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Mini Review

Infection, Surgery and Biomaterials: An Interesting Review with a Point of View

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Abstract

Reducing biomaterial-associated infections in surgery involves a change in the operating attitude of everyone involved in all processes that are ongoing in the Operating Room (OR) towards decreasing contamination risks. Biomaterial-associated surgery by surgeons not familiar with the contamination risks and the ways of preventing them can be hazardous. To minimize these complications, the awareness of these contamination risks should be reflected in an appropriate protocol, adjusting of the peri and postoperative protocols and attitude of the surgeon and operating personnel. Looking at the essentials, however, the main goal is decreasing contamination by minimization of air disturbance.

Keywords: Biomaterials; Surgery; Infection

Introduction

The incidence of wound infection after clean surgery is often underestimated. Infection rates up to 15% can be found by meticulous follow up [53]. The consequences of these complications can be troublesome for the patient involved. Most of the time the post-operative recovery will be delayed and secondary healing of the operative wound will occur. The long-term consequences of the infection will mostly be within acceptable limits. When biomaterials are involved however in post-operative infectious complications, a totally different scenario is likely to occur and the longevity of the artificial organs and temporary assist devices is limited. Biomaterial-associated infections are usually resistant to antibiotics and removal of an infected implant is the outcome of most of these infections at high costs for the health-care system and discomfort for the patient. Ever since the description by Gristina of biomaterial-associated infection as "a race for the surface" [36,37] between microbial adhesion and tissue integration, there is a growing awareness of the risk of foreign body implantation. The design of a biomaterial surface upon which the race for the surface is fought, determines the outcome of it, as it depends upon a delicate fine-tuning of the properties of the biomaterial surface that has not yet been achieved. Some infected biomaterial implants are relatively easily removed, like contact lenses [56], voice prostheses [1] or dentures [72]. The total artificial heart [37], elongatable endoprostheses as used after extensive tumour resection in children, total hip and knee arthroplasties on the other hand are much more difficult to remove. Moreover, removal of these devices often constitutes a clinical dilemma, as for instance the removal of an infected Hickmann catheter in patients on chemotherapeutic treatment. Here the surgeon has to choose between two evils: leaving the infected catheter in place or removal at the expense of stopping the chemotherapy (note that a new catheter can only be safely inserted once the infection has fully cleared, otherwise recurrence will happen in due time). Biomaterial implants sometimes are complex devices made of a combination of different biomaterials. These materials need to be compatible with their biological environment, which is not always the first concern of the biomedical engineer, as mechanical and manufacturing properties often dictate the choice for a given material. (Tables 1 and 2) list commonly used biomedical implants in modern medicine with their incidence of clinical infections. Different biomaterials are prone to infection by different organisms. Staphylococcus aureus is generally found on metallic implants [5], while pseudomonas and Staphylococcus epidermidis are mainly isolated from polymeric implants [5,28]. Consequently, as biomaterials that are more different are involved in an implant, this increases the chance of a biomaterial-associated infection and the recognition of strains being pathogenic. S epidermidis was long considered a non-pathogenic and harmless member of the normal skin micro flora, but only became a pathogen in the era of biomaterial-implants. Surgery is supposed to be performed in a sterile way, but it can well be argued that completely sterile surgery is impossible. In a contamination study of primary total hip arthroplasties, 30% of the materials in contact with the prosthesis site harvested viable microorganisms [59]. Nearly the same percentage was found by Knobben et al. in two different studies [49,50]. Troublesome in biomaterial-associated infections is the long history of antibiotic therapy applied prior to the ultimate decision to remove the implant, giving the opportunity for antibiotic resistance to develop. Van de Belt et al. (1999) [94] described the culturing of antibiotic resistant staphylococci from gentamicin-loaded bone cement that was removed in a hip revision for infection. The path of entry of infecting microorganisms to a biomaterial implant can be directly along the parts of the implant itself, like along the polyvinylchloride drivelines of the total artificial heart [37] or through haematogenous spreading [77] or dental treatment [52]. Alternatively, it can be stated that, despite the use of intra-operative systemic antibiotic prophylactics, strict hygienic protocols, sterile operating theatres and special sterile enclosure, the possibility exists that prostheses become contaminated during surgery and will be implanted in this state. Subsequently, whether or not clinical signs of infection develop depends on interplay of the host immune system and the microbiological characteristics of the infecting organisms. In this chapter, we present an overview of the mechanisms of biomaterial-associated infection and its occurrence in various medical disciplines. Surgical procedures are critically reviewed comparing non

