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In vivo efficacy of daptomycin in experimental endocarditis caused by vancomycin-resistant Enterococcus faecium

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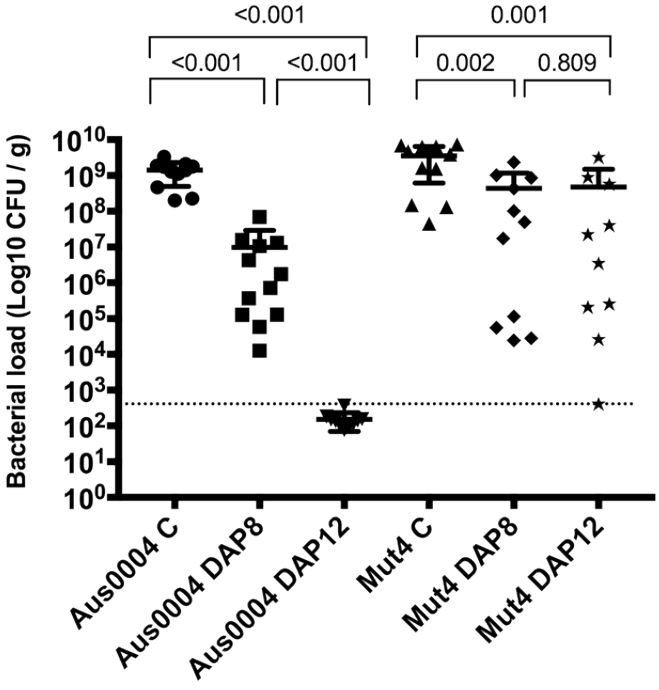
Background: Daptomycin (DAP) is a first-line therapeutic option for infective endocarditis (IE) due to vancomycin-resistant *Enterococcus faecium*. Whereas high doses (≥ 8 mg/kg) are often recommended, optimal dosages, particularly in case of strains exhibiting MICs close to the susceptibility breakpoint (4 mg/L), are still debated.

Material/methods: We evaluated the efficacy of daptomycin at dose equivalent to 8 (DAP8) or 12 mg/kg (DAP12) in humans, in a rabbit model of aortic valve endocarditis induced with 10^8 *E. faecium* reference strain Aus0004 (DAP MIC: 2 mg/L) and its *in vitro* mutant strain Mut4 (DAP MIC: 4 mg/L). Treatment was started 48h after infection and lasted 5 days. Bacterial counts of vegetations were compared and we evaluated the *in vivo* emergence of resistant mutants.

Results: With Aus0004, both DAP8 and DAP12 significantly decreased $\log_{10}$ CFU/g vegetations compared to control (6.99, n=12 and 2.18, n=10 versus 9.15 n=11, $\log_{10}$ CFU/g; $p<0.001$) while

DAP12 was more effective than DAP8 on bacterial count (p<0.001) and proportion of sterile vegetations (100% vs 0% respectively, p<0.001) (Figure). DAP-resistant mutants were detected in 8.3% of DAP8 treated vegetations. With Mut4 strain, DAP8 and DAP12 significantly decreased log_{10} CFU/g vegetations compared to control (8.64, n=11 and 8.68, n=10 vs 9.55, n=11; p=0.002 and p=0.001 respectively) with no difference between the two doses (p=0.809) (Figure). However, no vegetation was sterile and 7/11 (63.6%) and 7/9 (77.8%) vegetations exhibited resistant mutants with DAP8 and DAP12 respectively.



Conclusions: A 12-mg/kg dose seems to be the most successful strategy to treat IE due to a wild-type *E. faecium* strain exhibiting a daptomycin MIC of 2 mg/L. In IE due to a strain with a MIC of 4 mg/L, daptomycin used in monotherapy was poorly effective and leads to the emergence of resistant mutants. A reassessment of the DAP susceptibility breakpoint for enterococci seems to be necessary.