

STRATEGIES AND PERSPECTIVES FOR BIOMEDICAL CATHETERS DESIGNED TO PREVENT DEVICE RELATED INFECTIONS

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Abstract

The medical devices that have been associated with a higher rate of infections are the central venous catheters. In order to minimize this risks, the novel biomaterials must be antiadhesive to pathogens agents, colonisation resistant and refractory to biofilm formation. The advanced solutions were obtained by applying a coating of biocompatible polymers or by using the biopolymers as a matrix for the sustained delivery of antiseptics, silver compounds, or antimicrobial drugs. This paper reviews the arsenal of modified devices available and the promising perspectives.

Key words: biomedical devices, central venous catheters, impregnating, coating

1. INTRODUCTION

In order to minimize the risks of infections associated with the use of medical devices, nowadays, the medical technology strategies have proposed the use of novel biomaterials. The devices that have been associated with a higher rate of infection during regular interventions are the central venous catheter (CVC), particularly long-term catheters. The use of CVCs is essential for intravenous medications and nutrition in case of critically ill patients, but their related infections could be fatal.

The pathogenesis of catheter-related infections (CRIs) is complex and multifactorial, but most of them appear as a result from the migration of skin at the insertion site with colonization of the catheter (colonization outside of catheter) or the infections could develop through catheter hub or contaminated infusate solutions (colonization inside of catheter).

Although in available reported data the infected rate varies (according to each country and each hospital), between 11 and 37% of nosocomial infection have been related to implanted long-term catheters (Fätkenheuer et al. 2002). The increase in health-care costs is associated with prolonged hospitalization. (Fätkenheuer et al. 2002, von Eiff 2005 et al., Gahlot et al. 2014). Thus, it was estimated that related infections caused prolonged hospitalization for an average of 20 days, with hospital costs increased by 3000 Euro per case (Rello et al. 2009). The risk of infection depends not only by the conditions and the appropriate prevention measures during insertion or by the site of insertion, but also by the type of device used.

Several measures have been developed to reduce catheter risk infections (CRI). The medical guidelines concerning of technological and non-technological strategies for prevention have been proposed (Raad et al. 2007, Mermel et al. 2001, Marschall et al. 2008.). The protocols for good clinical practices (concerning hygiene, catheter insertion, manipulation and care) are effective if they are used in combination with adequate type of catheters. Thus, a reasonable way to reduce these risks is the use of modified catheters (impregnated CVC).

The modified catheters obtained by coating the CVC with different antiseptics or antibiotics were introduced in medical practice in the last three decades. From then, a lot of prospectives studies demonstrate that the use of antimicrobial catheters is associated with decrease risk catheter related infection compared to standard catheters. There were proposed different approaches concerning surface treatments for CVC (and generally for medical devices) in order to reduce the risk of nosocomial device related infection (Shintani 2005, Soussa et al 2011). The efficacy of such modified

medical devices is determined by the nature of the impregnated compounds (antiseptic, antibiotic, silver) as well as the technologies by which these are incorporated in the coating.

2. MODIFIED CATHETERS

2.1. Material characteristics

A catheter is a polymer tube, flexible but resistant, thin walled (with a high internal to external diameter ratio), with smooth and uniform surface. As any invasive medical device used in contact with the blood and tissue, it should be biocompatible and hemo-compatible. It must be bio-stable, and physically and chemically neutral (not affected by long contact with blood and infusion administered). The catheter materials are determinant for their properties and the selecting the adequate polymer requires the knowledge regarding their biological, physical and chemical characteristics. The selection of biomaterials used for device construction is important to minimize the risks of device-associated infections.

The first commercialized catheters were made of polyethylene (PE), or polyvinyl chloride (PVC) with disadvantage in terms of mechanical strength, resistance to chemical degradation and biocompatibility (Galloway & Bodenham 2004). Nowadays, the polymers most likely to be used for venous catheters are thermoplastic polyurethane (PU), polytetrafluoroethylene (PTFE), and polyethylene terephthalate (PET), that have been associated with higher biocompatibility (Sheth et al. 1983, Galloway & Bodenham 2004).

The polymer surface, with its physiochemical properties, play an important role in the interfacial behavior of devices in contact with body fluids and tissues. The surface modification involves different surface-treatment procedures. Present strategies have focused on modifying the device surfaces by: increasing the surface biocompatibility, decreasing the bacterial adherence and the bio-film production (Frasca et al. 2010).

2.2. Biofilm characteristic

The microbiological colonization of the catheter involves three stages: adhesion, attachment and colonization (Fig.1).