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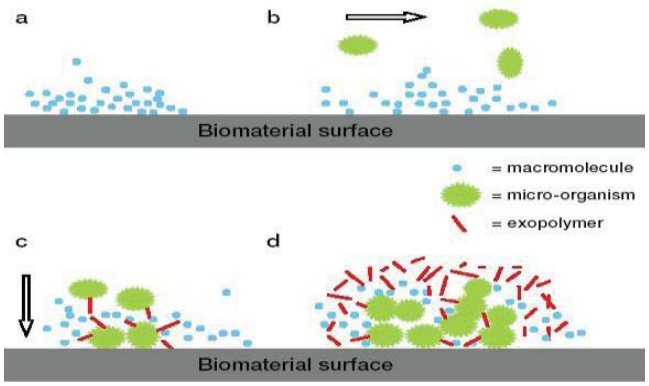

Figure 1: Sequential steps in the formation of biofilms on a biomaterial surface.
Including: a: Formation of a conditioning film. **b:** Microbial mass transport. **c:** Initial microbial adhesion and anchoring through exopolymer production. **d:** Growth of adhering micro-organisms.

biomaterial-associated versus biomaterial associated surgery and recommendations are given for biomaterial-associated surgery. The "race for the surface" and biofilm formation Several authors have proposed a model for biofilm formation in general [10,97] which has been developed from to the concept of "the race for the surface", as first formulated by Gristina in 1987 [36]. Microorganisms have a strong tendency to become attached to surfaces. On these surfaces, they form a micro-ecosystem in which different microbial strains and species grow in a slimeenclosed biofilm. Biofilm formation involves a sequence of events [10,97] represented in (Figure 1). The first step is the adsorption of small, macromolecular components that form a so-called "conditioning film" on the surface of the biomaterial involved. The formation of this conditioning film is extremely fast and occurs in seconds after exposure to a biological environment. The biological environment in which the biomaterial is placed determines the nature of the adsorbed macromolecules. For instance, dental restorative materials adsorb salivary proteins; contact lenses adsorb proteins and lipid components from tear fluid, while blood-contacting biomaterials adsorb a variety of different plasma proteins prior to the arrival of the first microorganism. A prerequisite for microbial adhesion to occur is an adsorbed conditioning film, which changes the physico-chemical properties of the interacting surfaces. Adherence of microorganisms on bare biomaterials surfaces is rare. The initial adhesion of microorganisms is reversible and depends on the overall physico-chemical characteristics of the microbial cell surface, the biomaterials surface and the biological bathing fluid. Firm anchoring through exopolymer production may change this reversible adhesion to an irreversible state. The exopolymers surrounding the microorganisms embed the biofilm to form the so-called "glycocalix" [66]. In addition to anchoring, the glycocalix offers protection against environmental attacks and antibiotics [42,79,85]. Multiplication of the adhering organisms is the main mechanism of growth in a biofilm and eventually leads to the formation of a thick film. The growth rate due to a lowered metabolism is generally slowed down in the biofilm as compared with a planktonic state of growth. Because of this lowered state of metabolism, the sensitivity for certain antibiotics is reduced. In addition, bacteria in this quiescent state are hard to detect with standard microbiologic techniques. This puts the concept of "aseptic loosening" in for example orthopaedic implant surgery in another perspective, as will be discussed later. In the final phase of biofilm formation organisms on the periphery of the expanding biofilm may detach or disaggregate, which plays an important role in the pathogenesis of septic processes. Biomaterials and microorganisms the host defence is significantly compromised in the presence of a foreign material [25]. In continuation of this concept the resistance of osteomyelitis and foreign body related infections to antibiotic therapy was rationalized by others [51,68]. Furthermore, the relatively avirulent S. epidermidis, normally not capable of establishing infection, has become the most common causative organism in biomaterial-associated infection [12]. The organisms causing a biomaterial-associated infection may have one or more of several sources. The first source is constituted by the skin. During insertion of the biomaterial, microorganisms from the skin can be pushed towards the implant surface. A second source is constituted by airborne microorganisms, which in varying concentrations are normally present in the operating theatre. They can reach the surface as early as before implantation [11,55]. A third source described is the haematogenous spread of microorganisms from distant foci in the body towards the biomaterial site. Anecdotal reports of sepsis following dental work and other bacteraemia-producing procedures like surgical incision of infectious processes are common. However, well documented accounts on this subject are rare [31,77]. Biomaterial-implants in permanent contact with skin and/or the outer human body environment form a class of implants that have by definition a contamination rate of 100%. This contaminated state makes them very susceptible to malfunction because of infectious complications [86] (Table 1). Clinical examples of these biomaterial-implants are intravenous catheters, peritoneal dialysis catheters, urinary tract catheters, voice prostheses, oral implants and percutaneous pins in external fracture fixation. Lower infection rates have been observed with totally implanted prostheses (Figure 2), the

