2400. Activity of a Long-Acting Echinocandin, Rezafungin, Tested Against Invasive Fungal Isolates Collected Worldwide

Michael A. Pfaller, MD; Shawn A. Messer, MS-MT; Paul R. Rhomberg, BS; Beth A. Schaefer, BS and Mariana Castanheira, PhD; JMI Laboratories, Inc., North Liberty, Iowa

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Background. Echinocandins are important agents for treating invasive fungal infections. We evaluated the activity of rezafungin (RZF; previously CD101), an echinocandin with extended half-life, and comparators using CLSI broth microdilution methods against 719 invasive fungal isolates collected worldwide during 2017.

Methods. Susceptibility tests were conducted on 616 *Candida* spp. (6 species), 25 *C. neoformans* (CNEO), 18 *A. flavus* (AFL), and 60 *A. fumigatus* (AFU) for RZF, anidulafungin, caspofungin, micafungin, and azoles. CLSI clinical breakpoint (CBP) and epidemiological cutoff value (ECV) interpretive criteria were applied.

Results. RZF inhibited 100.0% of *C. albicans* (CA) isolates, 96.3% of *C. tropicalis* (CT), 93.4% of *C. glabrata* (CG), 100.0% of *C. krusei*, and 100.0% of *C. dubliniensis* at ≤0.12 µg/mL. All but 2 (116/118 [98.3%]) *C. parapsilosis* (CP) isolates were inhibited by RZF at ≤2 µg/mL. Resistance to fluconazole was detected among 10.7% of CG, 10.2% of CP, 1.9% of CT, and 0.7% of CA. The activity of RZF against these 6 *Candida* spp. was similar to that of the other echinocandins, the vast majority of which were susceptible/wild type (WT) using CBP/ECV. Fluconazole and other triazoles displayed good activity against CNEO whereas echinocandins, including RZF, displayed limited activity against CNEO isolates (MIC90 >8 µg/mL). Echinocandins displayed good activity against ASF and AFL, and RZF activity was similar to that of anidulafungin, caspofungin, and micafungin. All isolates displayed WT MIC values for the mold-active azoles.

Conclusion. Rezafungin was as active as other echinocandins against common fungal organisms recovered from invasive fungal infections. The extended half-life and stability of rezafungin is very desirable for prevention and treatment, especially in patients who could be discharged on outpatient therapy.

	MIC/MEC$_{50/90}$ (µg/mL)			
Organism (no. tested)	Rezafungin	Anidulafungin	Caspofungin	Micafungin
C. albicans (267)	0.03/0.06	0.015/0.06	0.015/0.03	0.015/0.015
C. glabrata (121)	0.06/0.12	0.06/0.12	0.03/0.06	0.015/0.03
C. parapsilosis (118)	1/2	2/2	0.25/0.5	1/1
C. tropicalis (54)	0.03/0.12	0.03/0.06	0.03/0.06	0.03/0.06
C. dubliniensis (28)	0.06/0.12	0.03/0.12	0.03/0.03	0.015/0.03
C. krusei (28)	0.03/0.12	0.06/0.12	0.12/0.25	0.06/0.12
A. fumigatus (60)	0.015/0.015	0.015/0.03	0.03/0.03	≤0.008/0.015
A. flavus (18)	0.015/0.015	0.015/0.03	0.03/0.03	0.015/0.03

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2401. Risk Factors for Antimicrobial Resistance in Invasive Pneumococcal disease (IPD) in Toronto, Canada, 2012–2017

Thomas Fear, MD[1]; Karen Green, MSc, RN[2]; Agron Plevneshi, BSc[2]; Jeff Li, BSc[2]; Wallis Rudnick, MSc[2]; Sarah Nayani, PhD[3]; Allison McGeer, MD, MSc[4] and Toronto Invasive Bacterial Diseases Network; [1]Internal Medicine, University of Toronto, Toronto, ON, Canada, [2]Mount Sinai Hospital, Toronto, ON, Canada, [3]Microbiology, Sinai Health System, Toronto, ON, Canada, [4]Laboratory Medicine and Pathobiology, University of Toronto, Toronto, ON, Canada

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Background. Several studies have documented factors predictive of antimicrobial resistance (AMR) in invasive pneumococcal disease(IPD). However, the implementation of routine pediatric PCV programs, antimicrobial stewardship, and increasing immunocompromised in populating might be expected to change such factors. We report on predictive factors for AMR in IPD from 2012 to 2017.

