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Leading Opinion

The significance of infection related to orthopedic devices and issues of antibiotic resistance ☆

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Abstract

Over the last 15 years, with the advent of modern standards in the control of sterility within the operating room environment and adequate protocols of peri-operative antibiotic prophylaxis, the incidence of infections associated to orthopedic implants has become very low. Nevertheless, the event of infection still represents one of the most serious and devastating complications which may involve prosthetic devices. It leads to complex revision procedures and, often, to the failure of the implant and the need for its complete removal. In orthopedics, for the enormous number of surgical procedures involving invasive implant materials, even if nowadays rare, infections have a huge impact in terms of morbidity, mortality, and medical costs.

The difficult battle to prevent and fight bacterial infections associated to prosthetic materials must be played on different grounds. A winning strategy requires a clear view of the pathogenesis and the epidemiology of implant-related infections, with a special attention on the alarming phenomenon of antibiotic resistance. In this regard staphylococci are the prevalent and most important causative pathogens involved in orthopedic implant-related infections, and, thus, the main enemy to defeat. In this paper, we offer an overview of the complexity of this battleground and of the current and new, in our opinion most promising, strategies in the field of biomaterials to reduce the risks and counteract the establishment of implant infections.

Keywords: Orthopedic surgery; Microbial infections; Implant materials; *Staphylococcus*; Antibiotic resistance

1. Introduction

Hip or knee replacements, fracture fixation, ligament and tendon reconstruction and other surgical implant procedures have in recent years become valid and extremely common procedures to restore the function of affected joints, fractured bone segments and impaired limbs. In the US alone, total hip and knee arthroplasties currently accounts for over half a million interventions each year [1–3]. In light of this enormous population of patients with orthopedic implants, even a currently low risk of infection, estimated to be in the range of 0.5–5% for total joint replacements (less than 1–2% in institutions with highly trained surgeons), has to be considered very relevant for its serious consequences. During the first 2 years following the interventions of total knee arthroplasty, infections have variously been reported as the second main cause of revision just after instability [1,4–7], when not even the first one [8].

Simple debridement procedures with retention of prosthesis and chemotherapy with antimicrobial agents are treatments that are not always effective on infections that are already established [9]. Sometimes prosthesis removal and replacement, when not even joint fusion [10], represent the only salvage option to definitively eradicate severe infections. These drastic interventions bear obvious implications in terms of attendant patient trauma, prolonged

☆ *Editor's Note*: This paper is one of a newly instituted series of scientific articles that provide evidence-based scientific opinions on topical and important issues in biomaterials science. They have some features of an invited editorial but are based on scientific facts, and some features of a review paper, without attempting to be comprehensive. These papers have been commissioned by the Editor-in-Chief and reviewed for factual, scientific content by referees.

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hospitalization as well as in terms of health and social costs (it has been estimated that the treatment of each single episode of infected arthroplasty costs >$50,000 [11]). Furthermore, following revision surgery there is also a significantly high risk (up to 10%) of a recidive and implant replacement, which has additionally to be taken into consideration.

In the strategy for the prevention of infections, much has been done to improve the operating standards, minimize the possibility of contamination during surgery, reduce the establishment of infection by peri-operative antibiotic prophylaxis, and confine pathogenic strains by patient isolation [12,13]. Along these directions further improvements can still be made, but little advancements in terms of decreased infection rates are being expected in return of this type of efforts [14]. As a consequence, over the last 15 years, increasing attention has progressively been focused on the epidemiology and the pathogenesis of the infections, especially those associated to implant materials, in order to build knowledge and gain better control over this phenomenon. Many effort have been directed to investigate which are the most important etiologic agents involved, the pathogenetic mechanisms leading to microbial adhesion, colonization of implant surfaces, and evasion of the host defenses, the most crucial virulence factors, the nature and properties of microbial biofilms and, not last, the progressive alarming appearance of antibiotic resistant strains.

2. Pathogenesis of implant infections

The pathogenesis of peri-implant infections differs from that of other post-surgical infections for a series of phenomena that are strictly related to the presence of biomaterials. The interstitial milieu surrounding prosthetic implants is known to represent a region of local immune depression and a *locus minoris resistentiae*, often referred to as immuno-incompetent fibro-inflammatory zone [15], susceptible to microbial colonization, and favorable to the instauration of infections [16–18]. Experimental models have well enlightened that the critical dose of contaminating microorganisms required to produce infection is much lower when a foreign material is present at the surgical site [19–22]. Furthermore, in orthopedics, the micromovements of the prostheses inserted in hard tissues and the detrimental release of wear debris, as in the case of total arthroprostheses, can damage the tissues surrounding the implant, creating conditions, where the immune defenses are mostly depleted. Intrinsic chemical nature and superficial topography of implant materials can influence to a certain extent early microbial adhesion and the chances of successful colonization of the prosthesis. However, the local immuno depression present in the peri-prosthetic tissue generally facilitates the establishment of an infection for all implant materials.

Microorganisms responsible for this type of infections are often opportunists, which take advantage of the weakening of the body defenses at the implant surface–tissue interface. Bacteria are initially passively adsorbed on the biomaterial surfaces, but the establishment of prosthesis-associated infections relies also on specific active interactions of the bacteria with biomaterial surfaces. For instance, several microbial species possess adhesins, receptorial proteins which mediate cell anchorage and fixation to host extracellular matrix proteins (such as collagen, fibrinogen, fibronectin, and elastin) adsorbed on biomaterials [23–25], or elaborate a complex polysaccharidic glycocalix, forming adherent biofilms on implant surfaces [26–29]. Biofilm-forming bacteria exhibit increased protection from the host defense and enhanced resistance to antibiotic treatments. Several of these active adhesion mechanisms are currently regarded as crucial virulence factors and frequently considered for the characterization of the clinical isolates in studies of molecular pathogenesis and epidemiology.

3. Diagnosis of orthopedic implant-related infections and main pathogens involved

A fundamental and, at times, very difficult step in clinical orthopedic practice is the differentiation of the condition of implant infection from that of aseptic failure. While early post-operative and haematogenous prosthetic joint infections are often characterized by acute onset of symptoms and signs of infections, late post-operative prosthetic joint infections, which generally occur after the first 3 months following surgery, show more subtle signs of inflammation, chronic persistent post-operative pain and/or early loosening of the implant [5,30,31]. The absence of a standardization in the criteria to determine the diagnosis of implant infection, and the possibility of both false-negative and -positive culture results have often led to a certain variability in the esteems of the prevalence of the pathogens causing this type of infections [5,32].

In spite of the changes due to the different criteria applied in the diagnosis of infections and in the inclusion of pathogens as real causative agents and not mere contaminants, it is well established that the vast majority of implant-related infections in orthopedics is due to Gram-positive aerobes, staphylococci in first place [33]. Recent technological advancements such as automated ribotyping, for a rapid and accurate pathogen identification, gave us the possibility of easily and finely resolving down to the species and subspecies level also bacteria, which in the routine of many clinical laboratories are often generically classified as Coagulase Negative Staphylococci (CoNS) [34,35]. Since the year 2000, at our institution we regularly collect all clinical isolates derived from surgical and prosthesis-associated infections, following the criteria described in full detail in Arciola et al. [36]. Each single strain is processed for species identification, typed for antimicrobial susceptibility by the disc diffusion technique, and characterized for selected virulence traits such as biofilm formation in the case of staphylococci. Based on