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Mini-review: Antimicrobial central venous catheters – recent advances and strategies

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Central venous catheters (CVCs) nowadays constitute critical devices used in medical care, namely in intensive care units. However, CVCs also represent one of the indwelling medical devices with enhanced risk of nosocomial device-related infection. Catheter-related infections (CRIs) are a major cause of patient morbidity and mortality, often justifying premature catheter removal and an increase in costs and use of resources. Adhesion and subsequent biofilm formation on the surfaces of indwelling catheters is elemental to the onset of pathogenesis. Seeking the prevention of CVC colonisation and CRI, a variety of approaches have been studied, tested and, in some cases, already applied in clinical practice. This review looks at the current preventive strategies often used to decrease the risk of CRIs due to colonization and biofilm formation on catheter surfaces, as well as at the more recent approaches under investigation.

Keywords: antimicrobial; bacterial adhesion; biofilm; catheter-related infection; central venous catheter; nosocomial infection

Introduction

Bacterial adhesion to surfaces of medical devices is considered to be the basic pathogenic mechanism of implant infections. The major medical implants that can be compromised by infections are intravascular; cardiovascular; neurosurgical; orthopaedic; ophthalmological or dental (von Eiff et al. 2005). Catheters, such as central line, intravenous or urinary catheters, constitute potential surfaces for biofilm formation (Davey and O'Toole 2000).

The main complication with the use of catheters is the development of an infection which can be either localised, within the bloodstream or distal (Raad and Hanna 2002; Casey et al. 2008). Catheter-related bloodstream infection (CRBSI) is a leading cause of nosocomial infection in the intensive care unit (ICU), increasing the duration of hospitalization, additional medical costs and with significant morbidity (McGee and Gould 2003; Frasca et al. 2010).

Complete and adequate barrier precautions during insertion of the CVC (sterile gloves, long-sleeved sterile gown, mask, cap and large sterile sheet drape) can significantly decrease the frequency of CRBSI in comparison with standard precautions (sterile gloves and small drape) (O'Grady et al. 2002). However, these precautions have not been sufficient.

After insertion, the surface of the catheter is rapidly conditioned by a film of extracellular proteins such as

fibrin, fibrinogen, fibronectin, collagen, elastin, laminin, vitronectin, thrombospondin, or Willibrand's factor that promote microbial adhesion and consequent biofilm formation (Casey et al. 2008). Indeed, only a few days after insertion, microorganisms can start to colonize indwelling catheters forming biofilms, ie sessile communities of microorganisms irreversibly attached to surfaces and enclosed in a matrix of exopolymeric products (Sekhar et al. 2010). These biofilms can result in CVC-related infections (CVC-RIs) and the leading microorganisms often responsible for these infections include coagulase-negative staphylococci, namely *Staphylococcus epidermidis*, but also *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Enterococcus faecalis* (Costerton et al. 1999). Moreover, approximately 80% of patients with candidemia possess a CVC, which highlights the importance of yeasts from the genus *Candida* as common causes of CVC-RIs (Ben-Ami et al. 2008). These causative microorganisms should be seriously considered in determining preventative strategies.

The process of CVC insertion disrupts the integrity of the skin making infection either with bacteria or fungi possible, highlighting the need for the development of antimicrobial catheters that should be active on both the internal and external surfaces.

Moreover, pathogens in biofilm form become more tolerant to conventional antibiotics and

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opsonophagocytosis (Stewart and Costerton 2001). The treatment of a CVC-RI is usually performed using conventional antimicrobial agents which are based on standardized antimicrobial susceptibility test results, and are often revealed to be unsuccessful, requiring the removal of the CVC (Curtin et al. 2003). The problem related to these standardized antimicrobial Susceptibility tests is that they are usually performed with planktonic cells, whilst biofilm cells are much less susceptible to killing by antimicrobial agents (Nadell et al. 2009).

Strategies for prevention of CVC-RI

In order to combat CVC-RI and all the associated costs, a number of new strategies and approaches have been developed. This article provides an overview not only of the current, but also the latest new, approaches in the prevention of CVC-RI.

Removal of the CVC, and thus of the associated biofilm, has sometimes been used as the last resource treatment of serious CRBSI. However, this aggressive treatment in a critically ill patient, with a long tunnelled CVC, for example, has very significant practical problems and costs (Curtin et al. 2003). To avoid such extreme therapy there has been a major focus on the search for and development of the 'ideal catheter'.

