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Study of Vancomycin resistance among Staphylococcus aureus

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Abstract: Staphylococcus aureus (S.aureus) infections with Vancomycin resistance in hospital complexes are a concern, a significant increase in the number of these occurrences is observed since it is one of the last available antibiotic therapy routes available for the treatment of infectious processes bacterium. Thus, this work aims to present the main mechanism of resistance induction of S. aureus to Vancomycin. The research used the databases Medline, Scielo, the electronic site of the Google Scholar databases as well as specialized magazines in the area. Thus, the final considerations are that the cycle repeats itself and previously sensitive bacteria become resistant; thus, in this rhythm of emergence of bacterial resistance against antibiotic therapy is worrying, there will be a moment when there will be no antibiotic capable of acting in the fight against bacteria. This shows the need to understand the mechanism of resistance, the discovery of new antimicrobial drugs and the prevention of the spread of resistant microbes.

Keywords: Staphylococcus aureus, vancomycin, microbial drug resistance, vancomycin resistance.

Introduction

This is a literature review study, developed from August 2018 to March 2019, to identify scientific productions on the subject of Staphylococcus aureus (S.aureus) infections with Vancomycin resistance. The objectives of the review were established; the demarcation criteria for inclusion and exclusion of articles; the definition of the information to be extracted from the selected articles; the results and the discussion and presentation of the obtained data.

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In this way, the following databases were consulted: Medical Literature Analysis and Online Recovery System (Medline), Scientific Electronic Library Online (Scielo), Latin American and Caribbean Literature in Health Sciences (Lilacs).

A search was also performed on the Google Scholar database. The selected articles followed the following inclusion criterion: studies written in English, Spanish or Portuguese; original articles and reviews. In addition, a search was conducted directly on electronic sites of national journals specialized in the area of microbiology related to the subject.

Overview of increased resistance to antibiotics by S. aureus

Mortality due to S. aureus before antibiotic insertion in medical treatments was greater than 80% and more than 70% of those affected evolved to metastatic infections[1]. With the beginning of the use of penicillin in the 1940s, there were great improvements in the prognosis of these patients[1-2]. However, as early as 1942, reports of penicillin-resistant strains of S.aureus arose from the production of enzymes, beta-lactamases, which facilitate the hydrolysis of the beta-lactam ring2. Since then, resistance to penicillin has increased primarily in hospital settings and later in the community, so in the late 1960s the rate of hospital resistance was close to 90%, while in the community of 70% in some regions of Europe[3]. In the early 1960s, with the onset of methicillin and oxacillin momentarily, the problem of S. aureus resistance to penicillin was solved[2].

However, resistant strains appeared in 1961[2]. The presence of a gene called mecA in a chromosome leads to resistance to oxacillin, since such a gene is in charge of the production of PBP2a (penicillin-binding protein 2), which overlap with other PBPs in the membrane and which has lower affinity for several beta-lactam antimicrobials and as well as for oxacillin4. After that, the occurrence of resistance of S.aureus to oxacillin rose rapidly[1,2,5,6].

Initially MRSA were only found in tertiary hospitals and hospital complexes, however, in a short time smaller local centers of care were found[7]. Studies conducted in several countries show that there is a heterogeneous prevalence of MRSA depending on the region or site analyzed[7,8]. In the second half of the 1990s, MRSA became the majority of cases in S. aureus infections both in hospitals and in communities[9]. For the treatment of these cases the most commonly used therapy consisted of vancomycin[10].

In 1958 the glycopeptide antibiotic vancomycin was started to be used for therapies in conditions caused by gram-positive bacteria. Before this antibiotic was available for use resistance to it had already been achieved in the laboratory[11,12]. However, many believed that this resistance was unlikely to occur in a clinical setting because of the difficulty in inducing this resistance[13]. Thus, over the next 20 years the use of this drug has increased greatly due to the increasing prevalence of methicillin resistance in coagulase-negative staphylococci and S. aureus. In 1979 and 1983, however, the first cases of resistance to vancomycin in coagulase negative staphylococci appeared; however, these cases did not draw much attention because they were considered relatively non-virulent[15,16]. In 1997, increased resistance to vancomycin in S. aureus was reported in a report from Japan[17,18]. This was accompanied by other similarities from other regions and countries[19]. This raised the concerns of physicians to the issue of life-threatening S.aureus infections in patients both in hospitals and in the community[20]. Since S. aureus is seen as one of the major pathogens that affect humans and has a high occurrence and ability to cause diseases[21].

