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1217. In Vitro Activity of Ceftolozane-Tazobactam vs. Antimicrobial Non-Susceptible Pseudomonas aeruginosa Clinical Isolates Obtained from Across Canada as Part of the CANWARD Study, 2008–2016
Andrew Walkley, MD;1,2 Heather J. Adam, PhD;1,3 Melanie Baxter, MSc;1,2 Philippe Ligache-Wiens, MD;1,2 James Karlowsky, PhD;1,2 Daryl Hoban, PhD;1,2 and George Zhanel, PhD;1,4 Diagnostic Services Manitoba, Winnipeg, MB, Canada

Background. Ceftolozane-tazobactam (C/T) is a novel β-lactam β-lactamase inhibitor combination with a broad spectrum of activity that includes Pseudomonas aeruginosa. The purpose of this study was to evaluate the in vitro activity of C/T and relevant comparators vs. a large collection of antimicrobial non-susceptible (NS) P. aeruginosa clinical isolates obtained from patients across Canada (CANWARD, 2008–2016).

Methods. From January 2008 to December 2016, inclusive, 12 to 15 sentinel hospitals across Canada submitted clinical isolates from patients attending ERs, medical and surgical wards, hospital clinics, and ICUs (CANWARD). Each center was asked to annually submit clinical isolates (consecutive, one per patient/infection site) from blood, respiratory, urine, and wound infections. Susceptibility testing was performed using broth microdilution as described by CLSI. Multidrug-resistant (MDR) P. aerugi- nosa were defined as isolates that tested NS to at least one antimicrobial from ≥3 classes. Extensively drug-resistant (XDR) P. aeruginosa were defined as isolates that tested NS to at least one antimicrobial from ≥5 classes.

Results. 3229 P. aeruginosa isolates were obtained as part of CANWARD. The in vitro activity of C/T and relevant comparators is presented below.

Conclusion. C/T demonstrated excellent in vitro activity vs. antimicrobial NS P. aeruginosa clinical isolates, including MDR, XDR, and meropenem NS subsets. It may prove useful in the treatment of infections caused by these organisms.

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1218. In Vitro Activity of Lefamulin against S. aureus Collected Worldwide from Hospitalized Patients with Bacterial Pneumonia
Susanne Paukner, PhD;1 Robert K. Flamm, PhD;2 Jason Schuchert, PhD;3 Steven G. Sanders, MD;2 and Helio S. Sader, MD;2,4,5 Nabriva Therapeutics, Wien, Austria, 1JMI Laboratories, Inc., North Liberty, Iowa, 2JMI Laboratories, North Liberty, Iowa, 3Nabriva Therapeutics AG, King of Prussia, PA

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Background. S. aureus (SA) is a well-recognized cause of pneumonia from both the community and hospital settings. The clinical management of SA pneumonia is complicated by the invasive infection it can cause and the high prevalence of methicillin-resistance (MR). Lefamulin (LEF) is the first semi-synthetic pleuromutilin antibiotic for IV and oral use in humans. LEF is the first semi-synthetic pleuromutilin antibiotic for IV and oral use in humans and it specifically inhibits bacterial protein synthesis. LEF is currently in Phase 3 trials for the treatment of community-acquired bacterial pneumonia (CABP). This study investigated the in vitro activity of LEF and comparators against SA strains collected from patients hospitalized with pneumonia in 2015.

Methods. 1273 unique SA isolates were collected from hospitalized patients with pneumonia worldwide in 28 countries (33 sites) in 2015 as part of the SENTRY surveillance program. Isolates included 401 hospital-acquired (HA) SA (259 from ICU, 152 from ventilator associated pneumonia, VAP). Susceptibility testing was conducted using the CLSI broth microdilution method and susceptibility was interpreted per CLSI 2017 breakpoint criteria.

Results. LEF was the most potent compound tested, with 99.7% of all SA isolates being inhibited at a concentration of ≤0.25 mg/L (MIC≤50 values of 0.06/0.12 mg/L) and irrespective of the collection source (ICU/non-ICU, VAP/non-VAP). 31.6% of isolates (n = 402) were MRSA of which 99.3% were inhibited at a LEF concentration of ≤0.25 mg/L (MIC≤50). Susceptibility rates for all SA isolates were >90% for ceftaroline, vancomycin, linezolid and doxycycline. Susceptibility to azithromycin, levofloxacin and clindamycin was limited, particularly among MRSA (see Table). Conclusion. SA strains collected from patients hospitalized with pneumonia including HAP and VAP were highly susceptible to LEF regardless of the resistance phenotype to the other antibiotics tested. Due to its potent activity against resistant SA and the most prevalent typical and atypical respiratory pathogens, as well as the availability of IV and oral formulations, LEF has the potential to play a role in the empiric treatment of CABP and supports evaluation in HAP and VAP caused by SA.