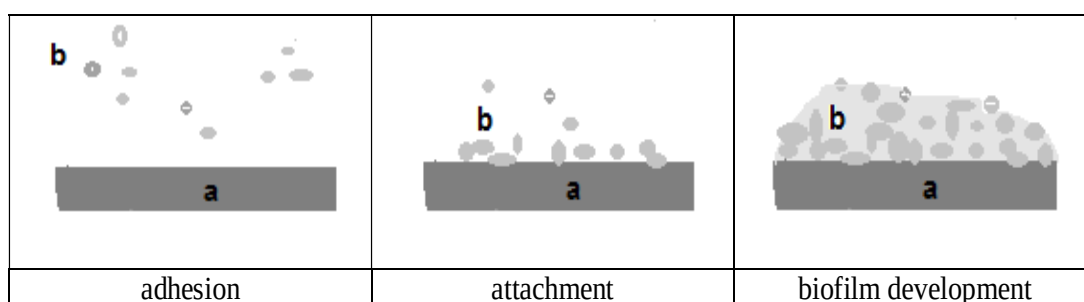


Fig. 1. Representation of biofilm formation

(a-device surface; b-bacteria)

In the first stage – adhesion - the pathogen agent gets in contact with the catheter surface through the weak interactive forces. In this case, the bonds with the surface can be easily broken. In the second stage - attachment - there are more microorganisms and therefore more bounds between them and the catheter surface. The rate of cell attachment depends on the physicochemical characteristics of the surface. Thus, the chemical properties of the polymeric biomaterials (hydrophobic or hydrophilic) and the surface characteristics (rough or smooth) can facilitate or not the adhesion to the surface. In the

third stage – colonization - the pathogens begin to produce and release special molecules from their surfaces that strengthen not only their adherence to the catheter surface, but also the adherence of the bacteria to each other. By irreversible attachment to the surface of the catheter, the microorganisms form a biofilm (a complex aggregation of microorganisms growing on a surface), producing a matrix of extracellular polymeric substances (von Eiff et al. 2005, Francolini & Donelli 2010).

Various technologies have been developed in order to interrupt the first step in the pathogenesis of infection - the bacterial colonization on the surface. These aim to prevent the biofilm formation with antibiofilm agents that prevent and inhibit the microbial attachment process without bactericidal agents) or to inhibit the biofilm formation with bactericidal or bacteriostatic agents (Danese 2002, Francolini & Donelli 2010). Thus, the technologies used provide the CVC with a modified surface without releasing drugs (through hydrophilic coating) or containing antibacterial agents (through their bactericid action) (Fig. 2, Tab. 1)

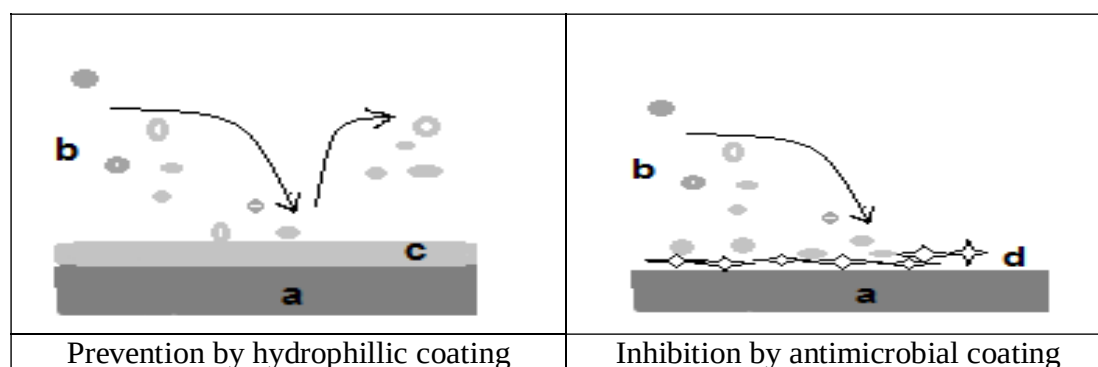


Fig. 2. Surface coating: principle of action

(a - device surface; b - bacteria; c - hydrophilic coating; d - antimicrobial coating)

Table 1. Catheter surface modification technologies

Type of catheter	Method	Procedure
Catheters without antimicrobial agents	Hydrophillic coating	- hydrogel technology, - radiation techniques, - glow discharge techniques
Catheters with antimicrobial compounds ○ antiseptics ○ antibiotics ○ silver	Antimicrobial coating	- direct deposition (applies the microbial agent as thin-film on a catheter surface), - ion bonding antimicrobial agents, - entrapment of anti-microbial agents in a polymer matrix

2.3. Catheter surface modification technologies

2.3.1. Hydrophilic coating

In order to achieve a reduction of bacterial adhesion which lead to prevent microbial colonization and biofilm formation, the current technologies used the modification of medical device surface. CVCs, as the medical devices made of polymeric materials, are in general hydrophobic. Microbial adhesion depends on hydrophilicity and surface charge of the materials constituting CVC (Francolini & Donelli, 2010).

