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Evaluation of Telavancin Activity versus Daptomycin and Vancomycin against Daptomycin-Nonsusceptible *Staphylococcus aureus* in an *In Vitro* Pharmacokinetic/Pharmacodynamic Model

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Daptomycin-nonsusceptible (DNS) *Staphylococcus aureus* strains have been reported over the last several years. Telavancin is a lipoglycopeptide with a dual mechanism of action, as it inhibits peptidoglycan polymerization/cross-linking and disrupts the membrane potential. Three clinical DNS *S. aureus* strains, CB1814, R6212, and SA-684, were evaluated in an *in vitro* pharmacokinetic/pharmacodynamic (PK/PD) model with simulated endocardial vegetations (starting inoculum, $10^{8.5}$ CFU/g) for 120 h. Simulated regimens included telavancin at 10 mg/kg every 24 h (q24h; peak, 87.5 mg/liter; $t_{1/2}$, 7.5 h), daptomycin at 6 mg/kg q24h (peak, 95.7 mg/liter; $t_{1/2}$, 8 h), and vancomycin at 1 g q12h (peak, 30 mg/liter; $t_{1/2}$, 6 h). Differences in CFU/g between regimens at 24 through 120 h were evaluated by analysis of variance with a Tukey's *post hoc* test. Bactericidal activity was defined as a ≥3-$\log_{10}$ CFU/g decrease in colony count from the initial inoculum. MIC values were 1, 0.25, and 0.5 mg/liter (telavancin), 4, 2, and 2 mg/liter (daptomycin), and 2, 2, and 2 mg/liter (vancomycin) for CB1814, R6212, and SA-684, respectively. Telavancin displayed bactericidal activities against R6212 (32 to 120 h; −4.31 $\log_{10}$ CFU/g), SA-684 (56 to 120 h; −3.06 $\log_{10}$ CFU/g), and CB1814 (48 to 120 h; −4.9 $\log_{10}$ CFU/g). Daptomycin displayed initial bactericidal activity followed by regrowth with all three strains. Vancomycin did not exhibit sustained bactericidal activity against any strain. At 120 h, telavancin was significantly better at reducing colony counts than vancomycin against all three tested strains and better than daptomycin against CB1814 ($P < 0.05$). Telavancin displayed bactericidal activity *in vitro* against DNS *S. aureus* isolates.

There are limited treatment options for multidrug-resistant Gram-positive pathogens, including daptomycin-nonsusceptible (DNS) *Staphylococcus aureus*. Currently, DNS *S. aureus* isolates are defined by the Clinical and Laboratory Standards Institute (CLSI) as organisms with a daptomycin MIC of >1 mg/liter (7). Although relatively rare (0.01 to 0.1%), DNS *S. aureus* presents a unique treatment challenge to clinicians when encountered, as it often occurs in high-inoculum infections requiring prolonged therapy, such as endocarditis, osteomyelitis, septic joint infections, and complicated bacteremia (4, 13, 21, 30). The optimal therapy for infections with DNS *S. aureus* remains undefined. Potential treatment options for DNS *S. aureus* infections cited in the recent guidelines from the Infectious Diseases Society of America on the treatment of methicillin-resistant *S. aureus* (MRSA) infections are based on limited data and include quinupristin-dalfopristin, trimethoprim-sulfamethoxazole, daptomycin plus trimethoprim-sulfamethoxazole, linezolid, and telavancin (21).

Telavancin is a new lipoglycopeptide with activity against Gram-positive organisms, including *S. aureus*. Telavancin acts through a dual mechanism that includes inhibition of phosphatidylglycerol synthesis and disruption of bacterial membrane barrier function (22, 23). It is hypothesized that this dual mechanism accounts for the increased potency and low MIC_{90} values of 0.25 mg/liter against *S. aureus* (27, 28). This dual mechanism of action may therefore afford telavancin an advantage in treating drug-resistant Gram-positive organisms, including DNS *S. aureus*. In the current investigation, we evaluated telavancin versus daptomycin and vancomycin against DNS *S. aureus* isolates in an *in vitro* pharmacokinetic/pharmacodynamic (PK/PD) model of simulated endocardial vegetations.

(This study was presented as a poster presentation at the 51st Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), Chicago, IL, 2011.)

