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 (iclaprim, 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^+, $TSST\text{-}1^+$, PVL^-) and 04014 (CDC strain 368–04; AH^+, $TSST\text{-}1^-$, 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 erythrocyte lysate 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, iclaprim and trimethoprim delayed the onset of mRNA production and shifted its peak production to later time points. Both iclaprim and trimethoprim suppressed AH production in both strains of MRSA and delayed, but did not reduce, maximal TSST-1 production in MRSA1560. Trimethoprim significantly increased maximal PVL production over both untreated and iclaprim-treated cultures.

Conclusion. The folic acid antagonist antibiotics, iclaprim 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 iclaprim is 15-fold more active than trimethoprim (MICs = 0.13 and 2.0 ug/ml, respectively), provide additional rationale for the use of iclaprim 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)

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Background. CABP is the number one reason for death by infectious diseases 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 (88.0%), 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 being inhibited at a concentration of ≤0.25 mg/L ($MIC_{50/90}$ values of 0.06/0.12 mg/L) and its activity was not affected by resistance to other antibiotic 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, tetracycline and clindamycin, respectively. Lefamulin also showed potent activity against *H. influenzae* ($MIC_{50/90}$ of 0.5/1 mg/L), including 22.0% of ß-lactamase producing strains, and *M. catarrhalis* (0.06/0.12 mg/L).

Conclusion. Lefamulin demonstrated potent *in vitro* activity against this global collection of contemporary respiratory pathogens and its activity was unchanged regardless of resistance phenotype to the other antibiotic classes including macrolides, ß-lactams, tetracyclines or fluoroquinolones. These data support the continued clinical development of lefamulin for the treatment of respiratory tract infections, including CABP.

Table: *In vitro* activity of lefamulin and comparators.

		$MIC_{50/90}$ [mg/L]					
Organism	N	Lefamulin	Amoxi/Clav	Ceftriaxone	Azithromycin	Levofloxacin	Tetracycline
S. pneumoniae	1835	0.06 / 0.12	≤0.03 / 2	0.03 / 1	0.06 / >4	1 / 1	0.25 / >4
Penicillin non-susceptible [a]	644	0.06 / 0.12	1 / >4	0.5 / 1	>4 / >4	1 / 1	>4 / >4
Macrolide resistant	633	0.06 / 0.12	0.5 / 4	0.25 / 1	>4 / >4	1 / 1	>4 / >4
H. influenzae	536	0.5 / 1	0.5 / 2	≤0.015 / ≤0.015	1 / 1	≤0.015 / ≤0.015	0.5 / 0.5
ß-lactamase positive	118	0.5 / 1	1 / 2	≤0.015 / ≤0.015	0.5 / 1	≤0.015 / ≤0.015	0.5 / 0.5
M. catarrhalis	446	0.06 / 0.12	0.12 / 0.25	0.25 / 0.5	0.015 / 0.03	0.03 / 0.03	0.25 / 0.25

[a], Using oral breakpoints of ≥2 µg/mL for resistant and 0.12-1 µg/mL for intermediate according to CLSI (2017)

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

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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 744 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). Bacteria were identified by standard algorithms and MALDI-TOF-MS. Susceptibility testing was performed by CLSI methods (M07-A10); interpretation of MIC results used CLSI (2017) and EUCAST (2017) criteria.

Results. *S. aureus* (62.2%) 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 results ($MIC_{50/90}$, ≤0.03/0.06 µg/mL) were ≥8-fold lower compared with DAPTO ($MIC_{50/90}$, 0.25/0.5 µg/mL) against all *S. aureus*. Among CoNS, (61.4% MRSA), DALBA ($MIC_{50/90}$, ≤0.03/0.06 µg/mL) was the most potent agent, followed by DAPTO ($MIC_{50/90}$, 0.25/0.5 µg/mL), LNZ ($MIC_{50/90}$, 0.5/1 µg/mL), and VAN ($MIC_{50/90}$, 1/2 µg/mL). DALBA inhibited all *E. faecalis* isolates at ≤0.25 µg/mL (FDA S breakpoint), except for 3 VAN-resistant (VanA) isolates. High susceptibility rates for ampicillin (98.3%; CLSI), DAPTO (100.0%), LNZ (100.0%), TEI (93.3%) and VAN (93.3%) were obtained against *E. faecalis*. DALBA, DAPTO, LNZ, ceftriaxone, penicillin, and VAN were active against all BHS (100.0%S), while DALBA ($MIC_{50/90}$, ≤0.03/0.06 µg/mL; 100.0%S) was the most active agent against VGS, inhibiting all isolates at ≤0.06 µg/mL. Ceftriaxone, LNZ, DAPTO, and VAN were also active against VGS (93.1 – 100.0%S; CLSI), whereas CLI (82.8%S) had marginal activity.

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 cocci.

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1222. Activity of Delafloxacin When Tested Against Bacterial Surveillance Isolates Collected in the US and Europe During 2014–2016 as Part of a Global Surveillance Program

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Background. Delafloxacin (DLX) is an investigational anionic fluoroquinolone with an NDA that is under US FDA review to treat acute bacterial skin and skin structure infections and is undergoing Phase 3 studies to treat community-acquired bacterial pneumonia.

Methods. A total of 36,683 Gram-positive (GP) and -negative (GN) bacteria isolated during 2014–2016 were selected from medical centers in the US and Europe. Susceptibility testing (S) was performed by frozen-form broth microdilution methods for DLX and comparators.

Results. DLX was very active against *Staphylococcus aureus* (SA, n = 9,355; $MIC_{50/90}$, 0.008/0.5 mg/L) while the levofloxacin (LEV) $MIC_{50/90}$ was 0.25/>4 mg/L (67.9%S). The $MIC_{50/90}$ for methicillin-resistant SA (MRSA) was 0.12/1 mg/L. For MRSA, all isolates were S to vancomycin and daptomycin (DAP), linezolid and tigecycline (TGC) S was ≥99.9%. Decreased rates of S were noted for LEV (29.8%), clindamycin (72.9%), and erythromycin (17.3/17.8%; CLSI/EUCAST). Minocycline ($MIC_{50/90}$, 0.12/0.25 mg/L), ceftaroline ($MIC_{50/90}$, 0.25/0.5 mg/L), DAP ($MIC_{50/90}$, 0.5/0.5 mg/L), and DLX ($MIC_{50/90}$, 0.015/0.5 mg/L) were the most active agents tested against coagulase-negative staphylococci. Against *Streptococcus pneumoniae* (SPN), the $MIC_{50/90}$ for DLX (0.015/0.03 mg/L) and TGC (0.03/0.06 mg/L) were the lowest among the agents tested. The DLX $MIC_{50/90}$ values did not vary among the penicillin-S, -intermediate, and -R subgroups of SPN. The $MIC_{50/90}$ values for DLX against *S. pyogenes* and *S. agalactiae* were 0.015/0.03 mg/L. DLX was highly active against *Haemophilus influenzae*. The DLX $MIC_{50/90}$ (≤0.001/0.004 mg/L) was the same for β-lactamase positive and negative *H. influenzae*. Against *Enterobacteriaceae*, 76.0% of DLX MIC values were ≤1 mg/L. Susceptibility to LEV was 80.8%, and S to ceftriaxone, ceftazidime (CAZ), and cefepime ranged from 78.5–86.3%. A total of 72.6% of *Pseudomonas aeruginosa* isolates exhibited DLX MIC values ≤1 mg/L, while LEV S was 73.2% and CAZ was 81.6%. The $MIC_{50/90}$ for both DLX and LEV were 0.5/>4 mg/L, respectively.