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Alternative Methods for Treating MRSA-Colonized and Infected Patients: Bacteriophages, Inhibitors of Wall Teichoic Acid Biosynthesis and Cultures of Not Drug-Resistant *Staphylococcus Epidermidis*

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Abstract

The colonization and infection with methicillin-resistant *Staphylococcus aureus* (MRSA) is a health problem of major importance in hospitals and long-term care facilities. Active decolonization measures are performed in MRSA-colonized patients; infections caused by MRSA are treated with vancomycin and other reserve antibiotics. The administration of bacteriophages could prevent the formation of MRSA biofilms. Inhibitors of wall teichoic acid biosynthesis could restore the efficacy of ß-lactam antibiotics against MRSA. A possibility to reduce MRSA colonization could be the administration of cultures of not drug-resistant *Staphylococcus epidermidis* or other physiological skin bacteria. Bacterial cultures should be taken regularly in order to control the descreased colonization with MRSA.

Keywords

Bacteriaemia, Colonization, Daptomycin, Decolonization, Linelozid, Methicillin-resistant *Staphylococcus aureus*, Multi-resistance, *Staphylococcus epidermidis*, Tigocycline, Vancomycin

Introduction

The bacterium methicillin-resistant *Staphylococcus aureus* (MRSA) which is resistant to several antibiotics, above all to ß-lactam antibiotics, is a problem of great importance in hospitals and long-term facilities [1]. In long-term care facilities, a great number of patients are colonized with MRSA. These patients are isolated in a single-room, and nurses perform the cure and disinfection wearing gloves, special clothing and masks. Above all elder patients, suffering a chronic heart disease, diabetes mellitus or showing a weak immune system or after a cancer therapy, are risk patients to acquire an infection with MRSA. These infections can occur through a self-infection or a cross infection and can concern the respiratory and/or urinary tracts or lead to wound infections or bacteriaemias, which still have a mortality of 20-30% [2]. A decolonization of MRSA patients can be performed through an exact disinfection. The antibiotic for the treatment of infections with MRSA is vancomycin, which shows resistances and causes nephrotoxicity [3]. In patients, who do not respond to an antibiotic treatment with vancomycin, an alternative treatment is the administration of daptomycin combined with fosfomycin [4].

MRSA

Methicillin resistance is conferred to the bacterium *Staphylococcus aureus*, once this bacterium has acquired a non-native gene encoding a penicillin-binding protein (PBP2a) [5]. This gene can be transferred to the physiological bacteria of the skin, *Staphylococcus epidermidis*. Then, the multi-resistant bacterium methicillin-resistant *Staphylococcus epidermidis* (MRSE) is formed [6].

Colonization with MRSA

Colonization with MRSA and other multi-resistant bacteria is a health problem often found in hospitals and long-term care facilities. In long-term care facilities in Gran Canaria (Spain), 235 residents were examined whether they were carriers of multi-resistant bacteria or of MRSA [7]. The study reported that 36.2% of the residents were colonized with multi-resistant bacteria, and among them, 10.2% were colonized with MRSA [7]. Patients' screening, in order to know whether they are carriers of MRSA, is generally not recommended on hospital admission [7,8]. Inpatients colonized with MRSA are isolated in a single room according to the guidelines of the Rober-Koch-Institute, whereas there are no guidelines, only recommendations, for residents in long-term care facilities [9]. Outpatients are advised to perform measures of decolonization [9]. Patients should be cared with an antiseptic soap, which contains chlorhexidine [10]. In a randomized study, carried out in three groups of adults and children with recurrent MRSA skin and soft tissue infection, a total household decolonization with intransal musiprocin and chlorhexidine gluconate body wash was examined. The first group was educated on routine hygiene, in the second decolonization without reminders was carried out, and in the third group decolonization with reminders was conducted. It has been reported that patients who showed a good compliance in the decolonization measures had a more rapid

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clearance of MRSA [11]. Bacterial cultures should be taken regularly from the nose, the armpit and the groin of the colonized patient and be examined, if they were positive for MRSA. When a nose culture is positive for MRSA, a locally disinfecting treatment with mupirocin should be performed twice daily for seven days [12]. Hand disinfection should be carried out very carefully; alcohol exerts a good bactericide effect. By this way, transmissions from nurses to patients or from patients to nurses are prevented.

Infection with MRSA

When an infection with MRSA (e.g., wound infection, pneumonia, infection of the urinary tract or a bacteriaemia) occurs and MRSA is diagnosed in the bacterial culture, disinfection with polyhexanide is the appropriate measure to disinfect the wound [12]. Vancomycin is the antibiotic of choice for the treatment of infections with MRSA. If the appropriate dose is used and the treatment interval is considered, the anti-infective action cures the infection. Common adverse effects are ototoxicity, nephrotoxicity, allergic reactions and neutropenia [4]. After a vancomycin-intermediate *Staphylococcus aureus* is diagnosed, a combination of daptomycin with fosfomycin is suggested [3]. In a clinical phase III study, it was found that this combination of antibiotics cured 60% of the bacteriaemias. Although vancomycin and reserve antibiotics are available, bacteriaemia remains a highly acute infection with disturbances of consciousness and shock symptoms with a high mortality [3]. In an Iranian referral hospital for children in Teheran, 172 sputum cultures were collected from patients suffering cystic fibrosis. 40% of them had colonization with MRSA. Among the cultures with MRSA, no resistance was found against vancomycin, linezolid or quinupristin/dalfopristin [13]. From 2004 to 2014, during the Tigecycline Evaluation and Surveillance Test, pathogens from 27 medical centers in Spain were collected. Among the cultures with *Staphylococcus aureus*, 34.1% of them were methicillin-resistant. All MRSA were susceptibile to vancomycin or tigocycline [14]. Fifth-generation cephalosporins, for example ceftobiprole and ceftaroline, can be used to treat infections due to MRSA. In the case of MRSA resistance against fifth-generation cephalosporins, non-mecA mechanisms are important for the development of resistance of these antibiotics against MRSA. The mecA resistance determinant encodes the penicillin-binding protein (PBP2a), to which some beta-lactam antibiotics bind, and also mediates resistance to these antibiotics [15].

