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Review

A review of the clinical implications of anti-infective biomaterials and infection-resistant surfaces

Davide Campoccia [a,*], Lucio Montanaro [a,b], Carla Renata Arciola [a,b,*]

[a] Research Unit on Implant Infections, Rizzoli Orthopaedic Institute, Bologna, Via di Barbiano 1/10, 40136 Bologna, Italy
[b] Department of Experimental, Diagnostic and Specialty Medicine, University of Bologna, Via S. Giacomo 14, 40126 Bologna, Italy

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ABSTRACT

Infection is currently regarded as the most severe and devastating complication associated to the use of biomaterials. The important social, clinical and economic impacts of implant-related infections are promoting the efforts to obviate these severe diseases. In this context, the development of anti-infective biomaterials and of infection-resistant surfaces is being regarded as the main strategy to prevent the establishment of implant colonisation and biofilm formation by bacteria. In this review, the attention is focused on the biomaterial-associated infections, from which the need for anti-infective biomaterials originates. Biomaterial-associated infections differ markedly for epidemiology, aetiology and severity, depending mainly on the anatomic site, on the time of biomaterial application, and on the depth of the tissues harbouring the prosthesis. Here, the diversity and complexity of the different scenarios where medical devices are currently utilised are explored, providing an overview of the emblematic applicative fields and of the requirements for anti-infective biomaterials.

1. Introduction

The beginning of the new millennium has been characterised, as never before in the human history, by the broadest application of medical devices in all fields of medicine. Current technological advancements have led to the highest level of refinement and optimization both in the selection of the most appropriate biomaterials and in the design at macro-, micro-, and recently even nano-scale levels. The substantial achievements in terms of biocompatibility associated to an always lower risk of failure [1] and the increasing demand for medical care from an aging population have both contributed to the successful expansion of the use of medical devices, now reaching numbers never seen before. In 2007 it was estimated that the worldwide use of medical devices was approaching half a billion of devices per year, with catheters alone counting for about 400 million pieces [2] and certainly figures have constantly grown since then. The huge numbers of individuals nowadays bearing indwelling devices often represented by permanent implants imply that, even if failures concern a minor proportion of patients, the overall impact on the entire population and on the costs for the national health systems are enormous [3,4]. This impact is particularly significant for septic failures, when microbial infections develop on biomaterial surfaces. Following an initial colonisation, bacterial biofilms develop and establish on contaminated surfaces, critically compromising the functionality and performance of the implant itself, recruiting inflammatory cells, affecting the integration in the surrounding tissues, but also posing the patient at serious risk of systemic infections, septicaemia when not even death [5]. More important, once a mature bacterial biofilm has established, conventional medical therapies based on systemic antibiotics are not efficacious [6] and implant removal often represents the only chance to eradicate the infection. Especially in orthopaedics, a two-stage substitution, where implant replacement is delayed and not contemporary to implant removal, is often required in order to achieve complete clearance from infection at the site of implantation. Even so, infection relapses are common especially by virulent pathogens such as methicillin-resistant *Staphylococcus aureus* (MRSA) [4]. Finally, although the risk of developing an implant-related infection is highest for acute and sub-acute events originated during surgery, a residual risk still remains for the possibility of late infections consequent to haematogenous spread from distant colonised anatomic sites. Considering all these elements, septic failures are certainly complications difficult to manage and imply significant morbidity to the

* Corresponding authors. Research Unit on Implant Infections, Rizzoli Orthopaedic Institute, Via di Barbiano 1/10, 40136 Bologna, Italy. Tel./fax: +39 0516366599.
E-mail address: carlarenata.arciola@ior.it (C.R. Arciola).

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patients and huge costs. Much has been done in terms of prevention. However, a point has currently been reached where significant efforts to tighten asepsis control result in just a relatively low advantage in terms of reduction in the rate of infections. Moreover small differences can be difficult to prove statistically even in very large epidemiologic investigations [6]. At present, there is not a single strategy that could totally eliminate the incidence of infections associated to biomaterials. More reliably implant-related infections can be efficaciously prevented by undertaking a series of complementary actions, each contributing to lower the rate of incidence. Control of asepsis, sterile procedures, adequate protocols of perioperative antibiotic prophylaxis and appropriate management of antibiotics for medical treatment have become the basic standards applied in the hospitals for contrasting post-surgical infections. More recently, epidemiological survey of outbreak events by virulent epidemic strains, control and confinement of patients and personnel colonised by MRSA or other antibiotic multiresistant strains are progressively being pursued by reference hospital settings. Along with all these preventive measures that are currently applied, an important strategy that has progressively been gaining ground over the years is the use of biomaterials that are less susceptible or even resistant to bacterial infections. Such biomaterials include, among others, materials with self-sterilising (or, more appropriately, self-disinfecting) surfaces, capable to deliver active concentrations of antimicrobial drugs locally and, if required, systemically, sometimes even useful to clear and eradicate pre-existing infections.