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1219. Effects of Iclaprim and Trimethoprim on Exotoxin Production by Methicillin-resistant Staphylococcus aureus
Amy Bryant, PhD;1 Eva Katahira, BA;1 David Huang, MD, PhD;2 and Dennis Stevens, MD, PhD;3 Infectious Diseases, Veterans Affairs Medical Center, Boise, Idaho, 1Motif Biosciences, New York, New York

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Background. Methicillin-resistant Staphylococcus aureus (MRSA) causes serious, often life-threatening, infections. Exotoxins such as alpha-hemolysin (AH), Panton Valentine leukocidin (PVL), and Toxic shock syndrome toxin 1 (TSST-1) mediate pathogenesis and inhibition of toxin production is an important consideration in choosing appropriate treatments. Vancomycin is recommended for severe MRSA infections; however, increasing vancomycin resistance, poor clinical outcomes and nephrotoxicity are serious concerns. Thus newer agents are needed.
including those that block bacterial toxin production. In the current study, we compared the effects of sub-inhibitory doses (sub-MIC) of two folic acid inhibitor antibiotics (iclaciprim, trimethoprim) with cell wall active agents (nafcillin, vancomycin) on transcription and translation of AH, PVL and TSST-1 in two clinical MRSA isolates.

Methods. Community-acquired MRSA strains 1560 (a USA400 strain; AH*, TSST-1*, PVL*) and 04014 (CDC strain 368–04; AH*, TSST-1*, PVL*) were studied. MICs were determined by standard microbroth dilution. Gene expression was studied by northern blotting and/or qRT-PCR, toxins were quantitated by ELISA (PVL and TSST-1) and rabbit Pseudomonas aeruginosa lipate assay (AH*). Results. In agreement with our previous findings, nafcillin increased production of AH, TSST-1, and PVL compared with untreated control cultures. In both MRSA strains, iclacramp and trimethoprim delayed the onset of mRNA production and increased its peak duration at later time points. Both iclacramp and trimethoprim suppressed AH production in both strains of MRSA and delayed, but did not reduce, maximal TSST-1 production in MRSAs1560. Trimethoprim significantly increased maximal PVL production over both untreated and iclacramp-treated cultures.

Conclusion. The folic acid antagonist antibiotics, iclacramp and trimethoprim, altered both mRNA synthesis dynamics and protein toxin production in MRSA at concentrations below those that inhibit bacterial growth. These results, plus the fact that iclacramp is 15-fold more active than trimethoprim (MICs = 0.13 and 2.0 μg/mL, respectively), provide additional rationale for the use of iclacramp to treat complicated MRSA infections.

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1220. In Vitro Activity of Lefamulin Against a Global Collection of Bacterial Pathogens Commonly Causing Community-Acquired Bacterial Pneumonia (CABP, SENTRY 2015)

Susanne Paukner, PhD;1 Helio S. Sader, MD, PhD;2 Jennifer M. Streit, BS;3 Robert K. Flamm, PhD;7 and Steven P. Gelone, PharmD;7, Nabhriva Therapeutics, Wien, Austria; JMI Laboratories, Inc., North Liberty, Iowa; Nabhriva Therapeutics AG, King of Prussia, PA

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Background. CABP is the number one reason for death by infectious disease worldwide and emerging resistance complicates its treatment. Lefamulin is the first semi-synthetic pleuromutilin antibiotic for IV and oral use in humans. It is currently in Phase 3 trials for the treatment of CABP in adults. Lefamulin effectively and selectively inhibits bacterial translation by binding to the peptidyl transferase center (PTC) via four H-bonds and other interactions at the A- and P-site resulting in an "induced fit." This study investigated the activity of lefamulin and comparators against a contemporary set of bacterial pathogens associated with community-acquired respiratory infections collected worldwide.

Methods. Unique patients’ isolates (n = 2817) were collected globally in US (19.7%), Europe (36.9%), Latin America (5.7%) and Asia-Pacific region (37.6%) (30 countries, 116 sites) from adult and pediatric patients with respiratory tract infection (88.9%), bloodstream infections (5.5%) and other infections (2.4%). Lefamulin and comparators were tested by CLSI broth microdilution and susceptibility was determined using the CLSI (2017) breakpoints.

Results. LEF was the most potent compound tested, with 99.7% of all S. pneumoniae isolates susceptible (S; MIC<sub>50/90</sub> 0.008/0.5 mg/L) and its activity was not affected by resistance to other antibiotics classes. S. pneumoniae isolates were largely susceptible to levofloxacin (99.1%) and ceftriaxone (96.5%), while 34.5%, 23.3% and 16.8% of isolates were resistant to macrolides, tetracyclines or fluoroquinolones. These data support the ongoing collection of contemporary respiratory pathogens and its activity was unchanged among CoNS, (61.4% MRSA), DALBA and β-lactamase positive and negative subgroups of SPN. The MIC<sub>50/90</sub> values were ≥8-fold lower compared with DAPTO (MIC<sub>50/90</sub> 0.25/0.5 mg/L) against all S. aureus. Among CoNS, (61.4% MRSA), DALBA (MIC<sub>50/90</sub> 0.03/0.06 mg/L) was the most potent agent, followed by DAPTO (MIC<sub>50/90</sub> 0.25/0.5 mg/L), LNZ (MIC<sub>50/90</sub> 0.51/1 mg/L), and VAN (MIC<sub>50/90</sub> 1/2 μg/mL).

