

# Preface

Modifying medical devices with antimicrobial coatings and biomaterials is one of the most effective approaches to prevent device-associated infections. This book explores current and emerging antimicrobial technologies, biofilm-related evaluation techniques, and regulatory challenges, with particular emphasis on the coatings and modifications on medical devices. An overview of antimicrobial technologies on critical care implants followed by the public health and the regulatory science challenges associated with these devices are discussed. Progress in characterization and evaluation of infection on medical devices, such as diagnostic assays evaluating cell adhesion and biofilm formation including molecular-based approaches, is introduced. This book covers coatings and modifications incorporating various antimicrobial agents, including traditional antibiotics and antiseptic agents, as well as alternative agents through “anti-antibiotic” approaches. Delivering antimicrobial agents with porous materials is introduced afterwards as an example of many efforts to improve loading and delivering efficacy. Antifouling surfaces with characteristics to reduce bacteria colonization and physical approaches such as light-induced antimicrobial modifications are reviewed.

The surface of medical implants is considered as a critical battleground of bacterial colonization, biofilm formation, and immune reactions. It is also an intensive target for applying antimicrobial coatings and modifications. Since catheter-related bloodstream infection (CRBSI), ventilator-associated pneumonia (VAP), and catheter-associated urinary tract infections (CAUTIs) comprise the most frequent and expensive device-associated infections, vascular catheters, endotracheal tubes, or urinary catheters usually are the ultimate test fields for many promising antimicrobial techniques to achieve in vivo and clinical results. The regulatory landscape provides clear pathways to market acceptance of several types of antimicrobial devices, with examples of devices on the market described in this book. These include medical devices with eluting antimicrobial compounds such as chlorhexidine and triclosan, traditional antibiotics including rifampin and minocycline, or combinations (e.g., chlorhexidine/silver sulfadiazine). Standardized test methods and regulatory designations for appropriate claims are well understood for these types of products. What is less clear and still under investigation is how the

understanding of biofilms and their role in infection will impact claims and testing for more novel devices still under development. For example, claims language such as “reduction in biofilm” or “prevent microbial colonization” are less well defined and indeed, there exist few standardized, reproducible test methods to demonstrate such claims. This book provides a concise review of those regulatory challenges facing device manufacturers today.

Key to designing these next-generation devices are a clear understanding of the mechanisms of attachment, proliferation, and dissemination of microorganisms at the device interface. Several authors review the currently known dogma of biofilm development as well as many traditional and novel techniques to characterize the interaction of microbes with device surfaces. Methods to quantify cell adhesion and proliferation at interfaces, including confocal scanning microscopy, atomic force microscopy, Raman spectroscopy, surface plasmon resonance imaging, and quartz crystal microbalance, are discussed. Several commercially available biofilm reactor systems are presented and their utility for specific applications described. Molecular techniques, such as ribosomal 16S RNA sequencing and 16S rRNA fluorescent *in situ* hybridization (FISH), denaturing gradient gel electrophoresis, fluorescent activated flow cytometry (FACS), and amplification of DNA and RNA using polymerase chain reaction (PCR), are important tools used to identify microbial species, understand genetic regulation, and characterize microbial behaviors and colonization of device surfaces *in vitro* and *in vivo*. These techniques are not only critical in understanding how the device design affects performance, but such data may provide evidence for mechanisms of action, efficacy, and safety claims as these devices are brought to market.

Several approaches to generating antimicrobial devices are presented. Immersing medical implants in an antimicrobial solution or coating the device with antimicrobial agents is commonly used to control over infections. The achievement of local delivery of significant quantities of active agents, and release of the drug throughout the period of implantation, represents a strong point in favor of this approach. These include the use of antibacteriostatic agents, such as chlorhexidine, or antimicrobials such as rifampin. A concise review of currently marketed antimicrobial medical devices, such as vascular access or urological devices, are discussed in terms of clinical efficacy, if known, as well as advantages or disadvantages of their use. However, not all of the antimicrobial agents are compatible with the substrate with enough loads, or can be released in a desirable manner. One key limitation of antimicrobial technologies marketed today is the duration of effect, as many devices are eluting by design and therefore have limited life once the agent is exhausted. Delivering agents as a response to infection, and covalently binding antimicrobial agents have been applied on medical device surfaces as one strategy to mitigate this issue. Various porous additives or biodegradable polymers have been developed to achieve controlled and prolonged release. Porous materials are discussed in a chapter as an example of achieving effective antimicrobial delivering. Additionally, novel approaches that do not rely on an eluting agent or an antimicrobial killing effect, including stimulating a targeted host immune response, either by modification of device surfaces to promote phagocytosis or the use of artificial opsonins, and

interference of microbial metabolism such as iron utilization, are discussed. An understanding of the molecular components and regulation of microbial biofilms has generated a number of antiadhesive molecules and disruptors, such as quorum sensing signal interference or amyloid inhibitors, to prevent microbial proliferation and biofilms on surfaces. Together, these topics cover a wide array of traditional and nontraditional pathways with the same goal in mind: prevention or mitigation of device-associated infections.

This book also addresses the growing threat of antibiotic resistance by presenting antifouling and physical approaches. Antifouling surfaces reduce bacterial attachment through unique surface characteristics. With no antimicrobial agents leaching from surfaces, antifouling surfaces achieve antimicrobial performance without introducing toxicity and drug resistance. In addition, some antifouling polymers also significantly reduce protein adsorption to a level that can inhibit thrombus formation or other device-related complications. Physical approaches such as light, acoustic energies, and mechanical stress are thought to be effective without concerns of side effects from active antimicrobial agents. Advances in light technology highlight the potential for light inhibition of biofilm formation in medical devices, which may be combined with photosensitizers, photocatalysts, or photocleavables. However, for these technologies, concerns such as reduced *in vivo* efficacy and safety make obstacles to get antimicrobial claims these devices. Clinical relevance between bacterial resistance and infection reduction still needs to be established.

Currently, more than a million infections are acquired in US hospitals each year including more than half associated with medical implants. The situation is being challenged by expanding application of invasive devices, increasing aging population, and diminishing effectiveness of antibiotics. Solutions may largely count on development of better and safer medical devices, together with improvement of diagnostic methods, regulatory science, and hospital operations. Hopefully, this book can provide the readers an overview of the exciting area from a few important perspectives, and inspire further research and stewardship that battle the device-associated infections.

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