Treatment of MRSA-colonized and infected patients with bacteriophages

Patients infected with MRSA might be treated with a cocktail of bacteriophages. In an animal model of osteomyelitis, it was examined the therapeutic effect when a cocktail of bacteriophages was administered to treat an osteomyelitis caused by MRSA [16]. Osteomyelitis is commonly caused by methicillin-resistant *Staphylococcus aureus*. Twenty-two rabbits were used in this experiment. The authors divided the animals into three groups: the first group was used to asses osteomyelitis, the second group started therapy after six weeks, and the third group started therapy after three weeks. The second and third groups were treated with a cocktail of seven virulent bacteriophages. These groups recovered from osteomyelitis and showed no sign of infections after the therapy with bacteriophages [16]. Enzymes derived from bacteriophages might inactivate MRSA biofilms. In this sense, the enzyme cysteine, histidine-dependent amido hydrolase/peptidase (CHAPK) has been isolated and, in an animal experimental model, this enzyme disrupted and prevented the formation of staphylococcal biofilms [17].

Tarocins and other other inhibitors of wall teichoic acid biosynthesis which restore efficacy of ß-lactam antibiotics against MRSA

The dramatically increasing emergence of MRSA-colonized and -infected patients in hospitals and long-term care facilities requests the need for new therapeutic strategies. By genetic and biochemical means, it was found that inhibitors of the teichoic acid biosynthesis, namely tarocin A and B which do not have an intrinsic activity, restore the anti-infective efficacy of ß-lactam antibiotics in combination with these inhibitors [18]. In clinical trials, it should be examined whether tarocin A and B might successfully treat infections caused by MRSA in combination with ß-lactam antibiotics [18].

Treatment of MRSA-colonized patients with cultures of not drug-resistant *Staphylococcus epidermidis*

In long-term care facilities, a high percentage of patients are colonized with MRSA having the risk to acquire an MRSA infection through a self-infection or by means a cross infection. Generally, these patients are treated with appropriate measures of disinfection [1]. It might be possible to administer cultures of *Staphylococcus epidermidis*, which have no antibiotic resistance, above all no methicillin resistance. Since genes can be transferred through a horizontal inter-bacterial gene transfer between MRSA bacteria and physiological bacteria, it is possible that physiological genes are transferred to MRSA bacteria or that MRSA genes are transferred to *Staphylococcus epidermidis* [19]. In a meta-analysis, it was found that among nursing students, the detection of MRSA was stable after measures of disinfection and that the colonization with other forms of Staphylococcus was increased [19]. If a decolonization of MRSA with cultures of not drug-resistant *Staphylococcus epidermidis* is performed, bacterial cultures should be taken from the skin and mucous membrane in order to control if the colonization with MRSA is decreased or increased [1]. In a fine-celled foam model with three growth regimes, namely simulated sweat, simulated serum and simulated sweat with simulated serum, it was investigated whether sessile cultures of the physiological skin bacteria *Staphylococcus saprophyticus* and *Corynebacterium xerosis* might inhibit the growth of MRSA and *Pseudomonas aeruginosa*. It was found that in both simulated sweat and serum, the physiological bacteria inhibited the integration of MRSA and *P. aeruginosa*. However, in the simulated sweat with simulated serum, both pathogens integrated into pre-established biofilms [20]. In preclinical studies, the ecological displacement of MRSA by physiological skin bacteria has been examined and it has been shown that its effect is not secure [20].

Conclusion

A colonization with MRSA and an infection with this multi-resistant bacterium is a health problem of major importance in hospitals and long-term care facilities. The decolonization of MRSA is generally performed by appropriate measures of disinfection. Bacteriaemias with MRSA are a highly acute infection with unconsciousness and shock symptoms showing a mortality of 20-30%. Vancomycin, daptomycin combined with fosfomycin, linelozid, tigocycline or fifth-generation cephalosporins is the reserve antibiotics to cure these infections. Alternative methods to cure an infection with MRSA might be the administration of bacteriophages or the treatment with inhibitors (tarocin A, B) of the wall teichoic acid biosynthesis, which restore the efficacy of ß-lactam antibiotics against MRSA. In clinical trials, the administration of these inhibitors, as an add-on therapy, to the treatment with ß-lactam antibiotics should be examined, i.e. tarocin A and B could successfully treat infections caused by MRSA. A possibility to decolonize MRSA-colonized patients might be the administration of cultures of not drug-resistant *Staphylococcus epidermidis* or other physiological skin bacteria, for example corinebacterium spp. In this case, genes could be transferred between physiological bacteria and MRSA bacteria. MRSA cultures should be taken from the skin and mucous membrane in order to control if the colonization with MRSA is decreased.

Conflicts of interest

None.

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