Table 1: Incidences of infection of different biomedical devices in permanent contact with skin and/or outer human body environment.

Body site Implant or device Incidence of infectious complications necessitating exchange
Urethra Foley catheter 2.8/1000 catheter days
(Luehm and Fauerbach 1999)
Venous system Peripheral inserted
central venous catheters
2-5/1000 catheter days
(Safdar and Maki 2005)
Arterial system Arterial catheters 0.4-0.7%
(Frezza and Mezgebe 1998)
Intraperitoneal Peritoneal dialysis catheters
11-13% (Thodis et al. 2005)
Extremities Pins in external fracture fixation
12-71% (Bernardo 2001)
Oral cavity Dental implants 5-10% (Ehrlich et al., 2005)
Laryngeal cavity
Voice prosthesis Every 4 months
(Van den Hoogen et al. 1996)

consequences being more serious though. Surgical precautions and consequences because implants in permanent contact with skin and/or the outer human body environment have a 100% contamination rate, they have a high chance of malfunction due to infectious complications. Therefore besides the regular surgical precautions, preventive measures are being developed. This is exemplified by the coating with silver of percutaneous catheters [14, 90] and percutaneous pins (Masse et al. 2000) [63]. In the field of preventing infection of percutaneous pins, the use of a small electric current has proved to be effective in animal experiments [96]. The consequences of the development of a microbial biofilm can be impairment of the function of the implant or device and/or worsening of the clinical state of the patient. Because microorganisms block the valve mechanism, a proper functioning of the voice prosthesis (Figure 3) is impaired or causes leakage of food into the trachea [61]. An exchange procedure every 4 months of the prosthesis is the result of this process [95]. Colonization by microorganisms of urinary tract catheters is inevitable. This can cause blockage or, more seriously, bacteriuria [68]. Infections of indwelling catheters, like for example central venous catheters, often results in bacteraemia, which can cause sepsis and endocarditis. With infections of implants in the circulatory system, a high mortality rate of 50% and 70% occurs for vascular grafts and prosthetic valves respectively [64]. Infection of deep tissue implants, for example orthopaedic implants, will usually result in serious complications like pain, swelling of the joint or limb and loosening of the implant, mortality rates up to 20% are reported with these kind of implants [6,30,41]. Up to a year after microbial seeding, clinical signs of deep implant infections are being reported to appear [62]. This long interval between inoculation of the bacteria and the onset of symptoms can be caused by the low-virulence organisms, which normally inhabit the skin and oral cavity. This may often mimic the natural "aseptic" loosening of prostheses [13,70]. Because of this low-virulence character of the organisms involved, in combination with the biofilm they grow in, a significant part of these infections is probably never recognized. As standard microbiological techniques are used to test the presence of infectious microorganisms, slow growing biofilm organisms often remain undetected [19,67,92,93]. This has important clinical implications for the concept of "aseptic loosening" and the recurrent nature of musculoskeletal infection. Nelson et al. (2005) [65] explained this with a sort of triple mechanism, including (1) inadequate techniques of removing adherent, biofilm associated bacteria; (2) small colony forming variants; and (3) intracellular S. aureus "residing" within osteoclasts. A surgeon needs to perform his surgical technique well with regard to placing the incision, soft tissue handling, meticulous haemostasis and operating time, but also with regard to simple things as the application of the correct time of scrubbing hands, proper wear of hair and mouth covers and the maintenance of a strict discipline in the operating theatre. The latter aspects are most important in biomaterial-associated surgery, and because of their relative unimportance in soft tissue surgery, are frequently overlooked in implant surgery. One must realize that the most common cause of biomaterial-associated infection is thought to be peri-operative contamination [2]. Avoidance of devitalisation by meticulous handling of tissue is an important variable in influencing the risks of deep infection. To prevent areas of skin necrosis between an old and a new incision, previous incisions should be used. Local factors such as scar tissue,

Table 2: Incidence of infection of different biomedical implants arranged according to body site.

