TITLE: VANCOMYCIN SUB-DOSAGE DECREASES *S. AUREUS* SUSCEPTIBILITY TO VANCOMYCIN, DAPTOMYCIN AND BACTERICIDAL ACTIVITY OF LEUKOCYTES.

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ABSTRACT

Bacteremia in patients undergoing hemodialytic treatment (PUHT) have showed increased rates of meticillin-resistant *S. aureus*, which justify the vancomycin (VAN) use in empiric therapy. Failures in VAN dosage adjustment and dose interval may result in serum concentrations below the therapeutic level (<10 µg/mL). Thus, we aim to investigate if subtherapeutical concentration of VAN alters *S. aureus* susceptibility to antimicrobials and to the bactericidal activity of leukocytes. Two reference strains of *S. aureus* ATCC 29213 and 33591 and 19 samples from bacteremia of PUHT were used in this study. Microorganisms were exposed to a VAN gradient (0 to 10µg/mL) for five consecutive days in agar plates to simulate empiric therapy of bacteremia in PUHT. Then, samples were evaluated for VAN, oxacillin (OXA) and daptomycin (DAP) susceptibility by broth microdilution. In bactericidal activity of leukocytes assay, the blood and bacteria suspension were mixed in proportion of two leukocytes for each bacteria ($2,6x10^6$ CFU/mL) (approved by the Research Ethics Committee of UFES – Nº 903.454). Tubes were incubated in 37ºC in hematological mixer (08 rpm/min). Viable bacteria count was made in zero, 30 and 60 minutes after the beginning of the incubation. We observed the reduction *S. aureus* sensibility for VAN and DAP, but not for OXA. MIC of VAN between 1 and 2 µg/mL are worrying due to the association with therapeutic failure. More than half of the samples (57%) was sensitive to DAP (MIC=1), but 38% was classified as not sensitive (MIC=2). So, the use of DAP as therapeutic alternative seems questionable. Furthermore, the samples showed increased resistance to the bactericidal activity of blood in 60 minutes, with average percentage of viable cells of 21,6 and 63,6 in control and VAN treated samples, respectively (p=0,008). Thus, we concluded that VAN sub-dosage decrease *S. aureus* susceptibility to VAN, DAP and bactericidal activity of leukocytes in the experimental conditions employed.

Keywords: Vancomycin sub-dosage, *S. aureus*, hemodialysis.

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