Methods. TIBDN performs population-based surveillance for IPD in Toronto/Peel (pop 4.5M). IPD cases are reported to a central office and one isolate/case is serotyped and has antimicrobial susceptibility testing performed by broth microdilution to CLSI standards.

Results. 2459 cases of IPD were identified from January 2012 to December 2017. Overall rates of resistance to penicillin, macrolides, fluoroquinolones, and TMP-SMX were relatively stable over the course were stable over the study. Risk factors for infection with resistant to penicillin at meningitis breakpoints as opposed to penicillin- susceptible pneumococci were current residence at nursing home (odds ratio [OR], 2.30; $P < 0.001$), immune compromised status (OR, 1.41; $P = 0.012$), HIV infection (OR 2.13, P = 0.016), history of receiving PPV23 vaccine (OR 1.38; $P = 0.007$). Infection with TMP-SMX-resistant pneumococci was associated with HIV infection (OR, 3.2; $P = 0.001$) and current residence in a nursing home (OR 2.4, $P = 0.002$). Infection with macrolide-resistant isolates was associated with any use of macrolide 3 months prior to infection (OR, 3.24; $P < 0.001$), or macrolide treatment failure of the current episode (OR, 6.64; $P = 0.003$). Infection with levofloxacin-resistant pneumococci was associated with current residence in a nursing home (OR, 13.7; $P < .001$), and fluorquinolone treatment failure of the current episode (OR 49.4, $P = 0.0034$).

Conclusion. Previous same class antibiotic exposure remains a major predictive factor for macrolide resistance. History of treatment failure is a predictive factor for macrolide and fluoroquinolone failure. HIV infection and immune compromise are risk factors for IPD infection with penicillin resistant pneumococci. Hospital acquisition of infection is no longer a risk factor for fluoroquinolone resistance.

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2402. Daptomycin Pulmonary Eosinophilia: Review of Cases and New Hyperacute Syndromic Presentation

Katelyn West, MS[1]; Kimberly Mackay, PharmD[2] and Graeme N. Forrest, MBBS, FIDSA[3,4]; [1]VA Portland Healthcare System, Portland, Oregon, [2]Pharmacy, VA Portland Healthcare System, Portland, Oregon, [3]Division of Infectious Disease, Veterans Affairs Portland Health Care System, Portland, Oregon, [4]Section of Infectious Disease, Department of Medicine, Oregon Health & Science University, Portland, Oregon

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Background. Daptomycin pulmonary eosinophilia (DPE) has been described as a rare event. Since the Food and Drug Administration (FDA) first described the syndrome which occurs about 3 weeks after starting the drug, it continues to be a miss diagnosed. Most outpatient antibiotic treatment (OPAT) programs focus on screening for CPK elevations. We describe an unusual increase in DPE at our center including acute reactions on re-exposure to daptomycin.

Methods. Retrospective review from local VA pharmacy and OPAT database of adverse drug events (ADE) with daptomycin from 2010 to April 2018. Data evaluated include, age, gender, weight, body mass index (BMI), daptomycin dosing, indication for use, duration of therapy, time to symptom onset, Creatinine clearance, white cell count (WCC), %eosinophilia (%eos), admission to intensive care unit (ICU), and clinical outcomes or interventions.

Results. There were 363 unique initiations of Daptomycin in the time period. There were 17 DPE (5%) and 3 CPK (0.6%) events in that time period. The medians for all DPE was; Age 68 years (range 55–95), BMI 29 m/kg^2 (range 21–49.5), daptomycin dose 500 mg (>7 mg/kg), baseline CrCl 35.5 mL/minute, eosinophilia at onset of DPE 9% (8–44%), and duration of therapy to onset was 21 days (1–33). All recovered on removal of daptomycin, but 5 patients required adjunctive corticosteroid therapy. Four patients had a severe and novel hyperacute DPE within 48 hours of a new initiation of daptomycin therapy. All 4 patients had prior exposure to daptomycin in the last 12 months. They presented with hypoxic respiratory failure, abnormal chest x-rays and/or CT chest scans, with preceding systemic fevers and fatigue after the first dose. All had low grade %eos (3–5%) on prior use, and all recovered rapidly with discontinuation of daptomycin.