MATERIALS AND METHODS

Bacterial strains. A total of three clinical DNS *S. aureus* isolates were evaluated: SA-684 (a MRSA strain recovered from a patient during therapy for tricuspid endocarditis; provided by G. W. Kaatz, J. Dingell VA Hospital, Detroit, MI); CB1814 (a methicillin-susceptible *S. aureus* isolate from the daptomycin bacteremia and endocarditis clinical trial); R6212 (a heteroresistant vancomycin-intermediate *S. aureus* [hVISA] isolate from Detroit Medical Center) (17). In all isolates, the DNS was stable to 5 serial passages on tryptic soy agar and was confirmed by daptomycin population analysis (data not shown).

Antimicrobials. Telavancin (Theravance, Inc., South San Francisco, CA) was provided by the manufacturer. Daptomycin was commercially purchased (Cubist Pharmaceuticals). Vancomycin was obtained from Sigma Chemical Company (St. Louis, MO).

Media. Mueller-Hinton broth II (Difco, Detroit, MI) with 25 mg/liter calcium and 12.5 mg/liter magnesium (MHB II) was used for all *in vitro* PK/PD models used to evaluate telavancin and vancomycin. Supplemented Mueller-Hinton broth (SMHB) supplemented to 75 mg/liter calcium (equivalent to 50 mg/liter of calcium in the presence of albumin) was used for all *in vitro* PK/PD models due to the dependency of daptomycin

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on calcium for antimicrobial activity (1, 19). MHB II and agar (Bacto; Difco, Detroit, MI) supplemented with 50 mg/liter of calcium were used for population analysis and daptomycin drug plates. Brain heart infusion agar (Difco, Detroit, MI) was used for vancomycin drug plates. Colony counts were determined using tryptic soy agar (TSA; Difco, Detroit, MI) plates.

Susceptibility testing. MICs were determined by broth microdilution to 10^6 according to the Clinical and Laboratory Standards Institute guidelines (7). All samples were incubated at 35°C for 24 h.

SEVs. Simulated endocardial vegetations (SEVs) were prepared as previously described (1, 5, 6, 15, 20, 29, 32–34). Organism stocks were prepared by inoculating three TSA plates with lawns for overnight growth at 35°C. Organisms were swabbed from the growth plates into 5-ml test tubes of SMHB, resulting in a concentration of approximately 10^{10} CFU/ml. SEVs were prepared in 1.5-ml siliconized Eppendorf tubes by mixing 0.05 ml of diluted organism suspension (final inoculum, 8.5 $\log_{10}$ CFU/0.5 g), 0.5 ml of cryoprecipitated human antihemophilic factor from volunteer donors (American Red Cross, Detroit, MI), and 0.025 ml of platelet suspension (platelets mixed with normal saline; 250,000 to 500,000 platelets per clot). A volume of 0.05 ml of bovine thrombin (5,000 units/ml; GenTrac, Inc., Middleton, WI) was added to each tube after insertion of a sterile monofilament line into the mixture. The resultant simulated vegetations were then removed from the Eppendorf tubes by using a sterile disposable plastic needle (Becton Dickinson, Sparks, MD) and introduced into the model. This methodology resulted in each SEV consisting of approximately 3 to 3.5 g/dl of albumin and 6.8 to 7.4 g/dl of total protein.

***In vitro* PK/PD model.** A two-compartment *in vitro* model consisting of a 250-ml two-compartment glass apparatus with ports, in which the SEVs were suspended, was utilized for all simulations (1, 5, 6, 15, 20, 29, 32–34). The apparatus was prefilled with medium, and antibiotics were administered as boluses over a 120-h time period into the central compartment via an injection port. The model apparatus was placed in a 37°C water bath throughout the procedure, and a magnetic stir bar was placed in the medium for thorough mixing of the drug in the model. Fresh medium was continuously supplied and removed from the compartment along with the drug via a peristaltic pump (Masterflex; Cole-Parmer Instrument Company, Chicago, IL) set to simulate the half-lives of the antibiotics. Simulated antibiotic regimens included telavancin at 10 mg/kg every 24 h (peak, 87.5 mg/liter; average half-life, 7.5 h), daptomycin at 6 mg/kg every 24 h (peak, 95.7 mg/liter; average half-life, 8 h), and vancomycin at 1 g every 12 h (peak, 30 mg/liter; average half-life, 6 h) (3, 31). All models were evaluated in duplicate.