The catheter material is critical in the prevention of CRI. It should be biocompatible, biostable, flexible, resistant, chemically neutral, not affected by administered drugs, deformable, and resistant to sterilization (Frasca et al. 2010).

Catheters coated with materials having antimicrobial and antiseptic properties have been proposed as a way to provide additional protection, since they decrease microorganism adhesion and biofilm formation, and further reduce risk of infection (Camargo et al. 2009). The use of such catheters may potentially decrease hospital costs, despite the additional acquisition cost of the antimicrobial/antiseptic coated catheter (Halton et al. 2009). Besides coated catheters, other strategies have been applied, such as antimicrobial locks and catheter surface modification, and other approaches are currently being investigated, for example new drug delivery systems, phage therapy, and antimicrobial peptides.

Antimicrobial locks

Antimicrobial lock therapy (ALT) is generally considered when a case of CRBSI is classified as representing a low to moderate risk of a poor outcome (Raad and Hanna 2002). Given that ALT is a therapy applied on the CVC *in situ*, it can be of special interest

in the attempt to preserve long-term tunnelled catheters (Krishnasami et al. 2002). With this therapy, a high concentration of antimicrobial agent is instilled into the lumen of the infected CVC for long periods of time, in order to try to overcome the relative antimicrobial resistance of the microbial biofilm (Berrington and Gould 2001). Generally, 2 to 4 ml of antimicrobial solution, at a concentration 100- to 1000-fold higher than the minimal inhibitory concentration or its usual target systemic concentration, are introduced into the lumen of the infected CVC. The solution is then allowed to settle (lock) for a period of time while the catheter is not in use to eradicate the microorganisms embedded in the biofilm formed on its inner side (Shah et al. 2002).

Even though vancomycin and heparin have frequently been used as ALT, for the treatment of catheter-related staphylococcal bloodstream infections, clinical studies have reported the failure of this combination (Bailey et al. 2002; Guedon et al. 2002). On the other hand, Raad et al. (2003) demonstrated, in a rabbit model and in hemodialysis patients, that a combination of minocycline and EDTA was synergistically active in eliminating bacterial and fungal biofilms. Also Raad et al. (2008b) suggested the addition of chelators such as EDTA and citrate to antimicrobial lock solutions as a method of providing a better alternative to heparin lock solution in the prevention and treatment of CRBSIs. This is because these high-affinity metal-binding chelators have the capacity of inhibiting microbial growth by disrupting surface adherence and preventing biofilm production in the inner lumen of the catheter. Bookstaver et al. (2009) evaluated *in vitro* the efficacy of novel antibiotic-anticoagulant lock solutions and according to their results, gentamicin, tigecycline, and daptomycin in combination with anticoagulants demonstrated powerful activity against the common pathogens responsible for CRBSIs, and should be considered for clinical trials. Other authors (Steczko et al. 2009) tested *in vitro* a lock solution containing citrate/methylene blue/parabens, against Gram-positive and Gram-negative organisms and fungi and the results revealed a synergistic effect with strong antimicrobial properties with respect to both planktonic and sessile microorganisms.

Concerning CRI caused by *Candida* spp., the current recommendation is the removal and replacement of the infected device (Mermel et al. 2009), which implies high costs and, in some cases, elevated risks for patients. Therefore, as an alternative, the ALT has been recommended for the prevention and treatment of CRI in specific situations by the Infectious Diseases Society of America and the Centers for Disease Control and Prevention (Mermel et al. 2009).

In the study of Cateau et al. (2008) it was demonstrated, through *in vitro* models, that the echinocandins caspofungin and micafungin reduce the metabolic activity of *Candida albicans* in biofilm. Data from animal studies also indicate that the use of caspofungin line locks reduces the spread of infection in mice with central venous catheters infected with *C. albicans* biofilms (Lazzell et al. 2009). The study of Ko et al. (2010) investigated the *in vitro* activity of ALT against biofilms formed by *C. albicans*, *Candida glabrata* and *Candida tropicalis*, using five antifungal agents (caspofungin, amphotericin B, itraconazole, fluconazole, and voriconazole). The results demonstrated that fluconazole, itraconazole, and caspofungin were most effective for *C. albicans*, *C. glabrata*, and *C. tropicalis* biofilms, respectively, highlighting that azoles may be valuable ALT agents in the treatment of catheter-related candidemia.

