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Beyond conventional antibiotics — New directions for combination products to combat biofilm☆

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ABSTRACT

Medical device related infections are a significant and growing source of morbidity and mortality. Biofilm formation is a common feature of medical device infections that is not effectively prevented or treated by systemic antibiotics. Antimicrobial medical device combination products provide a pathway for local delivery of antimicrobial therapeutics with the ability to achieve high local concentrations while minimizing systemic side effects. In this review, we present considerations for the design of local antimicrobial delivery systems, which can be facilitated by modeling local pharmacokinetics in the context of the target device application. In addition to the need for local delivery, a critical barrier to progress in the field is the need to incorporate agents effective against biofilm. This article aims to review key properties of antimicrobial peptides that make them well suited to meet the demands of the next generation of antimicrobial medical devices, including broad spectrum activity, rapid and biocidal mechanisms of action, and efficacy against biofilm.

Contents

Abbreviations: AMP, antimicrobial peptide; $\mathbf{C_{tox}}$, maximal tolerated concentration; CVC, central venous catheters; EPS, extracellular polymeric substance; hRBC, human red blood cell; MBC, minimum biocidal concentration; MBEC, minimum biofilm eradication concentration; MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *Staphylococcus aureus*; PD, pharmacodynamics; PK, pharmacokinetics; PLA, polylactic acid; PMMA, polymethylmethacrylate; t_E, half-time of elimination; t_R, half-time of release; ZOI, zone of inhibition.

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1. Introduction

Antimicrobial medical device combination products for local infection prevention is a rapidly growing area of research and product development that holds great promise for improving patient outcomes [1]. Device associated infections (26%) and surgical site infections (22%) together account for nearly half of all US health care-associated infections [2]. The rate of these infections as well as the involvement of multidrug resistant pathogens continues to increase with overall infection rates as high as 25–50% for heart assist devices, 10–30% for bladder catheters, 5–10% for fracture fixation devices and dental implants, 5–8% for central venous catheters (CVC), and 15–20% for patients receiving mechanical ventilation [3–6]. Most implant related infections are resistant to systemic antibiotics and will continue until the implant is removed [7]. In many cases, device removal is associated with substantial morbidity and costs. In addition, removal may not be an option for patients that are dependent on the device for function or that cannot withstand an additional surgery. Infection is also a major contributor to impaired healing in chronic wounds [8–12] and the most expensive complication in acute surgical, trauma, and burn wounds [11].

Perioperative systemic administration of antibiotics is standard practice for preventing infection associated with implanted devices [13–15]. Given the high number of device related infections, perioperative antibiotics are clearly not sufficient and once an infection has developed, systemic antibiotic therapy is largely ineffective. Similarly, there is little evidence to support the use of systemic antibiotics to improve healing of infected chronic wounds [16,17]. The poor efficacy of systemic antibiotics in these contexts is due to a number of factors including 1) difficulty of achieving effective antibiotic concentrations at the sight of infection [13,18] 2) high propensity of pathogens to form biofilms on the device surface, peri-device space, or wound bed [7,19] and 3) continuous development of microbial resistance and loss of susceptibility to existing antibiotics [20,21]. Successful approaches to prevent device and wound infections remains a pressing clinical challenge.

Local administration of antimicrobials provides an opportunity to overcome some of these challenges. Benefits of local delivery include greater control over the antimicrobial delivery rate, the ability to co-deliver one or more agents, and potential for high local drug concentrations with significantly lower overall systemic exposure [13,18,22]. Agents that may be considered for co-administration include those that work synergistically with the primary antimicrobial or agents that improve overall device patency by preventing fouling or promoting healing and tissue integration. Complimentary agents may include for example, biofilm inhibitors and disruptors [23], anti-adhesive materials to reduce protein deposition and microbial attachment [24,25], anti-inflammatory agents, growth factors and osseointegration promoters [26]. For blood contacting devices, most notably intravascular catheters, there is an association between thrombus formation and infection [27,28]. For these devices, there is clear need for approaches that provide protection against not only bacteria but also fouling.