Pharmacodynamic analysis. Two simulated endocardial vegetations were removed from the SEV model at 0, 4, 8, 24, 32, 48, 56, 72, 96, and 120 h (1, 5, 6, 15, 20, 29, 32–34). The SEVs were homogenized and diluted in cold saline to be plated onto TSA plates. If the vancomycin or daptomycin concentration at the anticipated dilution was within 1 tube dilution of the MIC or higher, then vacuum filtration was used to avoid antibiotic carryover. When vacuum filtration was used, samples were washed through a 0.45-μm filter with normal saline to remove the antimicrobial agent and recover the bacteria on the filter, which was then placed on a TSA plate. These methods have a lower limit of reliable detection of 1 $\log_{10}$ CFU/g. Telavancin carryover cannot be handled by this method, likely due to binding to the filter paper. If the telavancin concentration at the anticipated dilution was within 1 tube dilution of the MIC or higher, the samples were pelleted by centrifugation and the supernatant removed before being resuspended in 0.5 ml of normal saline. These samples were processed through a 5-μm filter needle twice (to bind telavancin) before the samples were drop plated as usual. This method has a lower limit of reliable detection of ~3.5 $\log_{10}$ CFU/g. Plates were incubated at 35°C for 24 h, at which time colony counts were performed. The total reduction in the $\log_{10}$ CFU/g over 120 h was determined by plotting time-kill curves based on the number of remaining organisms over the 120-h time period. Bactericidal activity (99.9% kill) was defined as a ≥3-$\log_{10}$ CFU/g reduction in colony count from the initial inoculum. Bacteriostatic activity was defined as a <3-$\log_{10}$ CFU/g reduction in colony count from the initial inoculum, while inactivity was defined as no observed reductions in initial inocula. The time to achieve 99.9% bacterial load reduction was determined by linear regression or visual inspection (if r^2 was ≤0.95).

TABLE 1 MICs for tested isolates

Isolate	MIC[a] (μg/ml)		
	TLV	DAP	VAN
CB1814	1	4	2
R6212	0.25	2	2
SA-684	0.5	2	2

[a] TLV, telavancin; DAP, daptomycin; VAN, vancomycin.

Pharmacokinetic analysis. Pharmacokinetic samples were obtained through the injection port of each model (in duplicate) at 0.5, 1, 2, 4, 8, 24, 32, 48, 56, 72, 96, and 120 h for verification of target antibiotic concentrations. All samples were stored at −70°C until analysis. Vancomycin concentrations were determined in a fluorescence polarization immunoassay (Abbott Diagnostics TDx). This assay has a limit of detection of 2.0 μg/ml with a coefficient variation (CV) of ≤12%. Concentrations of telavancin and daptomycin were determined by microbioassay by utilizing *Micrococcus luteus* ATCC 9341. For telavancin, holes were made in antibiotic medium 11 agar plates (Difco, Detroit, MI) preswabbed with a 0.5 McFarland suspension of the test organism and filled with standards or samples (50 μl) (2, 20). This assay has a limit of detection of 10.0 μg/ml with a CV of ≤4.5%. For daptomycin, blank ¼-in. disks were placed on a preswabbed plate of antibiotic medium 2 (Difco, Detroit, MI) and spotted with 10 μl of the standard or sample (CV ≤ 12%). Each standard and sample was tested in duplicate. Plates were incubated for 18 to 24 h at 35°C, at which time the zone sizes were measured using a protocol reader (Microbiology International, Frederick, MD). The half-lives, areas under the concentration-time curves (AUCs), AUC/MIC ratio, and peak concentrations of the antibiotics were determined by using PK Analyst software (version 1.10; MicroMath Scientific Software, Salt Lake City, UT). The AUC was determined by the trapezoidal method.

Resistance. Development of resistance was evaluated at multiple time points throughout the simulation at 0, 8, 24, 48, 72, 96, and 120 h for daptomycin and vancomycin. Samples of 100 μl from each time point were plated on MH agar (MHA) and brain heart infusion plates containing 3 times the MICs of daptomycin and vancomycin to assess the development of resistance. Plates were examined for growth after 24 to 48 h of incubation at 35°C. Since we observed additional drug carryover in the SEVs for televancin (due to lower MIC values), the SEV samples for televancin could not be plated directly onto MHA to assess the development of drug resistance. Therefore, the telavancin population analysis was performed on the initial isolate and the isolate at 120 h to assess any shifts in the population susceptibility from baseline.

Statistical analysis. Changes in CFU/g at 24, 48, 72, 96, and 120 h were compared by two-way analysis of variance with Tukey's *post hoc* test. A P value of ≤0.05 was considered significant. All statistical analyses were performed using SPSS Inc. (Chicago, IL) statistical software (release 10.07).