Nevertheless, a serious problem with the ALT is the risk of development of resistance, which is one of the reasons why this therapy continues to raise many questions among clinicians. Newer treatments, incorporating agents that are not classified as antimicrobial agents, appear to effectively eradicate biofilms in *in vitro* models and should be evaluated in studies with animals and patients (Donlan 2008).

Surface-modified polymeric catheters

Surface modification of biomedical devices, such as catheters, generally requires a complete modification of the surface, mostly with hydrophilic polymeric surface coatings, in order to achieve a non-biofilm forming surface, (ie a surface where protein adsorption and subsequent microbial adhesion are minimized) (Knetsch and Koole 2011). Despite the large number of research studies relating to surface modification of medical devices, not many of these studies pass to the next step, viz. clinical tests. Nevertheless, the hydrophilic polyvinylpyrrolidone-coated polyurethane catheter (known as Hydrocath[®]) developed by Tebbs et al. (1994) is an example of surface modified catheters clinically in current use. Catheters with a surface impregnated or coated with antimicrobial agents have been employed as a viable way of preventing CRBSIs in the ICU for two decades (Halton et al. 2009). Catheters impregnated with chlorhexidine and silver sulfadiazine or with minocycline and rifampicin are the best studied as well as the most commercialized and frequently used antimicrobial-impregnated catheters (Veenstra et al. 1999; McGee and Gould 2003). Metals with antimicrobial activity have also been exploited, specifically silver or silver nanoparticles, due to its good antimicrobial action and low toxicity (Knetsch and Koole 2011).

Chlorhexidine and silver sulfadiazine impregnated catheters

Catheters coated with chlorhexidine and silver sulfadiazine (C-SS) have been clinically shown to reduce the risk of colonization two-fold and the risk of CRBSI by at least four-fold, in comparison with uncoated catheters (Maki et al. 1997). The advantage of the use of both compounds together is that they act synergistically. Chlorhexidine disrupts the cytoplasmic membrane of the bacterial cell, thus increasing the uptake of the silver salts (Elliott 2007). The C-SS complex is highly active against Gram-positive bacteria, while demonstrating less activity against Gram-negatives such as coliforms. However, many of the trials have been carried out on first-generation C-SS catheters, coated only on the external surface. This has two main limitations, viz. (1) no protection was conferred with regard to microbial invasion of the internal surface of the catheter from contaminated hubs, since only the external surface of the catheter was coated, and (2) the catheters have reduced antimicrobial activity and poor efficacy with long term use (>2 weeks) (Raad and Hanna 2002). Therefore, these catheters have been shown to be particularly effective in reducing the risk for CRBSI associated with short-term CVCs (Veenstra et al. 1999) but failed to reduce the risk for CRBSI in situations of long-term catheterization (Logghe et al. 1997). More recently, second-generation C-SS catheters, which are also coated internally with chlorhexidine, have been produced, but they are still poorly studied, with a limited number of randomized trials made. However, these second-generation catheters are associated with a significant reduction in colonisation and CRBSI (Rupp et al. 2005). Despite the fact that chlorhexidine resistance has not yet been reported to be associated with the use of these catheters some adverse reactions to chlorhexidine have been described (Trautner and Darouiche 2004).

Minocycline-rifampicin impregnated catheters

Along with antiseptics, antibiotics have also been incorporated into CVCs. The minocycline-rifampicin CVC is the most studied device, with broad spectrum inhibitory activity. Furthermore, this coating has been studied both *in vitro* and *in vivo* against Gram-negative and Gram-positive bacteria, and also against *C. albicans*, showing that it prevents the adherence and biofilm colonization by the leading organisms that cause CRBSI, including those that are resistant to multiple drugs (Elliott 2007; Raad et al. 2008a). Prospective, randomized, multicentre clinical trials have demonstrated that minocycline-rifampicin impregnated CVCs significantly prevent bloodstream infections when compared to non-impregnated

catheters, decreasing the duration of stay and mortality in critically ill and haemodialysis patients (Darouiche et al. 1999; Marik et al. 1999). Nevertheless, the evaluation of their efficacy against second-generation C-SS catheters still requires more clinical investigation (Elliott 2007). In addition, there are concerns related to potential antibiotic resistance with regard to rifampicin (Darouiche et al. 1999; Raad and Hanna 2002), which should limit the widespread use of antibiotic-coated catheters.

