Host response against biomaterials: the role in the pathogenesis of biomaterial-associated infections
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Chapter 1

General Introduction
The implantation or insertion of biomedical devices, such as artificial heart valves, hips and knees, vascular prostheses and catheters, is virtually indispensable in modern medicine. Devices may be utilized briefly or intermittently (e.g. intravenous catheters) for months to years (e.g. intra-uterine devices), or permanently (e.g. artificial heart valves and hips). A serious problem, however, associated with the use of these so-called biomaterials is the occurrence of bacterial infections. Frequencies of infection vary from 0.1-1% for intraocular lenses to more than 20% for catheters used in chronic ambulant peritoneal dialysis (CAPD; figure 1) [1,2]. Infection causes considerable morbidity and mortality [1,2] because biomaterial-associated infections (BAI) are rather resistant to the host defense and to antibiotic therapy. Therefore removal of an infected biomaterial is often required [1-4].

The staphylococci, especially *Staphylococcus epidermidis* cause more infections associated with almost each type of device than any other microbial species; *S. epidermidis* accounts for 40-75% of the infections and *Staphylococcus aureus* for 10 to 20% (table 1). Less frequently yeasts, coryneforms, other gram-positive bacteria and various gram-negative bacteria are the causative organisms of BAI [1-3]. Gram-negative bacteria, such as *Enterobacteriaceae* and *Pseudomonas* are only a predominant cause of infection associated with urinary catheters or genitourinary implants, this probably due to the location of the implanted biomaterial [1-3].

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**Figure 1.** Overview of the frequencies of infections associated with the various biomedical implants used in humans. Data derived from Seifert H, Jansen B, Farr BM. Catheter-related Infections, Marcel Dekker New York, 1997; First Edition.
The ability of *S. epidermidis* to cause BAI is remarkable. Normally *S. epidermidis* lives in balanced harmony with the human host on the skin and on the mucosa of the upper respiratory tract as part of the microflora, and rarely causes infections other than BAI, except in immunocompromised patients [4-7]. Furthermore, the number of microorganisms present in the implantation site or on the surface of the device before implantation/insertion is very small, suggesting that the presence of the biomaterial itself predisposes for infection [8-10]. In contrast, *S. aureus* also residing in the skin and mucosal microflora of carriers is a common cause of various infections, both in patients with impaired host defense and in healthy immunocompetent persons.

**Table 1. Frequency of microorganisms isolated from infected biomaterials.**

<table>
<thead>
<tr>
<th>Organism</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Staphylococcus epidermidis</em></td>
<td>40-75</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>10-20</td>
</tr>
<tr>
<td>Yeasts</td>
<td>5-10</td>
</tr>
<tr>
<td>Enterococci/streptococci</td>
<td>2-5</td>
</tr>
<tr>
<td>Coryneform/diptroide species</td>
<td>2-5</td>
</tr>
<tr>
<td>Gram negative species</td>
<td>2-5</td>
</tr>
<tr>
<td>Miscellaneous organisms</td>
<td>1-3</td>
</tr>
</tbody>
</table>

For effective prevention a basic understanding of the underlying mechanisms leading to BAI is essential. The pathogenesis of BAI, however, is poorly understood. Enhancement of the susceptibility to infections due to the presence of a biomaterial in humans was described for the first time by Elek en Conen more than 4 decades ago [11]. Also in various animal studies a 1,000 to 100,000 fold reduction of the infection dose of *S. aureus* and *S. epidermidis* were observed in the presence of a biomaterial [12-15]. It is assumed that the adherence of bacteria to the biomaterial, is the initial step in the pathogenesis [2]. Slime production by bacteria and so-called “adhesins” (e.g. polysaccharide adhesin (PS/A) and polysaccharide intercellular adhesin (PIA)) seem to play a role in the adherence of bacteria to biomaterial surfaces [16,17]. Bacteria may adhere directly to the biomaterial or to the biomaterial covered with absorbed host proteins [1,3]. Shortly after implantation or insertion various host proteins, e.g. fibrinogen, fibrinonectin, trombospondin and albumine, adhere to the implanted biomaterial [18-20]. Some host proteins e.g. fibrinogen and fibronectin promote, whereas others, e.g. albumine, inhibit the adherence of bacteria [18-22]. Furthermore, blood platelets deposited on the biomaterial surface promote the adherence as well [23]. Once microorganisms adhere to the biomaterial, production of extracellular substances by bacteria (slime, glycocalix), and the involvement of host proteins (e.g. host proteins, blood platelets) lead to formation of a compact matrix (biofilm) at the biomaterial surface [5,24-28]. This biofilm, is assumed to contribute to the (localized) persistence of bacteria. Various studies demonstrated that bacteria
embedded in biofilms have an enhanced resistance to host defense mechanisms and antibiotics [25,26,29-36].