RESULTS

MIC results for selected isolates are summarized in Table 1. CB1814 and SA-684 were confirmed non-hVISA/non-VISA, and R6212 was determined to be hVISA by modified population analysis. Observed peak and $t_{1/2}$ values for vancomycin were 29.2 to 33.7 μg/ml (target, 30 μg/ml) and 5.2 to 6.5 h (target, 6 h). For telavancin, achieved peak values were 82.2 to 91.2 μg/ml (target, 87.5 μg/ml) and achieved $t_{1/2}$ values were 7.6 to 9.1 h (target, 7.5 h). Daptomycin exhibited peak (target, 95.7 μg/ml) and $t_{1/2}$ (tar-

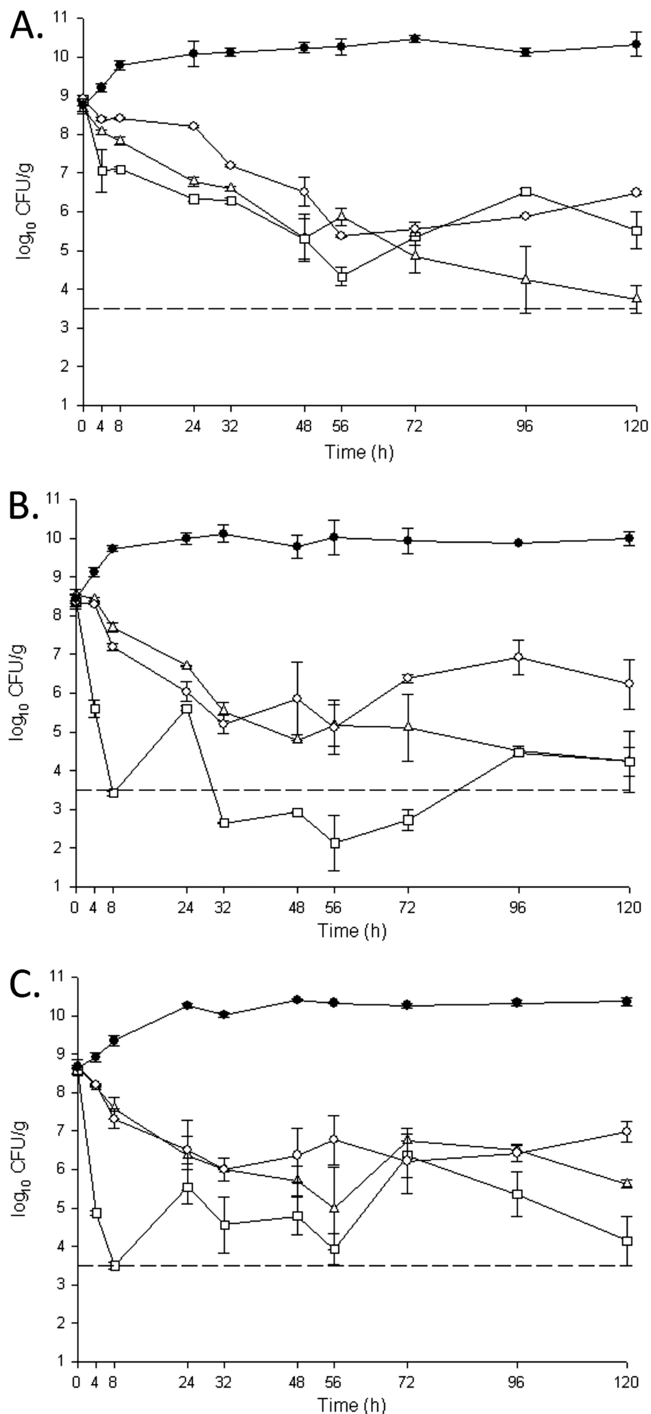

FIG 1 Activity of telavancin, daptomycin, and vancomycin against CB1814 (A), R6212 (B), and SA-684 (C). Telavancin, open triangles; daptomycin, open squares; vancomycin, open circles; growth control, filled circles; dashed line, telavancin limit of accuracy.

get, 8 h) values of 101.8 to 111.1 μg/ml and 7.1 to 9.1 h, respectively.