Metals-coated polymeric catheter materials – silver nanoparticles

The antimicrobial activity of silver, copper and other metal ions is well known and, of all the elements, silver has been described as having the highest level of toxicity for microorganisms and the lowest toxicity for animal cells (Guggenbichler et al. 1999). This metal has a broad spectrum antimicrobial activity against both Gram-positive and Gram-negative bacteria (Elliott 2007). It inhibits replication by binding to the microbial DNA and it also switches off important enzymes, leading to microbial death (Chaiyakunapruk et al. 2002).

Silver-containing nanomaterials are now considered to be one of the most promising strategies to combat bacterial infections related to indwelling medical devices, such as intravenous catheters. Nanoscale materials have recently appeared as new antimicrobial agents due to their high surface area to volume ratio and unique chemical and physical properties (Rai et al. 2009). Nanomaterials of different kinds, such as copper, zinc, titanium, magnesium, gold, alginate and silver have been developed in recent years. Nevertheless, silver nanoparticles (NPs) have demonstrated more effectiveness with good antimicrobial activity against bacteria, viruses and eukaryotic microorganisms (Gong et al. 2007). Furthermore, silver NPs have not been shown to cause bacterial resistance, which is presumably due to the fact that, unlike antibiotics, silver NPs do not exert their antibacterial effects only at a particular site but at several sites such as the bacterial wall, proteosynthesis and DNA (Shrivastava et al. 2007). The considerable surface-to-volume ratio of NPs enables a constant local supply of Ag^+ ions to be maintained at the coating-tissue interface, allows an improved and longer contact with microorganisms (Rai et al. 2009), and also protects the outer and inner surfaces of devices (Darouiche et al. 1999). Although some studies have raised some concerns regarding the biosafety of silver NPs (Johnston et al. 2010), they are emerging as a next-generation of antibacterial agents and there are currently reports demonstrating the efficacy of silver

NPs in reducing or preventing biofilm formation on catheter-materials both *in vitro* (Samuel and Guggenbichler 2004) and in animal models (Roe et al. 2008; Hsu et al. 2010). Studies with patients are still few in number.

Novel drug delivery carrier systems

The efficacy of the strategies mentioned above to prevent biofilm formation on catheters, by impregnating or coating the surface of the device, is generally limited by the feeble drug adsorption to the surface, as well as by the fast and not-controlled elution of the drug in the first hours subsequent to the insertion. Drug delivery has been a subject of intense study over recent years. The objective is to accomplish sustained (or slow) and/or controlled drug release and therefore to improve efficacy, safety, and/or patient comfort (Varshosaz 2007).

These new drug delivery carriers can be considered as a way of preventing colonization and biofilm formation, and the most exploited for elimination of microbial biofilms on biomedical devices are lipid- and polymer-based carrier systems.

Liposomes as drug carriers

Liposomes are appealing drug carrier systems, specifically against colonizing microorganisms, due to factors such as compatibility with biological components, the wide range and extent of drugs that they can carry, the protection provided by the encapsulation of the drug in the biological milieu, which decreases toxicity, and also transportation, for long periods of time, of the drug to target specific sites (Tamilvanan et al. 2008). There have been several studies on the interaction between liposomes and bacterial biofilms. Halwani et al. (2008) reported a new successful strategy for the use of liposomes as drug carriers, by delivering two agents at the same time to prevent *P. aeruginosa* biofilm formation and resistance *in vitro*. Finelli et al. (2002) evaluated the efficacy of a ciprofloxacin delivery system consisting of a liposomal hydrogel that reduced bacterial adhesion to a silicone catheter in a rat model of persistent *P. aeruginosa* peritonitis, opening perspectives for the development of new antimicrobial peritoneal dialysis catheters or other types of catheters. Buckler et al. (2008) also reported that liposomal antifungal lock therapy can be considered as a possible alternative to catheter removal in pediatric patients. Thus, the use of liposomes as drug carriers seems to be advantageous over other therapies used to prevent biofilm formation on biomedical surfaces because liposomes can target matrix or biofilm bacteria by specific attachment,

allowing the drug to be released in the vicinity of the microorganisms. This would significantly increase the local drug concentration and simplify targeted delivery. Nevertheless, there are still problems associated with specific liposome binding to the bacterial matrix surface that demonstrate the need for more studies to be carried out.

