Drugs used to strains of treatment methicillin resistant *Staphylococcus aureus*

Fármacos usados no tratamento de *Staphylococcus aureus* resistente à meticilina

Drugs used to strains of treatment methicillin resistant *Staphylococcus aureus*

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ABSTRACT

This review aims to know the main forms of treatment and clinical application currently in use in Brazil for Methicillin resistant *Staphylococcus aureus* (MRSA) strains. Thus, an active search for periodicals and specialized articles on the topic available in the databases was performed. Inclusion criteria for studies were found to therapy approach the use of antibiotics in the treatment of patients infected with MRSA, and comparative studies of this and other treatment modalities. Thus, it is necessary a greater discretion to the use of antibiotic therapy with the use of protocols for the treatment of serious diseases known and greater investment in research and new technologies in medical science, seeking thereby to achieve a dignified and quality healthcare in our country.

Keywords: *Staphylococcus aureus*, MRSA, Antibiotic therapy.

RESUMO

Esta revisão almeja conhecer as principais formas de tratamento e emprego clínico em uso atualmente no Brasil para infecções por cepas *S. aureus* resistente ao beta-lactamico sintético meticilina/oxacilina (MRSA). Assim, foi realizada uma busca ativa de periódicos e artigos especializados na temática disponíveis nos bancos de dados. Os critérios de inclusão para os estudos encontrados foram à abordagem terapêutica do emprego dos antibióticos no tratamento de pacientes infectados por MRSA, e estudos comparativos entre esta e outras modalidades de tratamento. Desta forma se faz necessário um maior critério ao uso de antibioticoterapia com emprego de protocolos para tratamento de doenças graves conhecidas e um maior investimento em pesquisa e novas tecnologias na ciência médica, buscando assim alcançar uma saúde digna e de qualidade em nosso país.

Palavras-Chave: *Staphylococcus aureus*, MRSA, Antibioticoterapia.

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RESUMO
Esta revisión anhela conocer las principales formas de tratamiento y empleo clínico en uso actualmente en Brasil para infecciones por cepas S. aureus resistente al beta-lactámico sintético meticilina / oxacilina (MRSA). Así, se realizó una búsqueda activa de periódicos y artículos especializados en la temática disponibles en los bancos de datos. Los criterios de inclusión para los estudios encontrados fueron el enfoque terapéutico del empleo de los antibióticos en el tratamiento de pacientes infectados por MRSA y estudios comparativos entre esta y otras modalidades de tratamiento. De esta forma se hace necesario un mayor criterio al uso de antibióticoterapia con empleo de protocolos para tratamiento de enfermedades graves conocidas y una mayor inversión en investigación y nuevas tecnologías en la ciencia médica, buscando así alcanzar una salud digna y de calidad en nuestro país.

Palabras clave: Staphylococcus aureus, MRSA, Antibioticoterapia.

INTRODUCTION
Antimicrobial resistance is a phenomenon that occurs when microorganisms, such as bacteria, viruses, fungi and parasites, are no longer affected by an antimicrobial they were previously sensitive to. When microorganisms become resistant to most known microbicidal agents, they are often referred to as “supermicrobes”. Multidrug resistance in nosocomial infections is an important public health problem because a resistant microbial strain decreases therapeutic success and has a rapid spread, burdening patients and private and governmental health institutions (WHO, 2017; RIBEIRO and CORTINA, 2016).

Antibacterial resistance is usually the result of genetic changes in bacterial DNA, such as a mutation or the acquisition of new genes. Among the existing forms of gene transfer, bacterial conjugation is extremely important and recurrent in the dissemination of plasmids in hospital settings. Often bacteria use more than one strategy to prevent the action of antimicrobials. Among the mechanisms used are alteration of the drug's site of action, enzymatic inactivation and so-called “efflux pumps”. In addition to the forms of acquired resistance, it is worth mentioning the occurrence of bacterial groups naturally resistant to certain classes of antibiotics, such as Escherichia coli, which has intrinsic resistance to penicillin's. Antibacterial resistance renders drugs ineffective and triggers therapeutic failure, increasing the risk of hospital stay and increasing the number of deaths from bacterial infections (BRASIL, 2016; VAZ, 2009).