The quantitative changes in the $\log_{10}$ CFU/g for the tested regimens against the three strains are displayed in Fig. 1A to C. As shown, telavancin displayed sustained bactericidal activities against all three strains. Against CB1814, telavancin displayed sustained bactericidal activity ($-4.9 \log_{10}$ CFU/g at 120 h) and a statistically significantly greater reduction in CFU/g at 120 h than daptomycin or vancomycin ($P < 0.05$). Telavancin also displayed early (32 h) and sustained bactericidal activity ($-4.31 \log_{10}$ CFU/g at 120 h) against R6212. Against SA-684, telavancin maintained bactericidal activity at 120 h ($-3.06 \log_{10}$ CFU/g). Vancomycin did not display sustained bactericidal activity against any strain. At 120 h, telavancin reduced the CFU/g significantly more than vancomycin against R6212 and SA-684 ($P < 0.05$). Daptomycin displayed initial bactericidal activity followed by regrowth for all three strains. No isolates with additional nonsusceptibility to daptomycin or resistance to vancomycin were recovered. Evaluation of isolates by telavancin population analysis revealed similar profiles before and after exposure to telavancin in the SEV *in vitro* PK/PD model, with a slight shift for SA-684 (Fig. 2).

DISCUSSION

The optimal treatment for DNS *S. aureus* infections remains to be defined, and current treatment options are based on limited evidence (4, 21). Increasing the treatment challenges associated with these infections, DNS *S. aureus* is most commonly found in deep-seated high-inoculum infections, such as osteomyelitis, septic arthritis, and endocarditis, which require long-term treatment (4). In this study we evaluated the activity of the new lipoglycopeptide telavancin against DNS *S. aureus* in an *in vitro* PK/PD model of simulated endocardial vegetations. This *in vitro* model incorporates a high inoculum of bacteria embedded into human fibrin and platelets, which are subsequently exposed to antibiotics dosed to achieve simulation of human pharmacokinetics over the course of the 5-day evaluation period. Under these experimental conditions, telavancin displayed bactericidal activities against all three strains tested and was statistically significantly more active than vancomycin. This additional activity compared to vancomycin is likely attributable to the dual mechanism of action of telavancin. Daptomycin displayed activity initially against all strains tested; however, regrowth occurred due to DNS.

The mechanism by which *S. aureus* develops nonsusceptibility to daptomycin is not fully understood; however, it appears to be due to a series of incremental changes commonly but not universally found in all DNS *S. aureus* strains (8, 12, 14, 16, 17, 26, 35–37). In general, DNS *S. aureus* strains are associated with increased cell surface charge, increased cell wall thickness, changes in membrane fluidity, and decreased cytoplasmic membrane depolarization by daptomycin (11, 25, 26). The increase in positive cell surface charge is hypothesized to decrease daptomycin activity via repulsion of the active positively charged daptomycin-Ca^{2+} complex and inhibition of daptomycin-induced membrane perturbation (18). Mutations in the *mprF* gene leading to overexpression of the MprF protein contribute to increased positive surface charge via translocation of positively charged phospholipids to the outer side of the cytoplasmic membrane and by lysinylation of membrane phosphatidylglycerol (11, 26). Increased D-alanylation of cell wall teichoic acids via increased expression of the *dltABCD* operon also contributes to the increased positive surface charge (35). An increase in cell wall thickness, which is most commonly observed in isolates with concurrent decreased susceptibility to vancomycin, may contribute to DNS via an affinity trapping mechanism similar to vancomycin in VISA strains (8–10, 36).

Our results demonstrate telavancin's activity against daptomycin-nonsusceptible strains of *S. aureus*. Indeed, the bactericidal activi-