In the history of medicine the early adoption of biomaterials endowed with bactericidal properties was initially driven by empirical experience rather than by a deliberate choice, because at the time the cause of infection was still unknown. A noble metal such as silver, nowadays broadly employed to produce a variety of antimicrobial surfaces, apart from the silver skullcap in the fanciful story of Baron Münchhausen [7], was the preferred material for indwelling catheters in gynaecology as early as in the mid of the 19th century [8,9]. The use of biomaterials expressing bactericidal activity became a deliberate and better conscious choice only with the advent of the microbiology science and the discovery of the first disinfectants around the end of the 19th century [10]. Thereafter, the development of antimicrobial biomaterials progressed slowly and only in the 40s' the first combinations biomaterial-antibiotic were being proposed in dentistry and gynaecology [11–13]. However, it is in recent years with the expansion of the use of medical devices that the interest for anti-infective biomaterials has reported a real progress, witnessed by the increased number of published papers per year on this topic. Well defined diversified strategies have been delineated to develop materials that hinder protein adsorption and early bacterial adhesion mediated by specific adhesins for the host extracellular matrix proteins [14–16], interfere with microbial colonization and biofilm assembly, express bactericidal activity at the interface with host tissues, deliver active concentrations of bactericidal substances, interfere with the physiology of pathogens, disrupt the structural integrity of single bacterial cells or even the complex organization of bacterial biofilms. In view to describe the state of the art in fact of anti-infective biomaterials, we offer an updating on the significance of biomaterial-associated infections in the most representative applicative fields of medical devices, considering their diversity in terms of anatomic niches, common routes of contamination and rate of infection, implications for the adverse events once the infection has established. This is a necessary premise to realize that anti-infective biomaterials have to respond to very diverse requirements based on the different applicative conditions.

First of all, however, it is necessary to clarify some aspects of nomenclature and propose appropriate definitions so as to avoid confusion deriving from the inappropriate use of terms often utilised as if they were synonymous. In Fig. 1, a series of definitions are reported in a hierarchical order. Much attention is currently focused on biomaterials capable to act on infections caused by bacteria and fungi. Nevertheless, biomaterials have also been formulated that release antiviral [17–20], antiprotozoal [21–24] and antihelminthic drugs [25] to prevent or treat infections caused by different types of pathogens and, consequently, the anti-infective biomaterial should appropriately be termed. In this review article the attention will be especially focused on the subcategory of antimicrobial biomaterials that are antibacterial, at present this certainly representing the broadest group of anti-infective biomaterials and the one of greatest interest in the war to implant-related infections. Implant-related fungal infections are in general less common. For instance the percentage of infections related to orthopaedic joint prostheses caused by *Candida* ssp. is less than 1%, considering a rate of infections of 1–3% this means 1–3 events per 10^4 patients [26]. This does not mean that infections caused by fungi bear fewer implications for the affected patients who, often tumoral or immunocompromised, are at high risk of mortality [27].

2. Diversity of the conditions of use of medical devices

Before introducing in detail the different strategies that are currently pursued to prevent or treat bacterial infections by means of antibacterial biomaterials, a few words should be spent on the diversity of conditions in which medical devices are used. As far as this is concerned, a first consideration should be made on the different degree of invasiveness of medical devices as this aspect is crucial not just to determine the potential risk of infection but also the severity of the consequences once a biomaterial-associated infection has developed. Rate of infections and severity of related sequelae are variables to be considered in the assessment of the balance benefits vs. drawbacks of anti-infective strategies, potency vs. toxicity. Additionally, the strategies based on anti-infective biomaterials should take in consideration the circumstances of use and the pathways implicated in the development of infections. There are obvious differences in the requirements for percutaneous implants left *in situ* for prolonged periods and for internal implants totally inserted in the tissues. A critical aspect relates to the concept of internal device. For instance percutaneous and permucosal implants pose a high extra-risk of infection with respect to other devices that, although entering the body, do not breach the epithelial barriers. Similarly, the implications of infections for sterile implants located within epithelial barriers and totally inserted in deep tissues are different with respect to medical devices in external contact with mucosal membranes, and therefore often in a contaminated environment (e.g. the digestive tract). Among totally internal implants, a classification often used is that distinguishing intravascular from extravascular devices in view of the different potential to cause bacteraemias, haematogenous spreading to distant sites and, eventually, sepsis. However, the possible anatomic sites of implant insertion, the respective tissues involved and the potential harm posed are very diverse, not last this wealth of conditions even includes transvascular devices. Fig. 2 illustrates examples of medical devices applied in different anatomical site of the body. In the following paragraphs the conditions of use of some representative categories of devices will be shortly reviewed enlightening the specific implications for the rate and severity of infections.

3. External and superficial medical devices

Medical devices include very broad categories of objects. They can be either totally external to the body and in contact with the

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