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Review

Staphylococcus aureus and *Staphylococcus epidermidis* infections on implants

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SUMMARY

Infections are one of the main reasons for removal of implants from patients, and usually need difficult and expensive treatments. *Staphylococcus aureus* and *Staphylococcus epidermidis* are the most frequently detected pathogens. We reviewed the epidemiology and pathogenesis of implant-related infections. Relevant studies were identified by electronic searching of the following databases: PubMed, ScienceDirect, Academic Google, and CAPES Journal Portal. This review reports epidemiological studies of implant infections caused by *S. aureus* and *S. epidermidis*. We discuss some methodologies used in the search for new compounds with antibiofilm activity and the main strategies for biomaterial surface modifications to avoid bacterial plaque formation and consequent infection. *S. aureus* and *S. epidermidis* are frequently involved in infections in catheters and orthopaedic/breast implants. Different methodologies have been used to test the potential antibiofilm properties of compounds; for example, crystal violet dye is widely used for in-vitro biofilm quantification due to its low cost and good reproducibility. Changes in the surface biomaterials are necessary to prevent biofilm formation. Some studies have investigated the immobilization of antibiotics on the surfaces of materials used in implants. Other approaches have been used as a way to avoid the spread of bacterial resistance to antimicrobials, such as the functionalization of these surfaces with silver and natural compounds, as well as the electrical treatment of these substrates.

Introduction

Biomaterials are natural or synthetic materials, including polymers and metals, used to replace any living tissue that has undergone some accidental damage or destruction due to some pathology or even plastic surgery repair [1]. Researches and technological advances in the development of biomaterials have shown rapid growth in order to maintain a demand at the population level; the biomaterials can replace or restore the shape and function of a compromised tissue, improving people's quality of life and longevity [2].

Cytocompatibility and preservation of the differentiated phenotype of the cells surrounding the implants are fundamental properties of the biomaterials designed to be integrated to tissues, such as orthopedic implants, whose main objective is the osseointegration [3]. Despite the benefits that implants can offer, they are susceptible to several problems such as lack of integration, inflammatory process, total

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rejection by the receiving individual, and bacterial infection, which is the main cause of implant loss [4]. Bacteria may adhere to form biofilms in foreign bodies placed in patients, such as central and peripheral venous catheters, and in breast/orthopaedic implants, thus establishing infection [5]. In addition, bacteria embedded in biofilms may exhibit greater resistance to environmental conditions as result of the high degree of horizontal gene transfer among them, including antibiotic resistance genes, favouring the infection [6].

Implant infections are most usually caused by staphylococci (about four cases in five). Two species, *Staphylococcus aureus* and *S. epidermidis*, account for around two-thirds of infections [7]. A strategy to eradicate implant infections is prolonged treatment with high doses of antibiotics, often using antimicrobials that act through different mechanisms [8]. However, in clinical practice, infected implants usually require their surgical removal in addition to long-term antibiotic therapy. These problems have stimulated advances in implant surface engineering research, in order to produce implants more resistant to bacterial colonization [9]. One of the most widely adopted strategies is the coating of surfaces with antibiotics; however, this is potentially a hazardous approach due to the risk of selection of drug-resistant micro-organisms, such as meticillin-resistant *S. aureus* (MRSA) [10].

This review aims to clarify mechanisms of *S. aureus* and *S. epidermidis* pathogenicity in implant infections, and to highlight some alternative approaches to preventing infections related to modifications on implant surfaces that could be used in the manufacture of biomaterials.

Methods

Studies were searched in electronic databases according to article titles, abstract contents, and relevance in the field of staphylococcal implant infections. The databases used in this research were PubMed, ScienceDirect, Academic Google and CAPES Journal Portal. The main terms applied were *S. aureus*, *S. epidermidis*, catheter, orthopedic implant, breast implant, infection, biofilm, antibiofilm activity and antibacterial implant surfaces. Articles were sought that provided new knowledge about the epidemiology of implant infections, the pathogenicity of *S. aureus* and *S. epidermidis* in these infections, and approaches to the prevention of implant-related infections. Each publication identified in the electronic searches was evaluated against these criteria by four authors (W.F.O., P.M.S.S., R.C.S.S. and G.M.M.S.); the selected articles were finally verified and approved by the other authors (G.M., L.C.B.B.C., and M.T.S.C.).

