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

Michael J. Satlin, MD, MSc1; Liang Chen, PhD2; Gregory Weston, MD,MSCR3; Angela Gomez-Simmonds, MD3; Tanaya Blowmark, MD4; Susan K. Seo, MD5; Steven Sperber, MD6; Angela Kim, MD7; Brandon Eilertson, MD7; Stephen Jenkins, PhD7; Michael Levi, ScD5; Anne-Carolin Ulledam, MD, PhD9; Melvin P. Weinstein, MD10; Yi-Wei Tang, MD, PhD10; Tao Hong, PhD11; Stefan Jurjetchko, PhD12; Thomas J Walsh, MD, PhD(Hem)13; Lars Westblade, PhD14 and Barry Kreiswirth, PhD15; Weill Cornell Medicine, New York, New York; University of Illinois at Chicago, Chicago, Illinois; Emory University, Atlanta, Georgia; New York Presbyterian Hospital, New York, New York; Albert Einstein College of Medicine, Bronx, New York; Northwell Health, New Hyde Park, New York; The Ohio State University, Columbus, Ohio; University of Regina, Regina, SK, Canada; Universidad El Bosque, Bogota, Distrito Capital de Bogota, Colombia; Universidad de la República, Montevideo, Uruguay; Memorial University of Newfoundland, St. John’s, Newfoundland; North Carolina State University, Raleigh, North Carolina; Memorial Sloan Kettering Cancer Center, New York, New York; Ohio State University, Columbus, Ohio; University of Saskatchewan, Saskatoon, SK, Canada; Emory University, Atlanta, Georgia; University of Illinois at Chicago, Chicago, Illinois; Weill Cornell Medicine, New York, New York; Albert Einstein College of Medicine, Bronx, New York; Northwell Health Laboratories, Lake Success, New York; Weill Cornell Medicine of Cornell University, New York, New York.

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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.

We conducted an observational study of 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. Independent risk factors for mortality were identified using univariate analysis. We then compared time to receipt of active antimicrobial therapy between patients whose positive blood culture bottles underwent testing for the Klebsiella pneumoniae carbapenemase gene (blaKPC PCR) and patients where this test was not used.

Results. We identified 178 patients with CRE BSI (K. pneumoniae: n = 204, 58%; Enterobacter cloacae: n = 26, 15%; Escherichia coli: n = 26, 15%). The 30-day mortality rate was 38%. An increasing Acute Physiology and Chronic Health Evaluation II score (adjusted odds ratio [aOR] 1.06, P = 0.005) was independently associated with increased 30-day mortality; age (aOR 0.97, P = 0.031), primary diagnosis (aOR 1.36, 95% CI 0.97–1.92), and source control (aOR 0.25, P = 0.001) were independently associated with survival. Initial targeted therapy with CAZ-AVI was associated with a 28% 30-day mortality rate, compared with a 49% 30-day mortality rate among patients who received a polymyxin or aminoglycoside (P = 0.05). Patients whose blood culture underwent blaKPC PCR were more likely to receive active antimicrobial therapy within 24 hours of BSI onset (42% vs. 28%; P = 0.07) and had a decreased median time until receipt of active therapy (25 hours vs. 46 hours; P = 0.07), although these differences did not achieve statistical significance.

Conclusion. The use of PCR to rapidly identify blood cultures with blaKPC and definitive therapy within 24 hours of BSI onset reduced mortality; whereas, use of blaKPC PCR (aOR 0.31, 95% CI 0.12–0.84; P = 0.02) may have prevented bacterial activity. BDQ resistance has been observed in several M. tuberculosis strains; however, the molecular mechanisms leading the development of V AN-intermediate S. aureus (VISA) and heterogeneous-VISA (hVISA) phenotypes are still unclear. We explored genetic signatures associated with hVISA phenotype in MRSA isolates recovered from bacteremic patients in 9 Latin American countries (2011–2014) in order to develop a genomic platform for possible identification of hVISA isolates.

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1828. Bedaquiline Resistance in Mycobacterium intracellulare Is Mediated by the Transcriptional Repressor MmpT5

Dave Alexander, PhD1; Yi Xueona2; Supriya Bhatia2; Teagan Oleksyn3; Jeffrey Chen, PhD4; and Cameron Androw, PhD2; Cadham Provincial Laboratory, Winnipeg, MB, Canada; University of Regina, Regina, SK, Canada; University of Saskatchewan, Saskatoon, SK, Canada; VIDO-InterVac, Saskatoon, SK, Canada.

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Background. Bedaquiline (BDQ) is an FDA approved antibiotic with antيميobacterial 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 MmpSL5 efflux system mediates BDQ resistance in M. intracellulare. Here, we examine the role of MmpT5 in transcriptional regulation of mmpSL5 and BDQ resistance.

Methods. In this study, mmpSL5-mmpT5 genes were cloned from 2 pre-treatment (wild-type mmpT5) and 2 relapse (mutant mmpT5) isolates of M. intracellulare and transformed into M. smegmatis. BDQ MICs were determined as well as expression of mmpSL5 and mmpT5. Reaction and qPCR analysis of BDQ. Transcription of the M. intracellulare mmpT5 and mmpSL5 promoters was monitored with luciferase reporter gene fusions in the presence of wild-type and mutant alleles of mmpT5. Single and multigene constructs were created using the MloI system, and transformed into E. coli DH5a. Constructs containing the M. tuberculosis rv0678 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 the mmpT5-mmpSL5 T5 construct was >1 µg/mL. Even so, strains containing mutant mmpT5 alleles showed enhanced survival after 24 hours exposure to 0.007 µg/mL BDQ. Bacterial colonies associated with mutant mmpT5 alleles exhibited altered morphology relative to wild-type strains. Transcription of mmpSL5 was repressed by wild-type mmpT5, but neither mutant mmpT5 nor rv0678 repressed transcription. The mmpT5 luciferase reporter was not active.

Conclusion. MmpT5 represses transcription of mmpSL5 whereas the operon is dysregulated by mmpT5 mutations. Although rv0678 regulates mmpSL expression in M. smegmatis, it cannot rescue the M. intracellulare mmpSL5 genes. The mmpSL5 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.

Disclosures. All Authors: No reported Disclosures.

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

Michael D. Barnes, PhD1; Madagala A. Taracila, MS2; Joseph D. Rutter, BS2; Minh-Hong Nguyen, MD1; Ryan K. Shields, PharmD, MS1; Cornelius J. Clancy, MD3; and Robert A. Bonomo, MD1; Case Western Reserve University, Cleveland, Ohio; Research Service, Louis Stokes Veterans Affairs Medical Center, Cleveland, Ohio; Louis Stokes Cleveland VA Medical Center, Cleveland, Ohio; University of Pittsburgh, Pittsburgh, Pennsylvania.

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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