Staphylococcus aureus with intermediate resistance to vancomycin (VISA)

The first reported occurrence of VISA was, in 1996, in Japan[22]. This isolate did not present the vanA gene and had a thicker cell wall than the common one, besides peptides with the ability to neutralize the action of vancomycin[23]. In this context, other cases of VISA appeared and these presented similarities as: thicker cell wall, slower growth than the population of the same species sensitive to vancomycin and had no resistance in the vancomycin-24-disc test.

Although they have intermediate resistance, when in the bloodstream it is a bacteremia whose treatment with vancomycin has no effect, the proof is that all reports of VISA were from treatments in which the use of this antimicrobial was flawed[25]. The fact is that S. aureus with this type of resistance has spread through several sites and it is believed that this type of resistance is related to the persistent contact of this bacterium with that to vancomycin[25,26].

Vancomycin-resistant Staphylococcus aureus (VRSA)

In 1992, the transition of genes that confer resistance to vancomycin from Enterococcus faecalis to the skin of a mouse was reported[27]. Thus, the research suggested

that in microorganisms present in the same or nearby environment a transfer of genetic material could follow[28]. In this context, other studies revealed that up to 62% of VRE patients also had S.aureus in their gastrointestinal tract, becoming potential reservoirs for the appearance of resistant strains[28]. In June 2002, the first case of VRSA in the United States was reported[29]. After 2 months, in the US state of Pennsylvania, the second case of VRSA30 was reported. The third case was reported in 2004 in New York. The common among these three cases is the presence of the vanA gene that makes S. aureus immune to vancomycin by replacing the final D-Ala-D-Ala peptidoglycan monomer with D-Ala-D-lactate[32]. That is, there is a change in the cell wall-forming peptidoglycan precursor substances, and the affinity of these novel precursors, in this case D-Ala-D-lactate, by the antimicrobial is about one thousand times less than that of the original monomer[32].

Several genes are responsible for mediating this resistance: vanS, vanR (regulatory genes), vanA, vanH, vanX (effector genes)[32]. With vancomycin the vanS protein undergoes autophosphorylation and promotes the transfer of a phosphate group to vanR, which is a transcription factor for other genes[32]. The non-incorporation of D-Ala-D-Ala into the cell wall is mediated by vanX which promotes the hydrolysis of these[32]. vanH allows the delivery of D-lactate, while vanA acts in the formation of D-Ala-D-lactate[32]. These microorganisms were found to be a conjugative plasmid, the Tn1546 transposon, which showed total homology with the DNA sequence found in VRE, thus showing that the resistance present in the VRE to vancomycin is transferable to S. aureus[33].

Conclusion

It can be noted that the VISA strains showed a new form of resistance through the inactivation of the vancomycin effect by the alteration of substances present in the cell wall by other substances with lower affinity, in which the antimicrobial does not have its altered structure, however it loses their ability to interact with the molecular target[34]. Some research describes this mode of resistance as a tactic in the evolution used by S. aureus strains to allow them to adapt to environments exposed to substances hostile to themselves as vancomycin[35]. However, the continuous exposure to antimicrobials and the existence of microorganisms that have genes that can give more resistance and can be transmitted, as in the case of transposons from the VRE that allowed the emergence of VRSA strains[35].

Although resistance to vancomycin is a reality in S. aureus, the situation is not as serious as predicted, since the strains reported have not been pan-resistant, and the

trimethoprim-sulfamethoxazole and linezolid therapies obtained good results[36]. Furthermore, these strains were found to be vulnerable to the most recent antimicrobial agents such as quinupristin-dalfopristin, daptomycin, oritavancin and tigecycline. However, this fact does not diminish the need for the adoption of evaluation and control measures for the discovery of new cases, so that they can be treated more efficiently and effectively and thus contribute to the more accurate and accurate use of antibiotics[37]. Since the possibility of the emergence of other resistances in the future can not be ruled out[37].

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