Conclusion. DPE may be underreported and is associated with doses of 500 mg or >7 mg/kg, with CrCl <35 mL/minute and older age. Of concern are the new cases of hyperacute DPE within 48 hours of re-exposure to daptomycin that we have seen, who had prior low-grade eosinophilia. Close monitoring of these factors may be warranted in at risk individuals.

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2403. Comparison of Daptomycin Combination Therapy With Ceftaroline or Oxacillin Against Methicillin-Resistant *Staphylococcus aureus* (MRSA) Isolates Causing Persistent Bacteremia

Jeannette Bouchard, PharmD[1]; Chelsea Jones, BA[2]; Ellen Kline, MS[2]; Louise-Marie Oleksiuk, PharmD[1] and Ryan K. Shields, PharmD[3]; [1]UPMC Presbyterian Shadyside, Pittsburgh, Pennsylvania, [2]University of Pittsburgh, Pittsburgh, Pennsylvania, [3]University of Pittsburgh, School of Medicine, Pittsburgh, Pennsylvania

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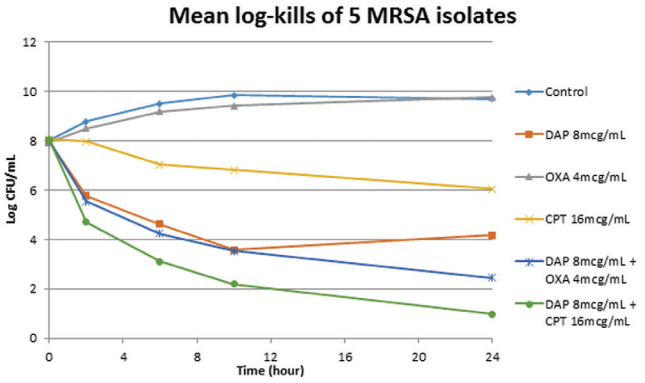
Background. Increasing evidence suggests that daptomycin (DAP) demonstrates *in vitro* synergy in combination with other anti-staphylococcal agents, including ceftaroline (CPT) and oxacillin (OXA), against MRSA. Nevertheless, optimal combinations remain undefined. Here, our objective was to compare DAP in combination with CPT or OXA against MRSA bloodstream isolates collected from patients with persistent bacteremia despite >7 days of vancomycin treatment.

Methods. Minimum inhibitory concentrations (MICs) for DAP, CPT, and OXA were determined in duplicate by reference broth microdilution methods. We used time-kill analyses (TKA) to test free peak concentrations (fC_{max}) of DAP (8 µg/mL), CPT (16 µg/mL), and OXA (4 µg/mL) alone and in combination against 1×10^8 CFU/mL to simulate high-inocula infections. Bactericidal and synergistic activity were defined as a ≥3-$\log_{10}$ decrease in CFU/mL and >2-$\log_{10}$ decrease in CFU/mL in combination compared with the most active single agent, respectively, at 24 hours.

Results. A representative isolate was selected from 12 patients with persistent MRSA bacteremia. Median (range) MICs were 0.5 (0.5–1), 0.5 (0.5–1), and 64 (64–≥128) µg/mL for DAP, CPT, and OXA, respectively. By TKA ($n = 5$ isolates), median log-kills were −3.81, −1.90, and +1.99 $\log_{10}$CFU/mL for DAP, CPT, OXA, respectively. Corresponding rates of bactericidal activity were 80%, 20%, and 0%, respectively. In combination, median log-kills were −7.83 and −4.82 $\log_{10}$CFU/mL for DAP+CPT and DAP+OXA, respectively ($P = 0.111$; Figure 1). DAP was synergistic in combination with CPT or OXA against 80% and 60% of isolates, respectively. Median log-kills in combination with CPT or OXA were higher than DAP alone ($P = 0.003$ and $P = 0.0497$, respectively). At 24 hours, colony counts were below the lower limit of detection (50

CFU/mL) against 60% and 20% of isolates exposed to DAP+CPT or DAP+OXA, respectively.