In vitro and in vivo studies demonstrated that increased hydrophilicity of a surface decreases the bacteria adherence (Shintani 2005). That's why the surface treatment proposed to modify the hydrophobic surface by increasing their hydrophilicity. The polymeric substrates used for CVC include, generally, polyurethanes (PU) or polyethylene terephthalate (PET). The catheter is coated with a hydrophilic substance activated by biological fluids, which reduces the potential adhesion of bacteria and, in the same time, facilitates the insertion of the device. As an example, clinically in current use is the polyvinylpyrrolidone-coated polyurethane catheter (*Hydrocath*).

The antiadhesive properties have been obtained by different methods: hydrogel technology, radiation techniques, glow discharge techniques, etc. It was found that the bacterial attachment is decreasing with the increasing surface tension of polymeric materials and that the bacteria adhesion is decreasing with the increasing negative free enthalpy values (Kohnen & Jansen 1995). Jansen et colab. (1987) proposed a modified catheter using 2-hydroxyethylmethacrylate covalently bound to a polyurethane surface by radiation grafting.

Tebbs et colab. (1994) demonstrated that *Hydrocath* catheters have a relatively smooth surface topography than polyurethane catheters. The detailed surface topography of different polyurethane CVC (*Hydrocath*, *Deltacath*, *Certofix trio*, *Arrow-Howes* and *Multicath three*) suggest that a CVC with a smooth and uniform surface, without surface defects, may reduce the risks of bacterial adherence and microbial colonization.

Recently, *BBrown* had proposed a novel catheter that releases no active compounds and that obtains its bactericidal effects through positively charged chemical structures on the internal and external catheter surfaces. Their *Certofix®protect* (*BBraun*) catheters combines an antimicrobial agent (polyhexanide) and an athrombogenic chemical group (polyethylene glycol and poly-methacrylate). Therefore, the adhesion of bacteria is prevented and the hydrophilic groups reduces the risks of thrombus aggregation on the catheter surface. The results obtained in prospective, randomized, controlled, double-blind clinical trial, suggest that the use of this CVCs is associated with a significant decrease of BSI but not with one regarding the colonization rate (Krikava et al. 2011).

2.3.2. Antimicrobial coating

One of the approaches to obtain a medical device resistant to biofilm formation is to coat the polymeric surface with bactericidal/bacteriostatic drugs.

A variety of active compounds have been incorporated in the catheter surface to achieve antimicrobial protection: chlorhexidine, benzalkonium chloride, silver sulfadiazine, silver, nanoparticles, platinum, rifampin, minocycline etc. There are many in vitro studies concerning the antimicrobial activities of central venous catheters impregnated with different antimicrobial agents which demonstrated efficacy against: *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Escherichia coli*, *Enterococcus faecalis*, *Candida albicans*, etc. The efficiency of this type of catheters depend both of the properties of antimicrobial agent (broad spectrum and antibacterial effectiveness) and the physiochemical properties of polymer matrix.

The strategies should focus on developing the optimal device surface and the adequate dosage and release rate of the antimicrobial agent coating/ incorporating in the polymer matrix (increase the local concentrations and sustained delivery of the therapeutic agents).

The procedure consists in impregnating the catheter with different antimicrobial agents (antiseptics /antibiotics) that elutes from the device and that have a bactericidal or bacteriostatic mechanism. Antimicrobials had been incorporated into the bulk material of CVC or could have been applied to their surfaces as a coating. The coated catheters were produced by impregnating polyurethane catheters. Generally, antimicrobial solutions are used alone or in a combination of antiseptic/ antibiotics through a sequential coating method. The impregnating catheters commercially available have the same mechanism of action, but differ in the method used to coated/impregnating (drug concentration, incubation time and temperature leads to the binding of adequate amounts of antimicrobial agent to the catheter).

The most effective antimicrobial CVCs that are recommended by CDC guidelines are those coated with antiseptics: as chlorhexidine and silver sulfadiazine or those coated with antibiotics: as minocycline - rifampin (O'Grady et al. 2011).