Body site Implant or device Incidence of infection
Subcutaneous Cardiac pacemaker 1-5% (Borer et al., 2004)
Tissue expanders 0.9% (Disa et al., 1999)
Chin augmentation implants
0.8% (Gross et al., 1999)
Soft tissue Mammary prosthesis 2-2.5% (Pittet et al., 2005)
Abdominal wall patches 3-8% (Deysine 1998)
Penile prostheses 2-10% (Schoepen and
Staerman 2002)
Nasal implants 3.2% (Godin et al., 1999)
Intraocular lenses 0.5% (Kahn et al., 2005)
Circulatory system
Prosthetic heart valve 1-3% (Ehrlich et al., 2005)
Dacron aortoiliofemoral bypasses
2-10% (Andreev 1995)
Bone Total Hip Arthroplasty 1% (Zimmerli et al., 2004)
Total Knee Arthroplasty 2% (Zimmerli et al., 2004)

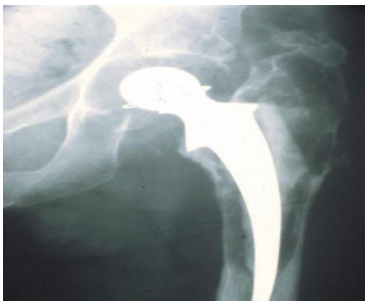

Figure 2: X-ray example of patient with a loosened cemented total hip prosthesis implanted on left side. Note the osteolysis around the femoral component.

depending on its size and localisation, can have a decreased vascularity and it may greatly increase the time required to perform revision surgery [11,48,99]. Especially when infection has been the reason for earlier operations, the outcome can be adversely affected (Jerry and Rand 1988, Schmalzried et al. 1992) [45,80]. Meticulous haemostasis and wound closure are essential in preventing haematoma or an area of wound necrosis. Operative time has to be kept to a minimum because of the association of operative time and the development of infection [11]. Biomaterial-associated surgery versus non-biomaterial associated Surgery. The incidence of infection after implant surgery is generally low (Table 2) and infection rates have decreased substantially over the past decades, but the often disastrous results of these infections make them important complications. Also because of the increasing incidence of for example total joint replacement infection still is a source of considerable morbidity [69]. Apart from the morbidity, the financial burden a joint prosthesis infection puts on health care systems is enormous. In the United States, the annual cost to treat the 3500 to 4000 infections that develop after arthroplasties each year is between 150 and 200 million US dollars [23]. In spinal

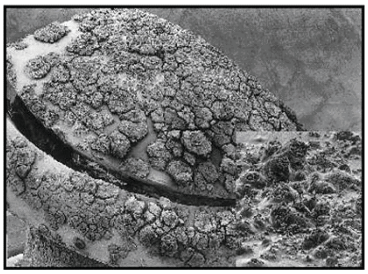

Figure 3: Example of a voice prosthesis covered with biofilm causing a malfunction in the valve mechanism.