Staphylococcus aureus is a pathogenic gram-positive coccus that can inhabit the nasopharynx and skin microbiota of up to 40% of individuals working in the health area. Such carriers are important carriers of this microbe in hospitals and health services (BRASIL, 2016; WHO, 2017). This bacterium is a frequent cause of serious infections in health units and in the community, and the development of mechanisms of resistance to the first line drugs for treatment by staphylococcal infections is common. Methicillin synthetic beta-lactam resistant S. aureus may be referenced by the methicillin-resistant Staphylococcus aureus (MRSA). Infections caused by MRSA strains increase the occurrence of hospital deaths by up to 64% when compared to patients infected with methicillin sensitive Staphylococcus aureus (MSSA) (WHO, 2017).

According to the MRSA Report of the Centers for Disease Control and Prevention (CDC, 2014) in 2014, estimates of cases of MRSA infections in the United States were 16,522 for community-associated infections and 55,144 cases for strains associated with health care, such as hospitals. In Brazil, according to Evangelista and Oliveira (2015), most of the cases reported in Brazil occurred in general in children, adolescents and adults, with an initial infection of the skin and soft tissues, leading to severe infections requiring hospitalization and use of antimicrobials for time prolonged data from the Agência Nacional de Vigilância Sanitária (BRASIL, 2016) indicate that the proportion of infections by MRSA strains is around 40% to 80% among patients in intensive care units.
Until the 1980s, MRSA were exclusive in-hospital strains. Since then, reports of MRSA strains have also been reported in communities in the United States, mostly cases involving drug users, immunosuppressed individuals, or previous hospital admissions. Recently, new reports of MRSA have been reported in people who apparently had not had previous hospital contact (BRASIL, 2016; BASTOS et al, 2013). Thus, due to the mechanisms of evolution, resistance and severity of the affections caused by this bacterium, it is necessary to construct a review about the current guidelines for the treatment of staphylococcal infections.

**METHODOLOGY**

An active search for periodicals and specialized articles on the topic available in the databases was performed. Inclusion criteria for studies were found to therapy approach the use of antibiotics in the treatment of patients infected with MRSA, and comparative studies of this and other treatment modalities.

**Methicillin-Resistant Staphylococcus aureus (MRSA)**

*Staphylococcus aureus* is an important pathogen of hospital and community infection with high morbidity and mortality rates. They are gram-positive cocci that can be part of the natural human microbiota, mainly colonizing the skin region and nasal cavities. There are strains highly pathogenic to its carrier and others that can become malefic when there is an imbalance of the host's immunity or in situations of loss of cutaneous contiguity, as in situations of trauma. (SANTOS 2015; SANTOS et al., 2007).

Initially, treatment against infections caused by *S. aureus* was reasonably simple and effective using beta-lactams. However, the indiscriminate use of these drugs favored the emergence and dissemination of resistant strains capable of molecular breakdown of penicillins by the action of beta-lactam enzymes. Thus, beta-lactamases, known as methicillin in the United States and as oxacillin in Brazil, were developed as beta-lactam antibiotics. Strains sensitive to this new drug were named as methicillin-sensitive *Staphylococcus aureus* (MSSA). However, due to the rapid evolution of resistance mechanisms developed and propagated by bacteria, new strains resistant to synthetic beta-lactams have appeared. These strains were titrated as MRSA (methicillin-resistant *Staphylococcus aureus*) (SANTOS et al., 2007; ENRIGHT et al., 2002; TAVARES, 2000).

The mechanism of resistance to methicillin is associated with the acquisition of the mecA gene, which is part of the "mec chromosome cassette". The mecA gene encodes the PBP2a proteins, a functional variant of PBPs (penicillin binding proteins). Methicillins have no affinity for PBP2a, thus preventing synthesis of the bacterial cell wall (BRASIL, 2016; 2007). A novel homologous mecA has recently been described in the literature as mecC, encoding a PBP2a protein with up to 63% homology to that encoded by mecA. This new homologous PBP2a has been reported in human and animal cases in several European countries (PATERTON et al, 2014).

Due to the high incidence of MRSA strains in hospital environments, empiric treatment with methicillin is contraindicated, with broad spectrum antibiotics such as glycopeptides (vancomycin) being recommended. The antimicrobials that are commonly used for the treatment of MRSA infections include vancomycin, which acts by disrupting cell wall synthesis, and linezolid, the main representative of the class of oxazolidinones whose site of action is the 50S ribosomal subunit thus inhibiting the protein synthesis (SANTOS et al., 2007; TAVARES, 2000).