Polymer carriers

In recent years, noticeable attention has been paid to the use of biocompatible or biodegradable polymers of both natural and synthetic origin, as controlled drug carriers of antimicrobial agents to the infections associated with implants. Among these products, polymeric microspheres, polymer micelles, and hydrogel-type materials have been shown to be effective nanocarriers in enhancing drug targeting specificity, lowering systemic drug toxicity, improving treatment absorption rates, and providing protection for pharmaceuticals against biochemical degradation (Şanlı et al. 2008). These polymer drug delivery systems are based on 'nano-carriers' which are formed by mixing polymeric chemical compounds with drugs, forming complex and large molecules, which 'carry' the drug across physiological barriers. Poly(rhylene-glycol)-poly(alpha, beta-aspartic acid), carboxylates, and heterobifunctional polyethylene glycol, are examples of such polymeric compounds (Varshosaz 2007).

Ruggeri et al. (2007) developed an antimicrobial polyurethane system containing two antibiotics, cefamandole nafate and rifampicin and, in order to increase the amount of the drug released, polyethyleneglycol was incorporated into the polymer bulk with antibiotics, and used as a pore forming agent at different molecular weights, giving promising results. More recently, Crisante et al. (2009) developed nanostructured polymer systems for antibiotic delivery using bovine serum albumin or polyallylamine as pore forming substances. Their results were corroborated by the work of Martinelli et al. (2011), which hypothesize that this system possesses suitable features for the manufacture of different types of antimicrobial medical devices, including intravascular catheters.

Phage therapy

Since bacteriophages were first recognized, early in the twentieth century, they have been the focus of significant attention and, considering the increasing apprehension regarding antimicrobial resistance in hospitals worldwide nowadays, there is renewed interest in phage therapy.

The use of phages to control biofilms and CRBSIs has advantages over conventional antimicrobial

agents, namely, because phages have very strong bactericidal activity and can replicate at the site of the infection, being available in abundance where they are most required (Azeredo and Sutherland 2008). According to Doolittle et al. (1996), progeny phage propagates radially throughout a biofilm, suggesting that a single dose of phage could treat a biofilm infection as progeny phage infects adjacent cells and degrades the biofilm matrix. In addition, it was demonstrated that some phages are able to produce enzymes (depolymerases) that hydrolyse and degrade the extracellular polymeric substance (EPS) matrix of a biofilm (Verma et al. 2010).

Curtin and Donlan (2006) demonstrated, using an *in vitro* model, that a phage active against *S. epidermidis* could be incorporated into a hydrogel coating on a catheter and significantly reduce biofilm formation on its surfaces. Recently, Fu et al. (2010) studied, *in vitro*, the effect of pre-treating hydrogel-coated catheters with *P. aeruginosa* phages on biofilm formation, and observed a significant reduction in the number of biofilm cells.

However, there are aspects which must be considered prior to the use of phage therapy in humans, such as the narrow host range of phage, bacterial resistance to phage, inactivation by the patient's immune system, impure phage preparations that could contain endotoxins, or phage-encoded virulence genes that can incorporate into the host bacterial genome (Donlan 2009). The use of an accurate selection of phage mixtures or engineered phages, the optimization of the material coating matrix, and validation using *in vitro* and animal model systems, can provide successful strategies to overcome these problems, as well as determine whether phage therapy will be clinically significant.

Antimicrobial peptides

Antimicrobial peptides (AMPs) are small cationic peptides, conserved components of the immune response, involved in the defence mechanisms of a wide range of organisms (Guaní-Guerra et al. 2010). Members of the AMP family are widely distributed in nature, more than 1500 AMPs having being reported from organisms such as bacteria, fungi, insects, plants or humans (Hancock 2001). Some classes of AMPs such as β -defensins, indolicidin, cecropin A, and magainins have demonstrated effectiveness in killing bacteria, fungi, parasites and even viruses (Hancock and Sahl 2006). Importantly, AMPs have also been found to be effective against superbugs that have developed resistance to antibiotics such as MRSA, and quinolone-resistant Enterobacteriaceae (Piper et al. 2009). AMPs have therefore

recently emerged as a class of antibiotics with therapeutic potential.

It is generally accepted that cationic AMPs interact by electrostatic forces with the negatively charged phospholipid headgroups on the bacterial membrane and cause disruption, either by permeabilizing them or translocating across the cytoplasmic membrane to attack cytoplasmic targets (Hilpert et al. 2009). Given that the killing mechanism of AMPs involves targeting the fundamental structures of bacteria such as the membrane, the emergence of resistant mutants is unlikely to occur due to the essential functions of the membrane in maintaining microbial homeostasis, metabolism and viability (Yeaman and Yount 2003).