surgery the use of spinal instrumentation clearly increases the risk for postoperative infection from 1% to a range of 2.1 to 8.5% [54]. A large amount of the $ 24 billion spent in 1990 on treating spinal disorders [82] will therefore account for the cost of treating spinal implant infections in the near future. With an increasing use of biomaterials in surgery, this financial problem will only continue to increase. It can be argued that sterile implantation of biomaterials is virtually impossible. The operation wound is contaminated to some extent in all procedures. Minimizing contamination by optimizing the operating-room environment, protocols and the operative technique is crucial. These are the factors that can be influenced by the surgeon and the operating personnel. Performing biomaterial-associated surgery means being aware of the possibilities of contamination during the procedure. This necessitates an Operating Room (OR) discipline in operating personnel, as well as in anaesthetists, nurses, students, porters and visitors who enter the aseptic zone. When a surgeon implants biomaterials, an important compromising factor concerning the host defence is introduced. In a classical study in man, it was shown that the presence of a subcutaneous suture reduced the required inoculum to produce infection with S. aureus from 106 to only 200 bacteria [25]. Therewith the presence of a foreign body presents another clinical challenge on its own. Whenever a biomaterial is introduced into the human body, surgical and mechanical trauma as well as the biomaterial itself will evoke an acute inflammatory response [44]. This acute inflammatory cascade results in localised cell necrosis and tissue degeneration and the formation of a very thin membrane between the prosthesis and the body, consisting of fibroblasts, vascular endothelium cells and macrophages. This immune response can disappear when the wound is healed and the biomaterial is encapsulated. In many cases however the host-biomaterials interface remains in a state of chronic inflammation, as few metals and plastics are completely chemically inert in the warm, wet and oxygenated environment of living tissues with a non-neutral p^H, causing the release of components of the biomaterial, like corrosion products, plasticizers and monomers which are able to incite an inflammatory reaction [20,36]. Chronic inflammation impairs host cell growth on the implant [43] and can cause chronic pain, while it may disrupt the anchorage of the implant into the surrounding tissues thus impairing its stability leading to failing performance. Historically orthopaedic surgeons are used to work with biomaterial implants on a large scale since the development of joint arthroplasties in the 1960's. Because they are familiar with the susceptibility of traumatized bone to infection, as has been shown in animal models of osteomyelitis [73,91] their OR manners and attitude towards minimizing contamination have since then been developed further and fine-tuned. Charnley already initiated this after concluding that his 7% post-operative infection rate with total hip arthroplasty was too high and operative protocols needed to be updated [11]. Contamination of the operative wound is influenced by the OR environment. Variables affecting the OR hygienic efficiency include the number of people inside [74] and their adherence to adequate protocols [9,60], the amount of traffic in the OR [74] and personnel present [35], the preparation of the operative site [26,83], the timing and technique of preoperative shaving [47] and the clothing of the operating personnel [8,57,78] including double gloving because the chance of perforation [88] and contamination [15]. Although there seems to be consensus on the importance of a clean air environment in the OR the role of laminar airflow in decreasing infection has remained controversial [29,55]. Some report an improvement in direct infection control [11,22,76] or indirect control by diminishing the prevalence of contamination of the surgical instruments [74]. Others report the influence of airflow on infection rates to be less important [27] or to be proven [85]. Although the above mentioned potential measures are important, the single most important variable influencing the development of postoperative implant infection is the appropriate use of peri-operative antibiotics [4,21,27,40]. Peri-operative antibiotics in implant surgery are now common practice [16,101]. The type of preferred antibiotic and its appropriate regimen has been studied by Tang et al. (2003) [87]. In addition, recording of the number of infections with feedback to the treating physician [100] should be integrated into a registration of complications in the department, as a part of a continuous education program. This recording should preferably extend also to personnel in operating rooms, bacteriological and sterilization departments [98]. Biomaterial-associated surgery protocol reducing biomaterial-associated infections in surgery involves a change in the operating attitude of everyone involved in all processes that are ongoing in the OR towards decreasing contamination risks. The non-biomaterial-associated surgeon is used to a more forgiving environment and therapy resistant infections are rare. Biomaterial-associated surgery by surgeons not familiar with the contamination risks and the ways of preventing them can be hazardous. To minimize these complications, the awareness of these contamination risks should be reflected in an appropriate protocol, adjusting of the peri-operative protocols and attitude of the surgeon and operating personnel. The exact content of such a protocol is hard to ascertain, because many statements are open for debate. Looking at the essentials, however, the main goal is decreasing contamination by minimization of air disturbance. Principles for achieving this goal in a biomaterial-associated surgery protocol are minimizing of personnel traffic in- and out the OR, personnel movement in the OR and of personnel communication. Strict obedience by all those involved and continuous education through performance feedback together with an appropriate antibiotic prophylaxis regime should minimize the inevitable post-operative infectious complications with their devastating effect on the function and lifetime of the biomaterials involved as well as on the patient who is the victim.

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