**Glycopeptides and Oxazolidinones**

The glycopeptides are important drugs used in the treatment of hospital infections caused by strains of multi-resistant bacteria. They act by disrupting cell wall synthesis through their firm attachment to the D-Alanyl-D-Alanine terminal end of the murein monomer unit, inhibiting transglycosidase and thereby blocking the
addition of murein moieties to the growing polymer chain. With the inhibition of cell wall synthesis, the bacterium is susceptible to osmotic disruption and cell death (YOO et al, 2017; TANG et al, 2017; OLIVEIRA et al, 2014; MIMICA and BEREZIN, 2008).

The principal representatives of this class are vancomycin and teicoplanin. Vancomycin, by virtue of its toxicity, is only used when an infection occurs by a bacteria resistant to other drugs, such as the case of MRSA (YOO et al, 2017; HSIEH et al, 2016). Among the toxic effects reported are ototoxicity and nephrotoxicity. Among the major side effects found in the use of vancomycin are hypersensitivity reactions and "red neck man syndrome," a flushing that occurs due to the release of excess histamine during rapid infusion of the drug into the therapy. The last exclusive reaction to vancomycin use. Contraindications for the use of this class are during gestation and lactation and patients with renal and hepatic impairment, and should be used with caution and only when their use is indispensable (SANTOS et al., 2011; BRASIL, 2007).

Oxazolidinone is a new class of synthetic antibacterial drugs whose only agent is linezolid. Its mechanism of action is the inhibition of protein synthesis, acting on the 50S ribosomal subunit of the bacterial ribosome. The main therapeutic indications of linezolid are soft tissue treatment, surgical site infections and respiratory infections such as pneumonia (SHARIQ et al, 2017). Among the most relevant adverse effects is myelotoxicity, with thrombocytopenia, mainly after 14 days of use. Other less serious symptoms, such as disorders of the gastrointestinal tract, headache and peripheral neuropathy, are also reported (DACH et al, 2017; QUEIROZ et al., 2012; BRASIL, 2007).

Due to the seriousness of its myelodysplastic side effects, linezolid should be reserved as an alternative agent only for the treatment of infections with multidrug resistant strains, such as beta-lactam resistant MRSA and glycopeptides. Linezolid should not be used when other agents are available, since its indiscriminate use may accelerate the appearance of strains resistant to this drug, a pitiful consequence because we would lose the last available treatment option in the market (SHARIQ et al, 2017; HSIEH et al, 2016; VASCONCELLOS et al, 2015; BRASIL, 2007).

To counter this lack of options in the market has been studied new alternatives of antimicrobials such as tedizolid, a 50S subunit of bacterial ribosome, a recent representative of the oxazolidinones class. Tedizolid has been approved in several countries, such as the United States, Canada and some members of the European Union for the treatment of cutaneous infections by bacteria, including MRSA strains (MCCOOL et al, 2017).

CONCLUSION

The discovery of antibiotics such as penicillin G used in the treatment of patients infected by Staphylococcus aureus was of paramount importance for the evolution of science and public health, but its indiscriminate use, therapeutic inadequacy among others, led to the emergence of mechanisms of resistance of these strains, which hindered the clinical management of certain pathologies and stimulated research by drugs that were effective for treatment. Even with the discovery of drugs capable of fighting MRSA like glycosides, the disparity between resistance mechanisms and drug evolution is enormous. The science and pharmaceutical industry cannot keep up with the speed with which innovations related to bacterial resistance occur.

Thus, it is necessary to update, train and train health professionals with the objective of promulgating and disseminating effective and effective actions to avoid the induction and dissemination of resistant bacterial strains. The clinical management of staphylococcal infections, the epidemiological profile, and the actions of hospital infection control committees also play an important role in this process. It should be emphasized that access to antibiotics by patients should be conscientious through educational actions, so that the time and dosage can be fulfilled during the handling of the prescribed medication.
According to WHO recommendations (WHO, 2017), to prevent and control the spread of antibiotic resistance, health professionals can: prevent infections by performing proper hand washing and hospital instruments; Only prescribe and dispense antibiotics when really necessary and in accordance with current guidelines; Reporting cases of antibiotic resistance; Talk to patients about the correct use of antibiotics, forms of resistance and the dangers of self-medication and misuse.

Thus, there is a need for government entities to invest in scientific research and new technologies, thus corroborating the greater control of health problems and improving the quality of life of the population.

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