

Staphylococci and treatment failure

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Staphylococcus aureus is Gram-positive microorganism. This is implicated in human skin and soft tissue infections, blood stream infections including using device associated infective endocarditis, osteomyelitis, pneumonia, and infections involving other implanted medical devices [1]. The use of penicillin, since its discovery in 1929 by Alexander Fleming in samples of *S. aureus*, worked well until about 1941 when they began show up isolates resistant to this antimicrobial, two years after the beginning of the industrial-producing. However, soon after the introduction of methicillin-resistant strains emerged also to this antimicrobial, calls MRSA (methicillin-resistant *Staphylococcus aureus*) [2].

The frequency of MRSA is high in tertiary hospitals. Studies show a frequency in tertiary hospitals that MRSA is responsible for 30–70% of infections by *S. aureus*, and has as its risk factors to infections by MRSA: chronic diseases, dialysis, malignancy, large exposure to antimicrobials agents, especially cephalosporin, aminoglycoside and fluoroquinolone, advanced age, insulin dependent diabetes, smoking, obesity, dermatitis and extended stay [1, 3].

The routine investigation of the main effects of MRSA inside the hospital is considered as an effective strategy in control of this microorganism; despite of being more expensive for the hospital, is a great benefit once the cost of control is lower than the treatment of infections by MRSA (Hospital-acquired Methicillin-resistant *Staphylococcus aureus* (HA-MRSA)) [4].

Infections caused by MRSA became common in community environment being known in healthy people that, before, did not show traditional risk factors to MRSA infections, acknowledging the second phenotype (community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA)) has distinct genotypic and phenotypic features that separate it from other MRSA variants, and third phenotype recognized in The Netherlands, livestock-associated MRSA (LA-MRSA) [5].

Since its availability in 1958, the vancomycin has been used as last choice for treatment of Staphylococci infections, however, currently, various phenotypes of the MRSA are found worldwide: VSSA (Vancomycin-sensitive *S. aureus*) with MIC ≤ 2 $\mu\text{g}/\text{mL}$, VISA (vancomycin-intermediate *S. aureus*) with MIC ranging from 4 and 8 $\mu\text{g}/\text{mL}$ for samples of intermediate resistance; VRSA (vancomycin-resistant *S. aureus*), with MIC ≥ 16 $\mu\text{g}/\text{mL}$ and hVISA (heteroresistant VISA), presenting samples with MIC ≤ 2 $\mu\text{g}/\text{mL}$, when tested by routine methods but which have subpopulations in the order of a hundred thousand colony forming units (UFC) with MIC between 4 and 8 $\mu\text{g}/\text{mL}$. In many cases, hVISA samples were detected in lengthy infections and associated with glycopeptide therapy failure [6].

Besides the significant efforts, the genetic determinants of hVISA were not completely solved [7]. A large number of useful methods exist for VISA detection, however most are not suitable for hVISA. Currently there is no a standardized method for exact detection of hVISA, which make that the lab tests and interpretations of the clinic meaning of hVISA, difficult [4]. There is no molecular assay available for detention of hVISA, nonetheless, each time large amount of data supports a right number of methods for screening and confirmation of infection by hVISA [7].

The pattern method to detection of hVISA is the analysis of population profile (PAP) in the area under the curve (AUC). Using PAP as the method of reference, hVISA sample can be detected in *S. aureus* samples with MIC's of vancomycin as low as 0.5 a 1 $\mu\text{g}/\text{mL}$ [8]. However, a number of tests for the detection of hVISA are also available, such as macromethod ϵ -test (MET) and

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Received: 10 July 2015

Published: 27 October 2015

the use of culture with vancomycin, sold commercially [7], Showing the definition of VISA is simpler, as defined based in MIC for vancomycin, while the definition of hVISA is more difficult and it is not standardized [8].

Typically, the resistant population is present in a frequency of $\leq 1/100,000$ to $1/1000,000$ cells, thence the difficult in detection of this phenotype of resistance using the methods of CLSI, where is used an inoculum of 5×10^4 UFC (MIC in broth) or 1×10^4 UFC (agar dilution).

The clinical meaning of hVISA and VISA have been difficult to be determined clearly, because of, in parts, the differences in definitions and lab detection, and many patients with serious infections by hVISA or VISA, evolve to bacterial persist even in adequate doses of vancomycin [9].

The presence of heteroresistant samples to vancomycin (hVISA) can represent a potential risk in the future [3]. The options of treatment became limited [10] and this phenotype became more worldwide isolated, however underreported in conventional tests of MICs [4, 8].

The appearance of hVISA samples and the high index of mortality, make this microorganism a serious problem of public health [7]. Although its clinical significance is still controversial, this factors justified the needs of clarifying the susceptibility to vancomycin of clinical samples of MRSA are related with the results in clinical patients.

Once the use of this antimicrobial treatment was repeatedly reported as hVISA selector, which is associated to vancomycin treatment failure, it is expected that studies have the focus on new antimicrobial drugs and mechanisms to prevent the spread of already existing pathogens.

Keywords: Heteroresistant, Microorganism, *Staphylococcus aureus*, Treatment failure

How to cite this article

de Melo GB, Dentista C. Staphylococci and treatment failure. Edorium J Microbiol 2015;1:1–3.

Article ID: 100001Mo8GM2015

doi:10.5348/Mo8-2015-1-ED-1

Author Contributions

Geraldo Batista de Melo – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising

it critically for important intellectual content, Final approval of the version to be published

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

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