During the last decades various strategies have been employed in the prevention of BAI, such as the use of strict protocols for preoperative skin preparation and postoperative wound care to reduce the risk for contamination of the wound and biomaterial and the use of systemic antibiotics perioperative prophylaxis. Additionally, regarding bacterial adherence as an essential step in the pathogenesis of BAI, the use of biomaterials with the ability to reduce bacterial adherence appeared to be a very attractive approach to prevent. Therefore, surface-modified biomaterials and biomaterials impregnated/coated with antiseptic agents or antimicrobial(s) have been developed [37,38]. Alternatively, catheters may be soaked in antibiotic solutions prior to their insertion [39]. Although promising results regarding inhibition of bacterial adherence and duration of antibacterial activity of such novel biomaterials are often found in vitro, the use of such biomaterials did not always result in a reduced infection rate in vivo [40,41]. This suggests that there are other factors, such as alterations in the host defense mechanisms due to an implanted biomaterial, may be important in the pathogenesis of BAI.

The implantation of either biomaterial provokes an inflammatory response [42,43]. At the host cellular level, the foreign body reaction starts as an acute inflammatory response, histologically characterized by recruitment of polymorphonuclear cells (PMN), followed by mononuclear cells and macrophages (figure 2). In later stages, macrophages may fuse to become polymucleated foreign body giant cells [42,43]. It should be noted that the intensity and timeframe of duration of this foreign body response is largely dependent on the size, shape, and chemical and physical properties of the implanted material [3,44]. Cytokines excreted by inflammatory cells in the vicinity of an implanted biomaterial are the most important modulators of the foreign body response.

Figure 2. The normal foreign body reaction to implanted biomaterials. (reproduced from J.M. Anderson, Trans Am Soc Artif Intern Organs 1988; 34: 101-107)
Little is known regarding the role of various cytokines in the inflammatory response to biomaterial. In vitro, however, the cytokine induction in predominantly leukocytes exposed to biomaterials have been studied extensively [45-49]. In these studies the induction of the pro-inflammatory cytokines interleukin (IL)-1, IL-6 and tumor necrosis factor-α was found, suggesting that a proinflammatory environment may surround an implanted biomaterial [45-49]. Furthermore, these studies showed that the various biomaterials differed significantly in their cytokine inducing properties if lipopolysaccharide (LPS), a major cell wall component of gram-negative bacteria, was present. This indicates that the presence of bacteria or bacterial cell wall in the vicinity of an implanted biomaterial can modulate or even enhance the inflammatory host response.

Alterations in the host defense due to the implanted biomaterial have been suggested frequently. In a tissue cage model complement-mediated opsonic activity was substantially reduced in the presence of biomaterials [15,50]. PMNs had decreased bactericidal activity in comparison to PMNs from peripheral blood or peritoneal exudate, and the PMNs from tissue cages had defective oxidative metabolism and granulocyte enzyme content [15,50]. Similar impairment of the bactericidal capacity of PMNs has been described if PMNs were exposed to non-phagocytosable surfaces [51-56]. Despite the high number of PMNs in the vicinity of an implanted biomaterial, PMNs are apparently not capable of sufficient host defense [51-56]. Also for mononuclear cells, impaired killing functions are described. In experimental animal models as well as in clinical series, MHC class II antigen (1a) expression on mononuclear cells [57], which is associated with low lysosomal activity, was suppressed around infected biomaterials. Suppressed 1a expression may result in decreased intracellular bacterial killing [57].

Hence, the pathogenic mechanism of BAI is a multifactorial process influenced by the properties of the material, host proteins, presence of bacteria with different virulence properties, bacterial components, and alterations in host defense. In the prevention of BAI all efforts are focussed on inhibiting the bacterial adherence, however, reversal of induced impaired host defense mechanisms in the vicinity of an implanted biomaterial may be an interesting approach as well. For this approach, the role of the various cytokines in the host response against implanted biomaterials, has to be studied.

The scope and outline of this thesis.

Whereas the range of biomaterial applications increases continuously, high frequencies of infection associated with the use of these materials are found. The pathogenesis of these biomaterial-associated infections is poorly understood. A predominant role is attributed to the
initial bacterial adherence as the first step in BAI, although alterations in host defense mechanisms in the vicinity of an implanted biomaterial have been frequently suggested. Therefore, the aim of this thesis is to obtain insight into the role of the host response against biomaterials in the pathogenesis of BAI. Especially the role of the various cytokines involved is studied. Insight in the role of cytokines may lead to immunomodulating strategies to prevent and treat BAI.

The second chapter of this thesis discusses the antibacterial activity over time of two clinically used hydrocephalus shunts soaked in solutions of various antibiotics and antibiotic combinations. The unexpected incompatibility reaction around a novel surface-modified hydrocephalus shunt, the enhanced inflammatory tissue response in the presence of (non-) viable bacteria and bacterial cell wall components are described in chapter 3. The possible implications for biocompatibility-testing protocols are also discussed. Chapter 4 describes the over time cytokine profiles around the two biomaterials which were discussed in chapter 2 and 3. It was shown that bacteria as well as their components are able to modulate the host defense, making the tissue in the vicinity of an implanted biomaterial more prone to infection. In chapter 5 intracellular survival of *S. epidermidis* in macrophages was found, which may be a pivotal process in the pathogenesis of BAI. The results in chapter 6 and 7 show that through immunomodulation, BAI in mice can be prevented. Finally, in chapter 8, the work of the preceding chapters and that of others is reviewed and discussed.

REFERENCES


