

Bactericidal Activity of Quinupristin-Dalfopristin against *Staphylococcus aureus*: Clindamycin Susceptibility as a Surrogate Indicator

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Of 516 *Staphylococcus aureus* strains tested, 97.1% were susceptible to quinupristin-dalfopristin, which was bactericidal for 22 (56%) of the 39 strains tested, comparable to vancomycin. All 17 clindamycin and macrolide-resistant strains were inhibited but not killed by quinupristin-dalfopristin, whereas all 22 clindamycin-susceptible strains (5 were macrolide resistant) were killed.

Quinupristin-dalfopristin is a parenteral streptogramin composed of quinupristin (a streptogramin B antibiotic) and dalfopristin (a streptogramin A antibiotic) in a 30:70 ratio (13). This combination has been shown to exhibit synergistic in vitro antibacterial activity against staphylococci and other gram-positive bacteria (17). Greater than 90% of *Staphylococcus aureus* isolates have been reported to be susceptible to quinupristin-dalfopristin at ≤ 1.0 $\mu\text{g/ml}$ (1, 3, 7, 10, 14, 17, 18), and this activity was not appreciably affected by methicillin resistance (1, 3, 17, 18) or quinolone resistance (1, 10). Although nearly all *S. aureus* strains are inhibited by quinupristin-dalfopristin, the bactericidal activity of this drug is much more variable (3, 6, 9). Previous studies have shown that *S. aureus* strains that have cross-resistance to macrolides, lincosamides, and streptogramin B antibiotics (MLS_B) were not killed in vitro by quinupristin-dalfopristin, nor did endocarditis in experimental animals due to such strains respond to quinupristin-dalfopristin therapy (5). Low quinupristin MICs were demonstrated to be predictive of quinupristin-dalfopristin bactericidal activity against staphylococci, and routine testing of quinupristin MICs was suggested for this reason (5). Since adding quinupristin to routine gram-positive susceptibility test panels would be a major step, it would be of interest to know whether susceptibility to clindamycin or erythromycin might be equally predictive of quinupristin-dalfopristin bactericidal activity. Thus, the present study was designed to determine the correlation between the bactericidal activity of quinupristin-dalfopristin and the MICs of quinupristin-dalfopristin, quinupristin, dalfopristin, erythromycin, and clindamycin.

Quinupristin, dalfopristin, and quinupristin-dalfopristin were provided by Rhone-Poulenc Rorer, Collegeville, Pa. Clindamycin, erythromycin, oxacillin, and vancomycin were procured from other commercial sources.

Broth microdilution tests (15) with 516 recent clinical isolates of *S. aureus* compared the bacteriostatic activities of quinupristin-dalfopristin, erythromycin, and clindamycin. The results are summarized in Table 1. Nearly all *S. aureus* strains were susceptible to quinupristin-dalfopristin, but macrolide resistance was not uncommon, especially among methicillin-resistant *S. aureus* strains. All strains were susceptible to vancomycin. From that series of 516 isolates, 39 strains were selected

to provide roughly equal numbers of strains susceptible and resistant to methicillin, erythromycin, and clindamycin. These 39 strains were then tested by the broth microdilution method for susceptibility to quinupristin and dalfopristin alone, as well as quinupristin-dalfopristin, erythromycin, clindamycin, vancomycin, and oxacillin (with 2% NaCl).

Time-kill tests were performed with quinupristin-dalfopristin and vancomycin (as the control drug) following the principles outlined by the National Committee for Clinical Laboratory Standards (16). The drug concentrations used in these studies were 10 $\mu\text{g/ml}$ for quinupristin-dalfopristin and 20 $\mu\text{g/ml}$ for vancomycin. For both drugs, these concentrations were 10 to 40 times their MICs for the organisms tested but were equivalent to readily achievable blood levels with standard dosing (2, 4, 8). The initial inocula were targeted to be 1.5×10^6 CFU/ml. Colony counts were performed on the control suspension (no antibiotic) at time zero and on the control and both antibiotic suspensions at 1, 3, 6, 8, and 12 h. A drug was considered bactericidal if it produced a ≥ 3 -log₁₀ reduction in colony counts during this incubation period ($\geq 99.9\%$ killing).