Therefore, their broad activity spectrum, the relative selectivity towards their targets (microbial membranes), the rapid mechanism of action and, above all, the low frequency in selecting resistant strains, have attracted considerable interest to AMPs as a potential new class of antimicrobial agents (Batoni et al. 2011). Nevertheless, the work of Perron et al. (2006) has demonstrated, *in vitro*, the development of some level of resistance to AMPs.

The essential property of cationic peptides is their net positive charge at neutral pH due to the presence of multiple arginines and/or lysines in their sequences (Hancock 2001). Given that the surface of several synthetic materials used as biomaterials, such as silicone and polyesters, that are normally subjected to microbial colonization and biofilm formation, are negatively charged at pH 7, this property permits binding of cationic molecules, such as AMPs (Chen et al. 2005). Therefore, and taking into account that biofilm tolerance to antibiotics is generally due to the slow growth rate and low metabolic activity of bacteria, the use of AMPs to inhibit biofilm formation could be a promising strategy. Considering that the main mechanism of action of AMPs is their ability to permeabilize and/or to form pores within cytoplasmic membranes, this means that they also have a high potential to be effective on slow growing or even inactive bacteria (Batoni et al. 2011).

Bagheri et al. (2009) have detected reduced activity of AMPs upon tethering to solid supports, which can significantly compromise their effectiveness as biomedical coating materials. Despite this, the therapeutic potential of cationic antimicrobial peptides is already being explored with synthetic peptides demonstrating efficacy in phase III clinical trials for prevention of catheter-associated infections (Hamill et al. 2008). So far, among the most explored AMPs categories for clinical purposes are lantibiotics, temporins, cathelicidins and defensins.

The work of Bower et al. (2002) was the first preclinical trial of implantable materials treated with

the lantibiotic nisin. This *in vivo* study showed no clinically evident adverse effects from placement of nisin-treated intravenous catheters and tracheotomy tubes in sheep or ponies during the experimental period. Regarding the activity of cathelicidin peptide BMAP-28 against *S. aureus* biofilms, Cirioni et al. (2006) reported good antimicrobial activity as well as a tendency to attach to the biomaterial surface, making the pre-treatment with BMAP-28 an attractive choice to control device-related infections caused by staphylococci. Etienne et al. (2004) developed a new strategy based on the insertion of a defensin into polyelectrolyte multilayer films and the biocompatibility and stability attained, together with the possibility of varying the number of adsorbed active proteins or peptides and their amounts, could lead to biomedical applications such as catheters protection.

The broad spectra of AMPs along with their multifunctional characteristics make these peptides unique natural molecules that can be exploited for the development of novel therapeutic strategies.

Other approaches

Quorum-sensing interfering molecules

Alternative approaches for prophylaxis/treatment of microbial colonization of polymeric surfaces include the use of molecules that interfere with quorum-sensing (QS). QS molecules allow bacteria to regulate biofilm formation and the use of QS inhibitors for biofilm control has already been demonstrated (Rasmussen et al. 2005).

Until now, one of the most studied QS inhibitors are furanones, which are able to control multicellular behaviour induced by autoinducer-1 (Manefield et al. 2002) and autoinducer-2 (Ren et al. 2004) in Gram-negative microorganisms. Lönn-Stensrud et al. (2009) also reported that synthetic furanones were able to inhibit biofilm formation by *S. epidermidis* without irritative or genotoxic effects in mice. Baveja et al. (2004) indicated that furanones did not promote significant changes in the characteristics of the coated material. This is especially applicable to commonly used biomaterials for implantable devices such as silicone, expanded polytetrafluoroethylene and polypropylene.

Enzymes targeting the EPS

Bacteria attached to surfaces produce large amounts of EPS, which binds the biofilm together as a matrix and anchors the biofilm to the surface. Therefore, enzymes targeting the EPS matrix of biofilms have also been used alone or in combination with antimicrobial agents to treat and dissolve biofilms (Alkawash et al. 2006).

Kaplan et al. (2004) demonstrated that during sessile growth, *Actinobacillus actinomycetemcomitans* produces a soluble β -*N*-acetylglucosaminidase, named dispersin B (DspB), able to disperse and detach mature biofilms produced by *S. epidermidis*, by exerting its hydrolytic activity against the exopolysaccharide matrix produced by staphylococcal strains, as well as some other bacterial species. Donelli et al. (2007) also showed that DspB could be successfully adsorbed to functionalized polyurethanes, maintaining its activity against the biofilm matrix. A synergistic effect was also observed when exposing biofilms to both DspB and the antibiotic molecule cefamandole nafate, highlighting these polymer – DspB – antibiotic systems as promising and highly effective tools for preventing bacterial colonization of medical devices such as catheters.

