physicochemical treatment in order to firmly anchor the cells to the probe may alter the cell surface properties, leading to false results.

Therefore, since the molecular and physical interactions that govern bacterial adhesion to biomaterials have not been understood in detail all the available preventive measures that decrease the rate of bacterial infections should be taken. These preventive strategies could be: experienced therapy teams to insert and maintain indwelling devices, maximum sterile barriers, such as sterile gloves, masks, gowns, caps, large drapes and careful handwashing. Use of these precautions has been linked to a four-fold decrease in the rate of bacteriaemia. Moreover, cutaneous antimicrobials and antiseptics, ionic silver cuffs, combination of antibiotics with heparin, antiseptic hubs and antimicrobial coatings of biomaterial surfaces have shown good results against microbial colonization and produced bacteriaemia, especially when the right antibiotics are chosen against each type of bacteria.

Concluding Remarks

A large amount of research work has been done and great achievements have been made in understanding the mechanisms of bacterial adhesion and prosthetic infection. However, since bacterial adhesion is a very complicated process affected by many factors, such as bacterial-material properties, environment, and, furthermore the experimental evaluation of the relative contributions of these factors is extremely difficult, more investigations are still needed to advance our understanding of the mechanisms of bacterial adhesion and prosthetic infection, and to attain appropriate methods to prevent them from happening. Most of the studies so far have utilized: different materials (glass, metals, polymers), different bacterial strains-species and concentrations, different experimental procedures (static, flow, AFM, time, environment). Polymer systems used in biointeraction studies do not allow for systematic-controlled variations in material surface properties. Surface chemical modification often leads to surface heterogeneity and increased roughness, trace impurities, in many polymers used, result in uncertainties. Therefore, a rigorous study of the effects of surface chemistry/topography on bacterial adhesion and protein adsorption requires a model system that allows precise control of the type and the configuration of functional groups at the substratum surface under dynamic conditions. All the techniques mentioned here, although they cannot be used routinely in the clinical field because of the cost, the complexity of the set up and the time they need in order to give results, they are necessary in the research field of quantitative definition of bacteria-material interactions.

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Discussion with Reviewers

L. Harris: In the section entitled "Serum or Tissue Proteins", the author mentions vWF factor. Can the author comment in more detail on the fact *S. aureus* in particular has an adhesin that recognises vWF factor?

Authors: *S. aureus* has the ability to interact with and bind to several different plasma and extracellular matrix proteins such as fibrinogen, collagen, vitronectin and laminin, via protein adhesins of MSCRAMM (microbial surface components recognizing adhesive matrix molecules) family, which, in most cases are covalently anchored to the cell wall peptidoglycan. The first molecularly characterized MSCRAMMs of *S. aureus* are fibronectin-binding protein A (FnBPA), a collagen-binding protein (Can) and a fibrinogen-binding protein, clumbing factor A (ClfA) (Foster and Hook, 1998). In addition to blood and matrix proteins, *S. aureus* interacts with platelets (Fallgren *et al.,* 2002). Among the factors released by platelets is von Willebrand factor (vWf), a large multifunctional glycoprotein characterized by high molecular weight multimers. Concerning bacterial proteins binding to vWf, there are only a few reports. The binding of *S. aureus* to vWf was first reported in 1997 (Hermann *et al.,* 1997) and later it was shown that protein A mediates the adherence of *S. aureus* to vWf (Hartleib *et al.,* 2000). In addition, a secreted *S. aureus* protein (vWbp) that binds vWf has recently been identified (Bjerketorp *et al.,* 2002). Therefore vWf binds to and promotes the surface adhesion of *S. aureus.*

L. Harris: Have the flow chambers been used to evaluate the influence of bacterial adhesins and their effect on adhesion to different biomaterials?

Authors: Dickinson *et al.* (1995, 1997) used a radial flow chamber in order to evaluate receptor-mediated bacterial adhesion under the influence of fluid shear and they showed that bacteria-surface interactions are influenced by the presence of proteins on the substratum surface (Figs. 14 and 15). Mohamed *et al.* (2000) used a parallel plate flow chamber and they showed that in the case of higher number of receptors/cell, *S. aureus* adhesion to collagen coated coverslips increases between shear rates 50-300 s^{-1} and then decreases for shear rates higher than 500 s^{-1} (Fig. 5). However, it has not been shown directly whether and how functional properties of bacterial adhesins are directly modulated by shear. To our knowledge, a directly related study of the influence of bacterial adhesins on adhesion, under the influence of flow conditions, is that

of Thomas *et al*. (2002) which showed that *E. coli* (expressing lectin-like adhesin FimH) attachment to erythrocytes switched from loose to firm upon a 10-fold increase in shear stress, due to increased bond formation (kinetic effects) and adhesin's ability to act as a force sensor. However, direct adhesin-biomaterial surface evaluation using flow chambers has not been reported yet.

J Douglas: What progress has been made in preventing bacterial adhesion to biomaterials either by changing biomaterial surface chemistry or by incorporating antimicrobial agents?

Authors: Coatings and surface treatments have been extensively studied (see Material Surface Characteristics) and a particular interest was devoted to silver as it combines antimicrobial activity and low human toxicity. Both physicochemical methods and surface engineering techniques (surface implantation) have been used in order to produce new, antibacterial surface properties. *In vitro* experimental results have shown that increased material hydrophilicity, antimicrobial coatings of biomaterial surfaces and especially ionic silver, and combination of antibiotics with heparin have good results against microbial colonization and bacteriaemia. Clinical trials have shown that silver coated hemodialysis catheter offered a 42%, 65% and 66% reduction in bacterial positive cultures from skin, blood and catheter tip respectively (Bambauer *et al.,* 1998).

J Douglas: What are the problems associated with such strategies?

Authors: The main problems associated with changing biomaterial surface chemistry (surface energy) and incorporating antimicrobial agents are first of all the probable heterogeneity of the produced surface, especially when we have to deal with rough surfaces, and the probable dissociation of the thin film antimicrobial coating, especially under high shear stresses. Moreover, surface treatments are not effective for long-term applications due to surface fouling and only surface bound antimicrobial technology offers advantages for long term applications. But even then, antimicrobial coatings should be checked for their bactericidal effects since immobilized ones are not as effective as soluble ones (James and Jayakrishnan, 2003) and atomic silver has not antibacterial effects in comparison to ionic silver (Davenas *et al.,* 2002).

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