Conclusion. Among persistent MRSA bloodstream isolates, combinations of DAP + CPT or OXA demonstrates synergy and statistically greater killing effects *in vitro* at fCmax concentrations than DAP alone. Log-kills were greatest with DAP+CPT, which merits further validation in pre-clinical models.



Disclosures. **All authors:** No reported disclosures.

2404. Telavancin (TLV) and Vancomycin (VAN) Activity and Impact on Mechanical Properties When Incorporated into Orthopedic Bone Cement

Aaron Bishop, MS[1]; Sunjung Kim, MS[2]; Matthew Squire, MD[3]; Heidi-Lynn Ploeg, PhD[2] and Warren Rose, PharmD, MPH[4]; [1]Department of Biomedical Engineering, University of Wisconsin – Madison, Madison, Wisconsin, [2]Department of Mechanical Engineering, University of Wisconsin – Madison, Madison, Wisconsin, [3]School of Medicine and Public Health, University of Wisconsin – Madison, Madison, Wisconsin, [4]School of Pharmacy, University of Wisconsin – Madison, Madison, Wisconsin

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Background. To increase available antibiotics for local administration in total joint replacements, this study investigated TLV and VAN added to Palacos® bone cement. Mechanical properties and antimicrobial activity of eluted antibiotics on common causative orthopedic implant pathogens were assessed.

Methods. Palacos (40 g package) samples were loaded with TLV or VAN powder (control 2.0 g) to test drug activity and mechanical properties: bending, compression, and fracture toughness. Samples were prepared following clinical standards and as previously described (Slane *et al.*, 2014 MSE 42: 168–176). All mechanical samples were wet cured for 21 days in PBS at 21°C before testing in accordance with ISO 5833. With a starting inoculum of 10^3 CFU/mL, antibiotic activity was measured for 14 days against: two methicillin-resistant *S. aureus*, one methicillin-susceptible *S. aureus* and one *S. epidermidis*.

Results. The eluted dosages from samples with 0.25 g VAN or more per Palacos package were sufficient to eliminate a 10^3 CFU/mL inoculum of *S. aureus* organisms. 2.0 g of TLV was required to achieve the same bactericidal effect. TLV 2.0 g was able to fully clear the initial inoculum of a high biofilm producing *S. epidermidis*. No tested vancomycin dosage replicated these results. Adding more than 0.5 g of TLV or VAN per Palacos package reduced compressive yield strength to (VAN) or below (TLV) the ISO 70MPa minimum. Fracture toughness and flexural strength were not significantly altered with either antibiotic.

Conclusion. Adding either TLV or VAN to Palacos before polymerization reduced bending properties similarly but maintained ISO standards. More VAN than TLV can be added and still maintain compressive yield strength above ISO requirements (1.0 g VAN vs. 0.5 g TLV). VAN eliminated the tested *S. aureus* strains at a lower added mass. However, TLV was more effective against a high biofilm producing *S. epidermidis*. VAN was highly effective at eliminating a bacterial inoculum consistent with surgical contamination while maintaining ISO standards. The authors would like to acknowledge Theravance Biopharma US, Inc. for their support and funding.

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2405. *In vitro* Synergistic Activity of Sitafloxacin in Combination With Colistin Against Clinical Isolates of Multidrug-Resistant *Acinetobacter baumannii* in Thailand

Vipavee Rodjun, Rescident[1]; Taniya Paiboonvong, MS[1]; Jantana Houngsaitong, MS[2] and Preecha Montakantikul, Assoc. Prof.[2]
[1]Faculty of Pharmacy, Siam University, Bangkok, Thailand, [2]Faculty of Pharmacy, Mahidol University, Bangkok, Thailand

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Background. Multidrug-resistant *Acinetobacter baumannii* (MDR-AB) is a major cause of nosocomial infections, and associated with high mortality rate. The objective of this study was to test synergistic effect of sitafloxacin and colistin against MDR-AB clinical isolates in Thailand.