N-acetyl-L-cysteine (NAC) has also been shown not only to reduce bacterial adhesion but also to detach bacteria adherent to surfaces (Mansouri and Darouiche 2007). It can also decrease biofilm formation by several bacteria by reducing the production of the EPS matrix and promoting the disruption of mature biofilms (Olofsson et al. 2003). Aslam et al. (2007) demonstrated the good synergistic effect of NAC and tigecycline in the treatment of catheter-associated biofilm, as they both act on different components of the biofilm. Similar results were obtained by Marchese et al. (2003), with a synergistic effect of NAC with fosfomycin against *Escherichia coli* biofilms. These results suggest that these combinations could be effective as catheter lock solutions or coatings for the treatment of catheter-associated bacteremia.

Nitric oxide

Nitric oxide (NO) is a small, naturally produced, hydrophobic, free-radical gas that has a major role in innate immunity. It exhibits broad reactivity and rapid diffusive properties through biological liquids and lipid membranes, with a short half-life in a physiological milieu (Subczynski and Wisniewska 2000).

The antimicrobial activity of NO was demonstrated more than 50 years ago, with recent *in vitro* studies showing inhibition of a wide variety of bacteria (Hetrick and Schoenfisch 2007). NO was shown to be bacteriostatic (Fang 1997), with *in vitro* evidence demonstrating bactericidal effects (McMullin et al. 2005). By utilizing coatings capable of releasing NO, the natural antimicrobial ability of the immune system may be augmented to prevent the survival of pathogenic bacteria at implant surfaces. There are numerous NO-releasing coatings on biomaterials currently under investigation, many of which have demonstrated decreased incidence of biomaterial-associated infections. NO-releasing carbon-based coatings added to

monofilament polypropylene meshes, as a means of reducing infectious complications after abdominal wall surgeries, had a significant bactericidal effect on *in vitro* biofilms of *S. aureus* and other pathogens (Engelsman et al. 2009). Regev-Shoshani et al. (2010) also presented a novel approach that creates an antiseptic barrier on urinary catheters by impregnating them with gaseous NO. These results open new perspectives for NO impregnation in other types of catheters or medical devices.

Electrical enhancement of antimicrobial activity

Approaches using electrical current have been proposed as a way to prevent biofilm formation and also to enhance the activity of antimicrobials against established biofilms, a phenomenon that is known as the bioelectric effect. This phenomenon can be described as the enhancement, by a relatively weak and continuous electrical current, of the activity of antimicrobial agents (eg an antibiotic) against biofilm microorganisms (Del Pozo et al. 2009b). With this method, the antibiotic concentration necessary to be effective against biofilm bacteria was lowered from ~5000 times to 4 times greater than those necessary for planktonic bacteria in the absence of electricity (Costerton et al. 1994). However, so far, there are only few publications with *in vivo* data on the potential therapeutic use of electrical current in medical device-related infection. Del Pozo et al. (2009a) introduced a new concept, the electricidal effect, by demonstrating dose- and time-dependent killing of *S. epidermidis* biofilms after prolonged exposure to low-intensity direct electrical current. The electricidal effect was also tested *in vivo* (Del Pozo et al. 2009c) in a rabbit model of *S. epidermidis* chronic foreign body osteomyelitis, confirming the bactericidal activity of low-amperage electrical current against bacterial biofilms. These results highlight the possibility of the use of this therapy on different medical devices, such as CVCs.

Ultrasound enhancement of antimicrobial activity

Despite the fact that ultrasound itself has been shown not to influence bacterial viability in a biofilm, it has been demonstrated to be effective in enhancing the activity of antibiotics and other antimicrobial agents against bacterial biofilms, which is known as the 'bioacoustic effect' (Qian et al. 1994).

It is thought that ultrasound induces cavitation within the biofilm, which increases transport of solutes, as antimicrobial agents, through the biofilm or outer bacterial membranes (Carmen et al. 2005). Several studies have demonstrated this bioacoustic effect against microbial biofilms in *in vitro* and in animal

model systems (Rediske et al. 2000; Carmen et al. 2005; Hazan et al. 2006). Rediske et al. (2000) reported that the combination of systemic gentamicin and application of pulsed ultrasound to a simulated implant infection in a rabbit model significantly reduced bacterial viability on the implant, without damaging the skin. In another study, Hazan et al. (2006) revealed that low-energy surface acoustic waves generated from electrically activated piezo ceramic elements are effective against bacteria as well as fungi. No adverse effects were observed, suggesting that this system may potentially be attached to a variety of indwelling medical devices, including endotracheal tubes and peritoneal dialysis or central venous or catheters.

