceae based on pooled data from a murine thigh-infection model among simulated patients with normal renal function

**Table 1.** Summary of candidate USCAST aminoglycosides in vitro test interpretive BKPT criteria and those of other BKPT organizations

| Pathogen/aminoglycoside | CLSI | USA-FDA | EUCAST | USCAST |
|-------------------------|------|---------|--------|--------|
| Enterobacteriaceae      |      |         |        |        |
| Amikacin                | ≤16  | ≤16     | ≤16    | ≤16    |
| Gentamicin              | ≤4   | ≤4      | ≤2     | ≤2     |
| Gentamicin - pneumonia  | ≤4   | ≤4      | ≤2     | ≤2     |
| Tobramycin              | ≤4   | ≤4      | ≤2     | ≤2     |
| Tobramycin - pneumonia  | ≤4   | ≤4      | ≤1     | ≤1     |
| Pseudomonas spp.        |      |         |        |        |
| Amikacin                | ≤16  | ≤16     | ≤16    | ≤16    |
| Tobramycin              | ≤4   | ≤4      | ≤4     | ≤4     |
| Staphylococci           | ≤4   | ≤4      | ≤1     | ≤1     |

* a. CLSI M100-S28 (2018) interpretive criteria.
  b. Amikacin package insert (Teva Parenteral Medicines, Inc.).
  c. Gentamicin package insert (Pfizer Inc., USA, LLC.).
  d. Tobramycin package insert (Akorn, Inc.).
  e. Based primarily on the assessment of high dose, extended interval regimens and the assumption of combination therapy.

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