Distinct Effectiveness of Oritavancin Against Tolerance-Induced *Staphylococcus aureus*

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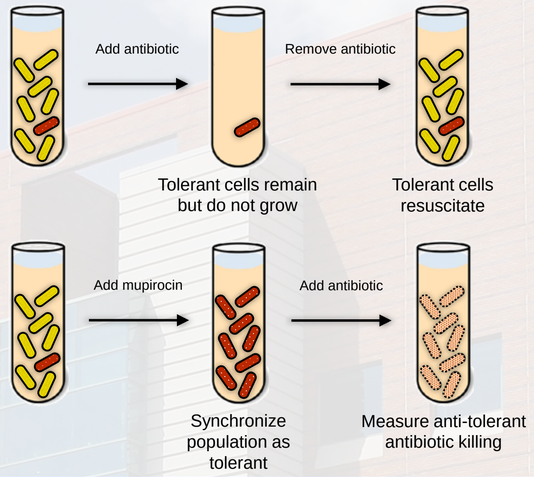
BACKGROUND

- Within a sufficiently large bacterial population, some of the members will naturally adopt an alternate, metabolically-active state favoring small molecule synthesis over cell division.
- In *Staphylococcus aureus* this process can be sharply accelerated by multiple factors present during infection including nutrient limitation, host cationic peptide exposure and polymorphonuclear neutrophil internalization.
- These isogenic "tolerant" subpopulations have variable responses during antibiotic exposure and can remain viable in the presence of typically bactericidal concentrations. Survivors of the antibiotic exposure can restart cell division upon cessation of antibiotics and cause relapse or recurrent infection.
- In this study we determine the ability of typical and atypical antistaphylococcal therapies to reduce the viability of tolerant *Staphylococcus aureus* bacteria.

METHODS

S. aureus strain ATCC29213 as well as four clinical isolates (three MSSA, one MRSA) were selected for analysis. Overnight cultures were diluted in pre-warmed broth (MHB50) to approximately 1×10^6 cfu/mL. Tolerance was induced by exposure to mupirocin (low [0.032 µg/mL] or high [3.2 µg/mL]) for 30 min. Tolerant cultures were exposed to vancomycin (35 µg/mL), ceftaroline (19 µg/mL), daptomycin (7 µg/mL), telavancin (10 µg/mL), dalbavancin (6 µg/mL) or oritavancin (14 µg/mL) and viability was assessed by dilution plating at pre-defined time points (0, 2, 6, 24, 48 h). The minimum duration for 3-log viability reduction from baseline ($MDK_{99.9}$) and culture viability at 48h were calculated independently for each of three biological replicates.

METHODS



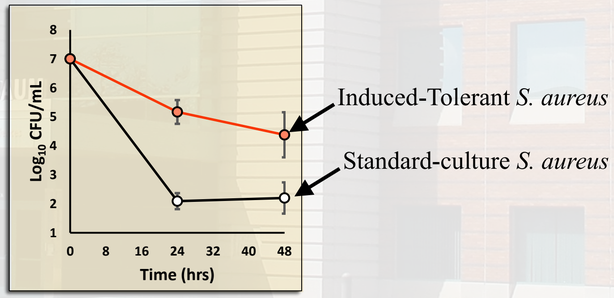
STRAINS

Strain Name	Source	Genetic Characterization
29213	ATCC	ST5 -MSSA spa t010 agr2
BSN10	Patient Isolate	ST45-MSSA spa t065 agr1
BSN11	Patient Isolate	ST15-MSSA spa t10135 agr2
BSN12	Patient Isolate	ST5 -MRSA-IVg spa t688 agr2
BSN13	Patient Isolate	ST97-MSSA spa t224 agr1

**All minimum inhibitory concentrations are "susceptible" by broth microdilution. Etest confirmation of specific values in process*

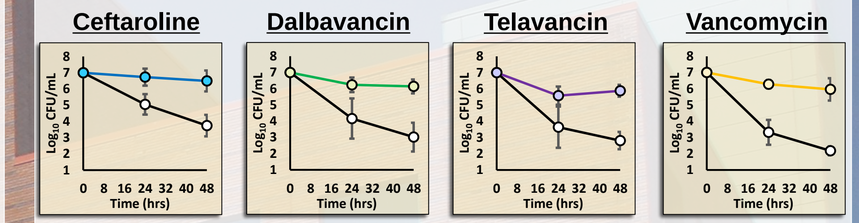
DAPTOMYCIN IS INEFFECTIVE AGAINST TOLERANT STAPHYLOCOCCI

Daptomycin

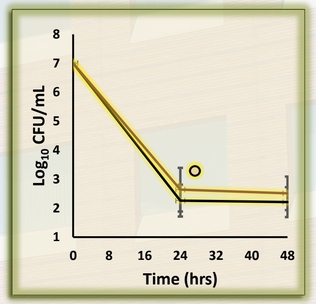


**Average ± Standard Deviation from 5 distinct strains, each assessed in triplicate*

OTHER AGENTS ARE INEFFECTIVE AGAINST TOLERANT STAPHYLOCOCCI



ORITAVANCIN IS EFFECTIVE AGAINST TOLERANT STAPHYLOCOCCI



	CPT	DAL	DAP	ORI	TLV	VAN
29213:	NA	19 ± 0	1 ± 0	1 ± 0	37 ± 0	13 ± 0
BSN10:	39 ± 0	NA	2 ± 0	1 ± 0	38 ± 6	22 ± 0
BSN11:	28 ± 1	35 ± 4	1 ± 0	1 ± 0	14 ± 0	18 ± 4
BSN12:	NA	34 ± 4	1 ± 0	1 ± 0	17 ± 5	20 ± 1
BSN13:	39 ± 5	17 ± 1	1 ± 0	1 ± 0	19 ± 1	24 ± 6

0.01 × MUP

CPT	DAL	DAP	ORI	TLV	VAN
NA	**24 ± 0**	**47 ± 2**	2 ± 0	**48 ± 0**	**21 ± 1**
NA	NA	**13 ± 1**	1 ± 0	44 ± 6	NA
36 ± 11	**46 ± 3**	1 ± 0	1 ± 0	**44 ± 6**	37 ± 10
NA	40 ± 5	**2 ± 0**	1 ± 0	13 ± 3	**36 ± 3**
47 ± 1	18 ± 1	1 ± 0	1 ± 0	22 ± 6	26 ± 8

1 × MUP

CPT	DAL	DAP	ORI	TLV	VAN
–	–	–	**5 ± 0**	–	–
–	–	–	**27 ± 7**	–	–
–	–	**40 ± 2**	1 ± 0	–	–
–	–	–	4 ± 2	–	–
–	–	**41 ± 10**	2 ± 1	–	–

**Time to bactericidal activity (h)*

CONCLUSIONS

- *S. aureus* that has become tolerant to typical antistaphylococcal therapies may respond favorably to **oritavancin**-based therapies.
- Oritavancin should be considered in cases of recurrent or relapse staphylococcal infections.

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