Microbial epidemiology of infections in intravascular catheter and orthopaedic/breast implants

The incidence of local or bloodstream infections associated with intravascular catheters is generally low. However, infections are important, because they are inconvenient to treat, and because serious infectious complications may occur, including sepsis and septic shock, infective endocarditis, and other metastatic infections [11].

Santarpia *et al.* studied 172 patients who had a total of 238 central venous catheters (CVC) used for home parenteral nutrition. Ninety-four of the catheters were associated with catheter-related bloodstream infection (CRBSI). Coagulase-negative staphylococci (CoNS) were the most frequent causative agents (52.8%); Gram-negative bacteria accounted for 18.6% of infections; 7.1% were caused by fungi, and 15% were by polymicrobial infections [12]. In another study of 85 patients receiving parenteral nutrition, 19% developed CRBSI. Again, *Staphylococcus* spp. (44%) were the most frequent species, followed by *Candida* spp. (25%) [13]. In a recent study by Wu *et al.*, 8% of patients with CVC following gastrointestinal surgery developed CRBSI, and once again CoNS were the most frequent cause of infection [14].

The main micro-organisms that cause infections in orthopaedic implants are Gram-positive bacteria such as *S. aureus*, *S. epidermidis*, and less frequently, *Propionibacterium acnes*; streptococci and enterococci tend to occur in later infections, and Gram-negative bacteria are seen far less frequently [15]. Montanaro *et al.* studied the microbial aetiologies of infections in 242 orthopaedic patients with infections, to investigate their aetiology. Overall, staphylococci accounted for ~75% of all isolates. *S. epidermidis* was the main pathogen in patients with knee and hip arthro-prostheses, whereas *S. aureus* was the main pathogen in patients with infections associated with internal and external fixation systems and in patients without implants [16]. A study of 163 patients aged 19–94 years with infected implants in the main joints or long bones of the lower limbs showed a predominance of *S. epidermidis* (51.5%), with 43.6% caused by *S. aureus* (43.6%), and both pathogens isolated from 4.9%. Older patients had a higher mortality rate and higher frequency of infection with meticillin- or multidrug-resistant bacteria [17]. In another study of 115 patients with *S. aureus* orthopaedic implant infections, those who had implants for bone fixation had a lower rate of MRSA infection than those who had arthroplasties. Other risk factors for MRSA were having an open fracture, nursing home residence, renal failure and hospitalization in an intensive care unit. This research raised the possibility of adapting antimicrobial prophylaxis for these higher-risk groups of patients [18].

The majority of isolates from breast-implant infection cases are *Staphylococcus* spp., particularly *S. aureus* and *S. epidermidis* [19,20]. A study with 37 cases of breast implant infection (81% silicone implants and 19% saline implants) showed that the most frequent aetiological agent was *S. aureus* (18 cases) [21]. However, Darragh *et al.* performed two retrospective audits: one with 86 patients undergoing 106 implant-based reconstructions, and another with 89 patients who underwent 105 implant-based reconstructions. In the first audit, bacteria were isolated in three cases, all of which were Gram negative (*Escherichia coli*, two cases; *Pseudomonas aeruginosa*, one case). In the second audit there were five infections, three caused by Gram-negative bacteria and one each caused by *S. aureus* and *S. epidermidis* [22].

Adhesion and biofilm formation: pathogenicity in medical devices

Multidrug-resistant nosocomial pathogens are the most common micro-organisms in medical device infections. They colonize the external and internal region of the catheters and proliferate at a rate of 0.5 cm of surface area per hour, being able to form a thick biofilm in 24 h on the surface of these