Conclusion. DALBA demonstrated potent in vitro activity against common gram-positive isolates causing CABP (2011–2016) and appears to be a viable candidate for treating BJI/osteomyelitis caused by gram-positive isolates.

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1221. Antimicrobial Activity of Dalbavancin and Comparator Agents Tested against Gram-Positive Clinical Isolates Causing Bone and Joint Infections in the United States (US) Medical Centers (2011–2016)

Helio S. Sader, MD, PhD; Rodrigo E. Mendez, PhD; Robert K. Flamm, PhD and Michael A. Pfaffer, MD; JMI Laboratories, Inc., North Liberty, Iowa

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Background. Bone and joint infections (BJI) comprise a series of disorders, including septic arthritis, osteomyelitis, and prosthetic joint infections. We evaluated the activity of dalbavancin (DALBA) against pathogens isolated from BJI in US hospitals.

Methods. A total of 743 organisms collected from 55 hospitals in 2011–2016 were evaluated, including 463 S. aureus, 88 coagulase-negative staphylococci (CoNS), 104 β-haemolytic streptococci (BHS), 60 E. faecalis, and 29 viridans group streptococci (VGS).

Results. Dalbavancin (DLX) (MIC<sub>50/90</sub> 6.2/12.5 mg/L) was the most common pathogen associated with BJI, followed by BHS (14.0%) and CoNS (11.8%). All S. aureus (41.5% methicillin-resistant (MRSA)) isolates were susceptible (S) to DALBA, linezolid (LNZ), teicoplanin (TEI) and vancomycin (VAN), while daptomycin (DAPTO) and clindamycin (CLI) showed susceptibility rates of 99.8% and 87.7% (CLSI), respectively. DALBA MIC<sub>50/90</sub> results (MIC<sub>50/90</sub> 0.03/0.06 mg/mL) were ≥8-fold lower compared with DAPTO (MIC<sub>50/90</sub> 0.25/0.5 mg/L) against all S. aureus. Among CoNS, (61.4% MRSA), DALBA (MIC<sub>50/90</sub> 0.03/0.06 mg/L) was the most potent agent, followed by DAPTO (MIC<sub>50/90</sub> 0.25/0.5 mg/L), LNZ (MIC<sub>50/90</sub> 0.51/1 mg/L), and VAN (MIC<sub>50/90</sub> 1/2 μg/mL).

Conclusion. DALBA demonstrated potent in vitro activity against common gram-positive isolates causing BJI (2011–2016) and appears to be a viable candidate for treating BJI osteomyelitis caused by gram-positive isolates.

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Table: In vitro activity of lefamulin and comparators.

| Organism (MIC<sub>50/90</sub> μg/mL) | LEF | DALBA | DAPTO | LNZ | VAN | TEI |
|-------------------------------|-----|------|-------|-----|-----|-----|
| S. pneumoniae (S) | 0.008/0.5 | 0.25/0.5 | ≤0.06/0.03 | ≤0.03/0.06 | ≤0.03/0.06 | ≤0.03/0.06 |
| S. agalactiae (S) | 0.008/0.5 | 0.25/0.5 | ≤0.06/0.03 | ≤0.03/0.06 | ≤0.03/0.06 | ≤0.03/0.06 |
| E. faecalis (S) | 0.008/0.5 | 0.25/0.5 | ≤0.06/0.03 | ≤0.03/0.06 | ≤0.03/0.06 | ≤0.03/0.06 |
| E. faecium (S) | 0.008/0.5 | 0.25/0.5 | ≤0.06/0.03 | ≤0.03/0.06 | ≤0.03/0.06 | ≤0.03/0.06 |
| S. aureus (MRSA) | 0.25/4 | ≥4/≥4 | ≤0.06/0.03 | ≤0.03/0.06 | ≤0.03/0.06 | ≤0.03/0.06 |

1. Using oral breakpoints of ≤0.5 μg/mL for resistant and ≤2 μg/mL for intermediate according to CLSI (2017)

Disclosures. S. Paukner, Nabhriva Therapeutics: Employee and Shareholder, Salary; H. S. Sader, Nabhriva Therapeutics: Research Contractor, Research grant; J. M. Streit, Nabhriva Therapeutics: Research Contractor, Research grant; R. K. Flamm, Nabhriva Therapeutics: Research Contractor, Research grant; S. P. Gelone, Nabhriva Therapeutics: Employee and Shareholder, Salary