Antibiotic resistance is increasing at an alarming rate resulting in many infections that are extremely difficult to treat or untreatable [29,30]. It is widely recognized that antimicrobial resistance is exacerbated by the fact that the majority of chronic human infectious diseases, including medical device and wound related infections, are associated with biofilm [31–35]. Microbial biofilms comprise polymicrobial communities enclosed within a self-produced extracellular polymeric substance (EPS) adherent to biological tissue and/or synthetic surfaces of medical devices [36,37]. The susceptibility of bacteria to conventional antibiotics is typically significantly lower in biofilms relative to their planktonic counterparts [38], requiring up to three orders of magnitude higher antibiotic concentrations and longer times to eradicate bacteria in biofilm [39–42]. There is a need to develop antimicrobial approaches for medical devices that rely on alternative antimicrobial agents that are effective against biofilm. This is important to not only ensure efficacy but also to help curb resistance development and preserve the potency of front line clinical antibiotics.

In this review, we present considerations for development of antimicrobial medical devices with a focus on requirements for local drug delivery, strategies for incorporating antimicrobials into devices, and promising approaches for combating device related infections that go beyond the use of conventional antibiotics.

2. Requirements for local antimicrobial delivery systems and combination products

Requirements for local anti-microbial delivery systems depend on the type of device, conditions of use, duration of implantation, and potential pathways and pathogenesis of infection [43,44]. Design requirements for the duration and strength of the antimicrobial effect should be dictated by the potential routes and duration of microbial invasion for the device's intended use. Perioperative exposure is widely recognized as the most common route for microbe introduction and device related infections for fully implantable devices. Pathogens may be introduced at the time of surgery from the patient's skin and clinical environment, including the hands of clinical staff [7,45–47]. Although infection due to haematogenous seeding is possible, the rate of occurrence is substantially lower for most devices [48–50]. Therefore, the duration of high risk for microbial invasion and device colonization is thought to be limited. Local delivery systems that provide antimicrobial protection of both the device surface and adjacent tissues for a time period sufficient for healing and recovery of host defenses are considered adequate for many such applications [13,19,22,34]. In the case of prosthetic joint devices, however, infections related to haematogenous seeding and late infections can be a significant problem and may justify longer term delivery approaches [51]. A different situation exists with access devices, percutaneous and permucosal implants that breach skin and epithelial barriers thus allowing for continuous microbial invasion during the entire period of device use [43]. For example, continuous invasion of mechanical ventilators and colonization of endotracheal tubes occurs via inhalation, aspiration from the oropharynx, reflux from the stomach and other routes [52]. In the case of intravascular catheters, microbial invasion pathways include the skin at the port of entry, catheter hubs, and infusate [47]. Devices with the risk of continuous microbial invasion require effective protection over the entire period of intended use.

Biofilm is a defining feature of foreign body related infections. In most cases, once a biofilm is established on the surface of a device, it is untreatable and the only viable option is device removal [34,43,49,53]. Therefore, strategies for development of antimicrobial medical devices should focus on preventing attachment of viable bacteria and biofilm formation following implantation. Depending on the specific application, local antimicrobial drug delivery systems may be applied to the site of device placement as a separate dosage form segregated from the device or it might be integrated with the device for example, by impregnation, admixing during device fabrication, or as a coating on the device surface [13,22]. One example of a segregated implantable antimicrobial delivery system is Collatamp® (EUSA Pharma), a gentamicin loaded, lyophilized resorbable collagen sponge. This product has been shown to reduce postoperative infection rates in patients that have undergone groin hernia repair by insertion of a prosthesis [54] as well as surgical patients with dirty-infected wounds [55]. Short term CVCs impregnated or coated with antiseptics and antibiotics are examples of integrated antimicrobial drug/device combinations that have demonstrated effectiveness in reducing catheter colonization and catheter related blood stream infections [56,57].

Although segregated antimicrobial implantable dosage forms appear feasible for some applications, the majority of devices will require integration of the antimicrobial delivery system either in bulk or on the surface of the device to cover spatial and overall performance requirements. This is a challenging endeavor that dictates balancing