Light-activated antimicrobial agents

An alternative method of surface disinfection is the use of a coating with light-activated antimicrobial agents (LAAAs). LAAAs are a class of chemicals that when excited with light of an appropriate wavelength, transfer energy or electrons to ground state molecular oxygen, generating reactive oxygen species, such as singlet oxygen and the hydroxyl radical, which are toxic to microorganisms (Page et al. 2009; Perni et al. 2009). These radical species have no specific target within a microorganism, which is very important because it avoids the potential problems of microorganisms developing resistance, given that resistance only arises when a specific site is targeted by a microbicide (Wilson 2003).

The use of a photosensitiser as an antimicrobial agent is a direct refinement of the technique of photodynamic therapy, a commonly used therapy to target and destroy cancerous tissues. The destructive power of the radicals produced by photosensitisers can be put to use in a microbicidal surface coating when the photosensitiser is immobilised within a polymer matrix and applied to a surface (Wilson 2003; Decraene et al. 2006). Among the most studied LAAAs are indocyanine green (ICG), methylene blue (MB), rose Bengal and toluidine blue O (TBO). *In vitro* studies have shown that photosensitisers can retain their antimicrobial properties when attached to polymers. The work of Wilson (2003) and Decraene et al. (2006) with immobilised photosensitisers, such as TBO and rose Bengal, in a cellulose acetate coating, demonstrated that the photosensitisers did not leach from the cellulose acetate matrix and produced a microbicidal surface active under visible (white) light conditions. Perni et al. (2009) incorporated TBO and TBO-nanogold mixtures into polyurethane and silicone polymers and observed that TBO-incorporated polymers showed kills of $>10^5$ cfu ml⁻¹ for MRSA after exposure for 1 min, which is probably the, or one

of the most, potent light-activated antimicrobial polymer combination reported to date.

Perni et al. (2010) have demonstrated that MB and TBO together with nanoparticulate gold could be incorporated into common catheter polymers such as polysiloxanes and polyurethanes. They have shown that these polymers have equivalent mechanical properties to polymers without the LAAA and that under hospital lighting or room lighting conditions these polymers show minimal degradation but an enhanced ability to kill bacteria. All these studies corroborate the possibility of using LAAAs incorporated into polymers as coatings of hospital surfaces, which could be activated by the ambient light conditions found in hospitals.

Conclusions

CVC-RIs due to biofilms will remain a major challenge in health care in the near future. They are still an important cause of morbidity and mortality and frequently the only solution to an infected intravascular catheter is its removal, which results in additional economic and health costs. The development of surfaces and coatings that can eradicate microorganisms in an active way is an important element of maintaining an aseptic environment and a large number of methods have been developed in recent years. Ideally these antimicrobial surfaces should be long-lasting or permanent and their mode of action should probably function simultaneously throughout multiple pathways, so that the development of resistance, as in the case of antibiotics, ultimately does not occur.

Current preventive measures to decrease the risk of these serious infections include antimicrobial agent-impregnated catheters and antimicrobial lock therapy. However, despite the good *in vitro* results in reducing bacterial colonization, some of these compounds have partially failed in preventing catheter-associated biofilm formation, with some resistant microorganisms arising. More clinical trials are also lacking. On the other hand, with the emergence of nanomaterials, nanosilver particles are a promising next generation of antimicrobial agents, as well as other new drug delivery technologies. Phage therapy has also been demonstrated to have a high potential but, before its clinical application, several issues must be clarified. Antimicrobial peptides have received attention due to their broad spectrum of activity and difficulty in finding resistance.

Promising technologies that incorporate novel approaches such as QS inhibitors, enzymes that dissolve biofilms, nitric oxide, electrical or ultrasound enhancement of antimicrobial activity, also seem to

provide useful approaches for the future. The light-activated antimicrobials offer particular promise as they function by generating reactive oxygen species that act on multiple targets within microbes.

In conclusion, the current widespread arsenal of antimicrobial coatings offers prospects for reducing catheter-related infections. However, the search for the ultimate catheter, a catheter that combines low-cost coating technology, wide-spectrum and long-lasting antimicrobial properties, and secure utilization, continues.

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