Figure 1 provides examples of typical time-kill curves achieved with quinupristin-dalfopristin and vancomycin. When both drugs were bactericidal (Fig. 1A), the time required to achieve $\geq 99.9\%$ killing was generally 2 to 6 h shorter for quinupristin-dalfopristin than for vancomycin. That is consistent with the findings of Hoban et al. (9). Overall, quinupristin-

TABLE 1. Susceptibility of 516 recent clinical *S. aureus* isolates to four antibiotics

<i>S. aureus</i> strains (no.) and antimicrobial agent	MIC ($\mu\text{g/ml}$)			% of strains susceptible ^a
	Range	For 50% of strains	For 90% of strains	
Methicillin resistant (199)				
Quinupristin-dalfopristin	≤ 0.12 –2.0	1.0	1.0	94.0
Erythromycin	≤ 0.12 –>16	>16	>16	7.0
Clindamycin	≤ 0.12 –>16	>16	>16	13.1
Methicillin susceptible (317)				
Quinupristin-dalfopristin	≤ 0.12 –2.0	0.5	0.5	99.1
Erythromycin	≤ 0.12 –>16	0.5	>16	79.2
Clindamycin	≤ 0.12 –>16	≤ 0.12	0.25	96.2

^a Susceptible to erythromycin and clindamycin at ≤ 0.5 $\mu\text{g/ml}$ and quinupristin-dalfopristin at ≤ 1.0 $\mu\text{g/ml}$.

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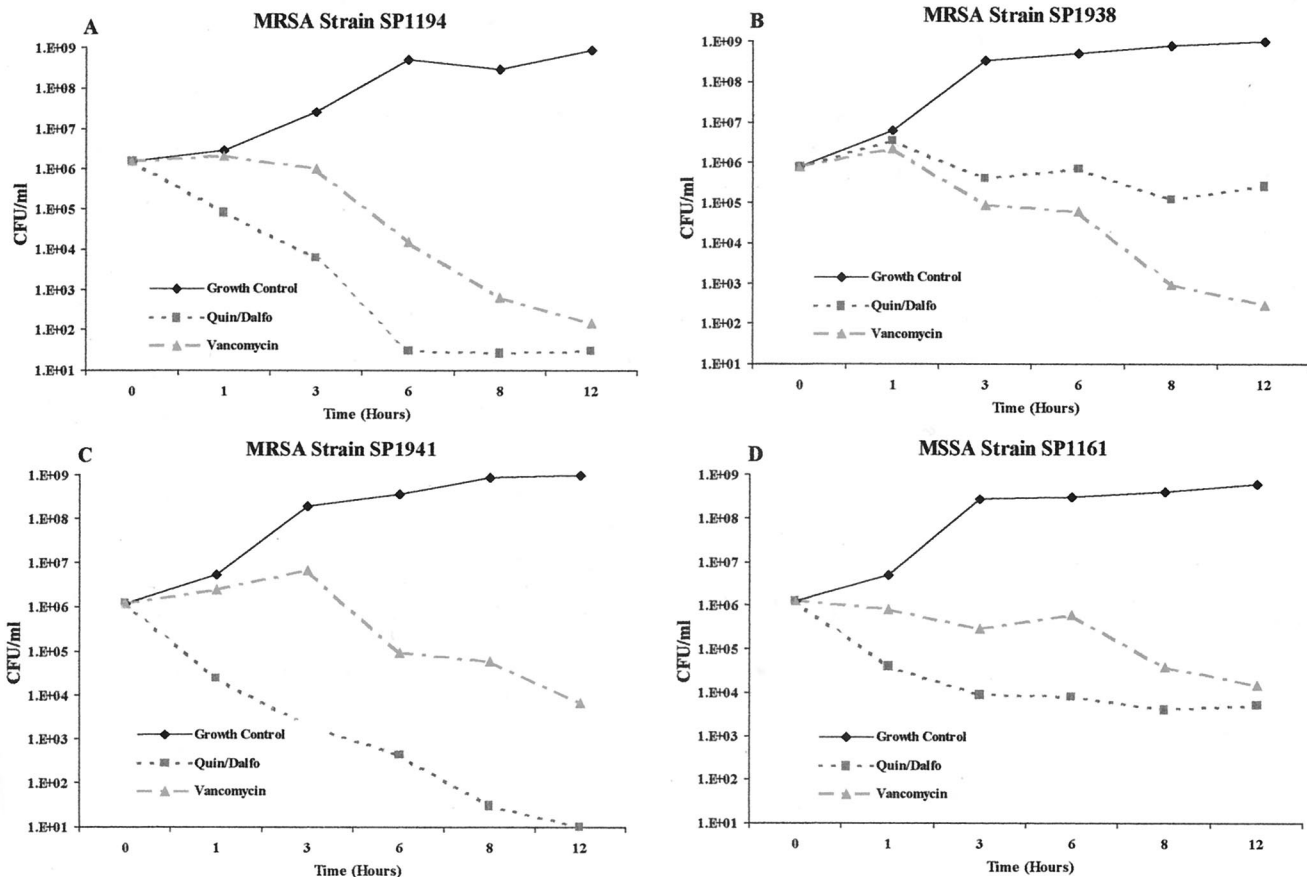


