1826. Impact of Rapid Diagnostics and Ceftazidime–Avibactam on Mortality after Bacteremia Caused by Carbapenem-Resistant Enterobacteriaceae

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Background. Patients with bloodstream infections (BSIs) due to carbapenem-resistant Enterobacteriaceae (CRE) have long delays until receipt of appropriate antimicrobial therapy and high mortality rates. Rapid molecular diagnostics and novel therapies, such as ceftazidime–avibactam (CAZ-AVI), offer promise to improve outcomes, but their clinical impact is unclear.

Methods. We identified 178 patients with CRE BSI from January 2016 to June 2018 at 8 New York and New Jersey medical centers. Patient demographics, comorbidities, clinical presentations, diagnostic methods, and treatments were compared between patients who died within 30 days of BSI onset and survivors. Multivariable conditional logistic regression for mortality was identified using univariate analysis.

Results. Compared with CRE BSI patients whose positive blood culture bottles underwent testing for the Klebsiella pneumoniae carbapenemase gene (blaKPC PCR) and patients where this test was not used.

Conclusion. The use of PCR to rapidly identify blood cultures with blaKPC and definitive therapy with CAZ-AVI instead of polymyxins or aminoglycosides were associated with decreased mortality after CRE bacteremia.

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1827. Genetic Characterization of Meticillin-Resistant Staphylococcus aureus (MRSA) Isolates Associated with the Development of Reduced Susceptibility to Vancomycin from Latin America

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Background. Vancomycin (VAN) is a first-line therapeutic option for severe MRSA infections, especially in Latin America where other options are limited. However, reduced susceptibility to VAN may lead to therapeutic failures. The molecular mechanisms leading the development of VAN-intermediate S. aureus (VISA) and heterogeneous-VISA (hVISA) phenotypes are still unclear. We explored genetic associations with hVISA phenotypes in MRSA isolates recovered from bacteremic patients in 9 Latin American countries (2011–2014) in order to develop a genomic platform to identify these isolates.

Methods. From 538 VAN-susceptible MRSA (MIC<2 ≈ 1 µg/mL) we identified 30 hVISA isolates using GRD and macromethod E-tests; from these, 3 were confirmed by PAP-AUC. Whole-genome sequencing was performed in all 30 isolates using Illumina platform. Based on previous studies, we selected 46 genes involved in hVISA development. Multiple blast alignments were performed using genomes of ATCC29213 and N315 (VISA-susceptible), Mu3 (hVISA) and Mu50 (VISA-resistant) as references.

Results. A total of 130 changes in 46 predicted proteins belonging to 8 functional categories were identified: 48 changes related to cell wall biosynthesis, 22 to DNA/RNA processing, 17 to regulatory systems, 12 to cofactors and enzymes, 11 to membrane biosynthesis, 9 to virulence, 6 to amino acid metabolism, and 5 to transport of nitrogen and putrescine/spermidine. The most common changes identified in all the hVISA were Y368H in Adh, N165 in BPB, S166A in RpoB, L141 in WalK and E156G in Yqf, compared with VISA strains. The proteins with the highest number of changes detected in the isolates confirmed by PAP-AUC were: CapD, DltA, Php4, TcaA, LytM (Cell wall biosynthesis); MusL, RpoB (DNA/RNA processing); Gra5 (Regulatory systems).

Conclusion. Changes in genes associated with cell wall biosynthesis, DNA/RNA processing, regulatory systems, and membrane biosynthesis were the most prevalent in Latin American hVISA strains. Genetic signatures in genes encoding GraR (N1975), RpoB (H481Y, H481N), VraS (I5N), WalK (L14F, R222K) and MrsR (E146K) are potentially associated with this phenotype. These changes could be used to develop a platform for possible identification of hVISA isolates.

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1828. Bedaquiline Resistance in Mycobacterium intracellulare Is Mediated By The Transcriptional Repressor MmpT5

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Background. Bedaquiline (BDQ) is an FDA approved antibiotic with antimycobacterial activity. BDQ resistance has been observed in several Mycobacterium species. High-level resistance is due to mutations in ATP synthase. Low-level resistance is attributed to drug efflux. Previously, we suggested that the MmpS5L efflux system mediates BDQ resistance in M. intracellulare. Here, we examine the role of MmpT5 in transcriptional regulation of mmpS5L and BDQ resistance.

Methods. In this study, mmpS5L-mmpT5 genes were cloned from 2 pre-treatment (wild-type mmpT5) and 2 relapse (mutant mmpT5) isolates of M. intracellulare and transformed into E. coli DH10A. Constructs containing the M. tuberculosis rvo678 gene, which mediates low-level BDQ resistance in M. tuberculosis, were also examined.

Results. The BDQ MIC for the M. smegmatis control strain, and all strains containing wild-type mmpT5 was 0.007 µg/mL. The BDQ MIC for the mutants containing mutant mmpT5 alleles showed enhanced survival after 24 hours exposure to 0.007 µg/mL BDQ. Bacillary colonies associated with mutant mmpT5 alleles exhibited altered morphology relative to wild-type strains. Trancription of mmpS5L was repressed by wild-type mmpT5, but neither mutant mmpT5 nor rvo678 repressed transcription. The MmpT5 luciferase reporter was not active.

Conclusion. MmpT5 represses transcription of mmpS5L whereas the operon is dysregulated by mmpT5 mutations. Although Rv678 regulates mmpS5L expression in M. tuberculosis, it cannot repress the mmpS5L promoters. The MmpS5L-MmpT5 genes have no impact on the BDQ MIC for M. smegmatis, but constructs containing mutant mmpT5 alleles do enhance bacterial survival. The altered morphology of these colonies suggests that BDQ resistance is mediated by cell wall changes in combination with drug efflux.

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1829. The Paradox of KPC Bearing Strains of Klebsiella pneumoniae with the D179Y Substitution: Resistance to Ceftazidime/Avibactam (CZA) and Susceptibility to Meropenem (MEM)

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