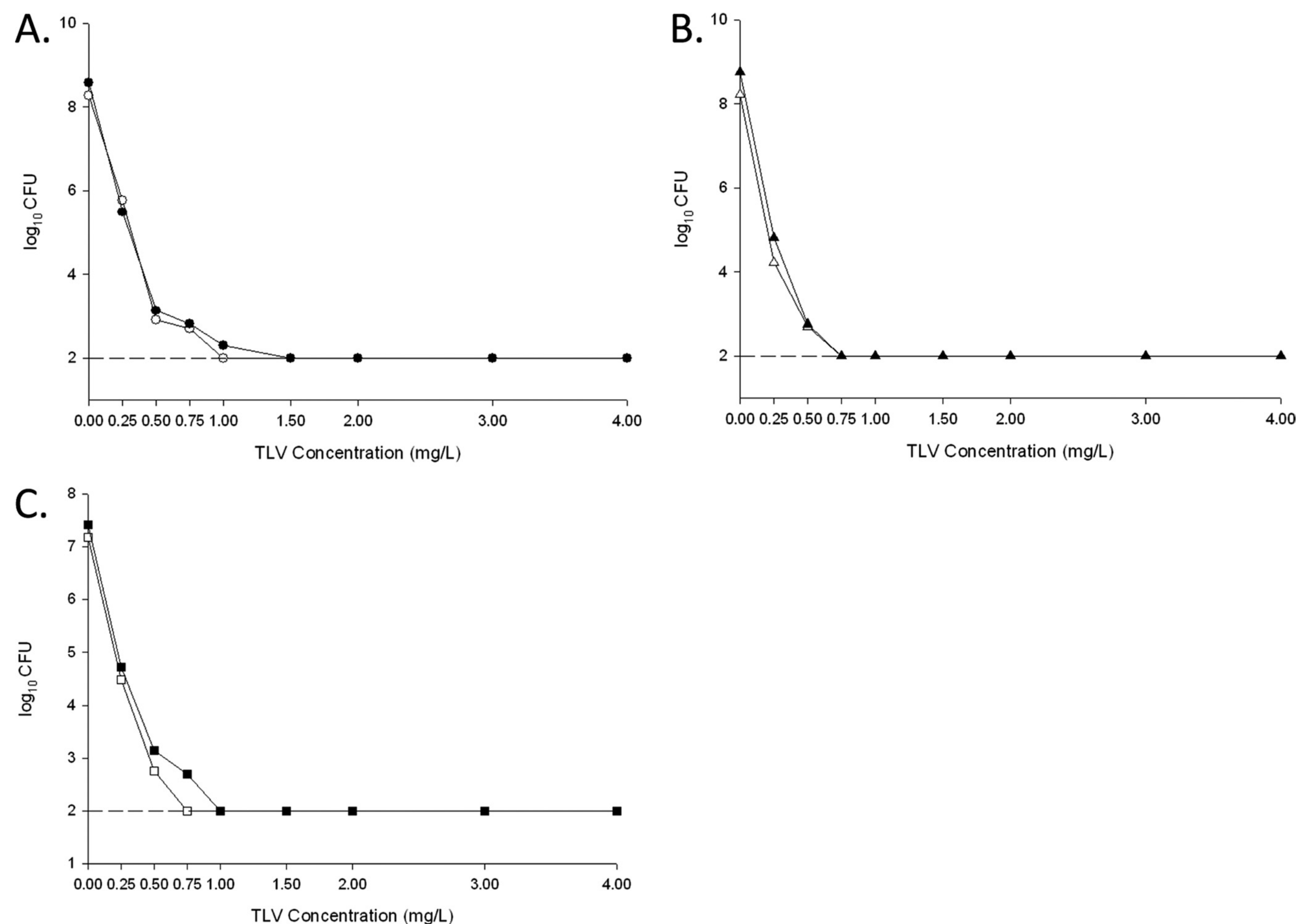

FIG 2 Telavancin (TLV) population analysis on CB1814 at 0 and 120 h (A), R6212 at 0 and 120 h (B), and SA-684 at 0 and 120 h (C). Open circles, CB1814 at 0 h; closed circles, CB1814 at 120 h; open triangles, R6212 at 0 h; closed triangles, R6212 at 120 h; open squares, SA-684 at 0 h; closed squares, SA-684 at 120 h; dashed line, limit of detection.

ties and decreases in colony counts in this study are similar to results of a previously published study examining the activity of telavancin against MRSA, hVISA, and VISA isolates (20). It is unknown, based on current data, however, if telavancin would maintain activity against DNS *S. aureus* isolates that were also VISA, as these strains were not included in either study.

Possible limitations of this study include its short duration and lack of strains displaying reduced susceptibility to both vancomycin and daptomycin. It is possible that the study period of 120 h (5 days) was not sufficient to elicit the full impact of a telavancin-DNS *S. aureus* interaction that might occur with longer exposures. As DNS in *S. aureus* has been associated with reduced susceptibility to vancomycin, it is likely that the activity telavancin displayed against DNS *S. aureus* in this study does not extrapolate to all strains of DNS *S. aureus* (24). In conclusion, telavancin displays bactericidal activity against DNS *S. aureus* and is more active than vancomycin. Further research is warranted to explore telavancin's activities against these strains.

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