Methods. The synergistic effect of sitafloxacin in combination with colistin against the 264 MDR-AB clinical isolates from 13 tertiary care hospitals in Thailand were tested. The fractional inhibitory concentration index (FICI) of combination was determined using the checkerboard method according to CLSI 2016. Time–kill assays were performed for 2 strains (H25 and K21) using sitafloxacin alone and in combination with colistin.

Results. The MICs of sitafloxacin and colistin range from 0.0156 to 8 µg/mL, and 0.5–16 µg/mL, respectively. The results of synergy testing for the 264 MDR-AB isolates are shown in Table 1. Sitafloxacin reduced the MIC of colistin 2-fold to 8-fold from the original concentrations (Figure 1). From 43 colistin-resistant isolates in combination tested, 39 isolates (90.7%) become susceptible to colistin. In the time-kill assay, synergistic effects were found for two isolates in all concentrations tested, and bactericidal activity was observed within 4 hours and maintained over 24 hours (Figures 2 and 3).

Conclusion. The synergistic effect of sitafloxacin and colistin combination was found. Most of isolates had at least a 2-fold decrease in MIC of colistin, which could be implied to reduce dose of colistin 50% from regular dose. Sitafloxacin combined with colistin may be benefit for alternative treatment of MDR-AB infections.

Table 1: Synergistic Effect of Sitafloxacin and Colistin Against MDR-AB Isolates (*n* = 264) Using the Checkerboard Assay

	No. of Isolates (%)				
Antimicrobial Agents	Synergy (FICI ≤0.5)	Partial Synergy (FICI >0.5–<1)	Additive (FICI = 1)	Indifference (FICI >1–<4)	Antagonism (FICI ≥4)
Sitafloxacin and colistin	9(3.4)	99(37.5)	75(28.4)	81(30.7)	0(0)

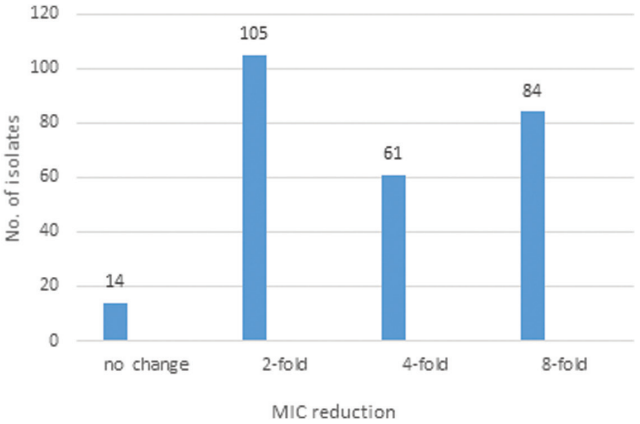

Figure 1: MIC reduction of colistin in combination with sitafloxacin against MDR-AB (*n* = 264).

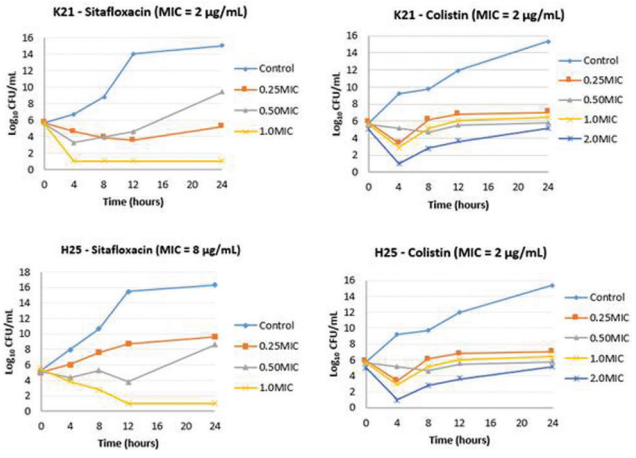

Figure 2: Time–kill curves for sitafloxacin and colistin alone against two isolates of MDR-AB.