FIG. 1. Kill curves for four strains of methicillin-resistant *S. aureus* (MRSA) for which both drugs were bactericidal (A) vancomycin was bactericidal but quinupristin-dalfopristin (Quin/Dalfo) was not (B); quinupristin-dalfopristin was bactericidal but vancomycin was not (C); and neither drug was bactericidal (D).

dalfopristin was bactericidal for 56% of our 39 selected strains and vancomycin was bactericidal for 64% of these isolates.

The MICs of dalfopristin ranged from 2.0 to 16 µg/ml, with 35 (90%) of the dalfopristin MICs being 4.0 or 8.0 µg/ml. MICs of dalfopristin could not predict the bactericidal activity of quinupristin-dalfopristin. However, quinupristin MICs did correlate well with clindamycin MICs and with the bactericidal activity of quinupristin-dalfopristin (Table 2). Quinupristin-dalfopristin was bactericidal for all clindamycin-susceptible isolates, including the five that were erythromycin resistant. Furthermore, none of the clindamycin-resistant strains were killed by quinupristin-dalfopristin. With one exception, isolates for which the quinupristin MICs were ≤16 µg/ml were clinda-

mycin susceptible and were killed by quinupristin-dalfopristin and those for which the quinupristin MICs were ≥32 µg/ml were not. The one exception was a clindamycin-resistant isolate for which the quinupristin MIC was 8.0 µg/ml that was not killed by quinupristin-dalfopristin. Although the quinupristin MICs were ≤16 µg/ml for all clindamycin-susceptible strains, the geometric mean quinupristin MIC for those strains that were erythromycin resistant was higher (8.0 µg/ml) than for those that were erythromycin susceptible (3.0 µg/ml). However, quinupristin-dalfopristin was bactericidal for both phenotypes.

These data confirm the observation that MLS_B-resistant strains of *S. aureus* are not killed by quinupristin-dalfopristin

TABLE 2. Susceptibility patterns of 39 *S. aureus* strains when divided by clindamycin and erythromycin susceptibility phenotype

Phenotype ^a	No. of strains	No. with quinupristin MICs (µg/ml) of:		No. (%) Oxa ^{ab}	Q-D MICs ^c	No. (%) of strains with ≥99.9% killing by:	
		≤16	≥32			Quinupristin-dalfopristin	Vancomycin
Clin ^s Ery ^s	17	17	0	4 (24)	0.25–0.5	17 (100)	12 (71)
Clin ^s Ery ^r	5	5	0	3 (60)	0.25–0.5	5 (100)	3 (60)
Clin ^r Ery ^r	17	1	16	14 (82)	0.5–1.0	0	10 (59)

^a Clin^s and Clin^r, clindamycin susceptible and resistant, respectively; Ery^s and Ery^r, erythromycin susceptible and resistant, respectively.

^b Oxa^r, oxacillin resistant.

^c Q-D MICs; quinupristin-dalfopristin MIC range (µg/ml).

(5). Furthermore, the data strongly suggest that clindamycin susceptibility is a good surrogate indicator of quinupristin-dalfopristin in vitro bactericidal activity; MICs of quinupristin alone may also serve as a useful surrogate. Since clindamycin is a common component of gram-positive susceptibility test panels, it may provide useful information for the clinical laboratory in this regard. It should be noted, however, that there are multiple mechanisms of MLS_B resistance among staphylococci (11), and these were not determined for the isolates studied here. The *ermA* gene is by far the most prevalent determinant of MLS_B resistance in *S. aureus* (12), and it is reasonable to assume that the majority, if not all, of our MLS_B-resistant strains resulted from this determinant. Whether other determinants of MLS_B resistance would yield similar results remains to be determined.

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