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P1442 Daptomycin-resistant MRSA strains display higher virulence and faster biofilm formation than wild-type strains in a prosthetic joint infection rabbit model

Houssam Bouloussa[1], Azzam Saleh-Mghir*[1], Vincent Humblot[2], Anne-Claude Crémieux[3]

[1]Université Versailles Saint-Quentin-en-Yvelines, INSERM UMR 1173, Garches, France, *[2]Université Pierre et Marie Curie, Laboratoire de Réactivité de Surfaces UMR 7197 UPMC-CNRS, Paris, France*, *[3]Hôpital Saint Louis, Université Paris 7 Diderot, Service des Maladies Infectieuses et Tropicales, Paris, France*

Background: Daptomycin resistance represents a serious threat in the battle against methicillin-resistant *Staphylococcus aureus* (MRSA) prosthetic joint infections (PJIs). However, its specific pathogenesis in the setting of PJIs remains poorly investigated to this date. An *in vivo* PJI model was used to compare the virulence of daptomycin-resistant (DR) MRSA strains *versus* wild-type (WT) strains in antibiotic-naive rabbits. In addition, comparative *in vivo* characteristics of biofilm growth patterns and organization were described.

Materials/methods: *In vivo* antibacterial activity: DR and WT MRSA strains were cultured in Brain Heart Infusion (BHI) at 37°C overnight. Twenty-four New-Zealand white female rabbits (2,8kg) underwent a unipolar knee joint replacement (TiAl6V4 tibial implant, 12 DR *vs* 12 WT). A 3.3 to 6.45 $x10^6$ CFU inoculum was injected following wound closure. Rabbits were sacrificed at day 2, day 3 and day 7 (8 rabbits each time, 4 DR and 4 WT). Proximal-third tibias were resected, crushed and cultured. **DR *vs* WT biofilm morphology:** all implants were systematically removed, rinsed with PBS and fixed in PBS/2.5% glutaraldehyde for imaging using Scanning Electron-Microscopy with Field Emission Gun (SEM-FEG).

Results: Bone bacterial density was overall 1.11±0.48 log_{10} higher in DR rabbits and systematically higher in DR rabbits *vs* WT rabbits over time (7.04±0.45 log_{10} *vs* 5.68±0.46 log_{10} at day 2, 7.10±0.41 log_{10} *vs* 6.55±0.11 log_{10} at day 3 and 7.70±0.92 log_{10} *vs* 6.28±0.75 log_{10} at day 7, $p<0.01$). **Biofilm morphology (Figure 1)**: DR rabbit implants displayed profuse polysaccharidic complex filaments that appeared richer than WT rabbit implant biofilm at 48h. However, there was no visible qualitative difference at day 3 and 7, titanium surfaces being saturated with multi-layer matrices in biofilm-covered areas in both groups. In both conditions, bacteria were rarely visible out of their matrix.

Conclusions: Daptomycin-resistant MRSA strains displayed higher virulence and faster biofilm formation than wild-type strains in this rabbit PJI model. Different biofilm patterns could partially account for the *in vivo* daptomycin resistance mechanism in MRSA.

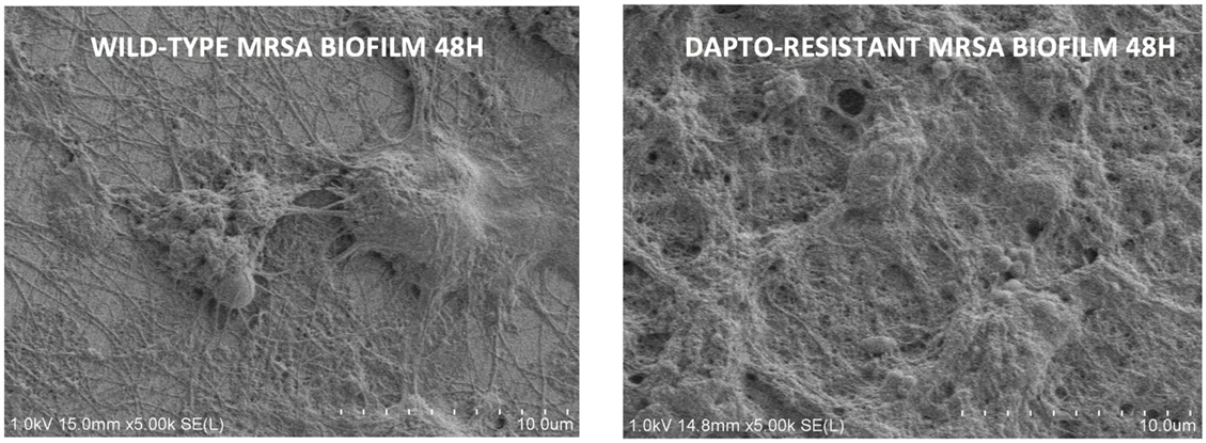

Figure 1. Comparison of MRSA biofilm development between WT (left) and DR strains (right) at 48h