- *Catheters with antiseptics*

The first modified catheters were obtained by coating the CVC with a very known antiseptic: chlorhexidine (CHX). After that, the medical device companies proposed catheters which contain a mixture of chlorhexidine and silver sulfadiazine in the coating on the external catheter surface (both agents are antiseptics with bactericidal effect). The first impregnated catheters including the chlorhexidine and silver sulfadiazine - coated CVC were manufactured by *Arrow International*. Their first-generation of catheters were coated only on the external surface. The reports (Raad & Hanna 1999, Darouiche 1999) suggest that the protection of the external surface of the catheter alone is not effective, and also that they are associated with a short antimicrobial durability (between 3 and 7 days). That's why, the same company proposed the second generation of catheters impregnated both on the internal and external surface, including extension lines and hubs. This efficiency in preventing infections in long-term catheterizations (≥ 14 days) by using these catheters is attributed to increase levels of chlorhexidine on the outer surface (three times higher than on original catheters) and the introduction of chlorhexidine on the luminal surfaces (Sampath et al. 2001, Bassetti et al. 2001).

Several studies demonstrate that combining the benzalkonium chloride, with a hydrophilic coating reduced the attachment of the pathogens to the catheter surfaces. The antiseptic CVC with benzalkonium chloride on the both surfaces had been developed and evaluated in vitro (Tebbs & Elliott 1993) and also in vivo. Thus, in several clinical trials these catheters showed a significant reduction of the incidence of microbial colonization on both the internal and external catheter surfaces (Moss et al. 2000), especially in patients with a high risk of infectious complications (Jaeger et al. 2001). These catheters with antiseptics reduce catheter related bloodstream significantly, but there are several reports of allergic reactions - case of anaphylaxis shock - during the placement of impregnated central venous catheters with chlorhexidine (Jee et al. 2009) or benzalkonium chloride (Shih et al. 2010).

- *Catheters with silver*

Silver (Ag) is known as an active antimicrobial agent. Ag is effective against many bacteria, including the common microbes that cause infection or the antibiotic resistant strains, but also is an effective fungicide. As mechanism, the bactericidal effect of the silver ions could be explained by altering the cell membrane properties (through reactions with thiol groups in cell-membrane related enzymes, blocking oxidative phosphorylation, and binding to the DNA helix in organisms (Guggenbichler et al. 1999). Silver had been used in medical devices in different forms (silver nitrate, metallic silver, silver-sulfadiazine, silver nanoparticles). The silver-treated catheters offer antimicrobial protection by releasing of Ag ions through the surface of the polymer. The concentrations required for bactericidal activity are considered to be around 10^{-9} mol/l.

There are two methods of silver delivery for medical devices: dissolution and controlled release mechanism. By a technology proposed by Guggenbichler et al. (1999), metallic silver is distributed in submicron particles in polyurethane and the interaction of electrolyte solutions with silver throughout the polyurethane releases bactericidal concentrations of silver.

Several studies reported that silver impregnated catheters are ineffective in preventing IVC related infection for long-term catheters, but it was suggested that they are effective for short-term catheters (3-7 days) (Raad 1998, Bong et al. 2003). According with a recent meta-analysis silver-impregnated CVCs are not associated with lower rates of catheter bacterial colonization or catheter-related blood stream infections compared to standard CVCs (Chen et al. 2014).

The development of silver impregnated catheter leads to new devices in which silver is in combination with other elements. The Oligon catheters (*Vantex, Edwards Lifesciences*), commercially available, are composed of polyurethane in which are incorporated: silver, platinum, and carbon. Oligon agent is integral to the polymer of the catheter, protecting both inner and outer catheter surfaces. The electrical conductivity of carbon particles facilitates a redox reaction between silver and platinum particles to produce a sustained release of silver ions (Crnich & Maki 2002). Several in vitro and in vivo studies noted that Oligon catheter is effective in limiting the catheter colonization rate (Yorganci et al. 2002, Ranucci et al. 2003, Fraenkel et al. 2006).

- *Catheters with antibiotics*

Various antibiotics were incorporated into polymers in order to prevent bacterial colonization and catheter associated infections.

Von Eiff et colab. (2005) investigated the incorporation of flucloxacillin, clindamycin and ciprofloxacin into polyurethane polymers and noted a reduction of the in vitro adherence of bacteria (*S. Epidermidis*). Kamal et colab. (1999) proposed the anionic antibiotic, cefazolin, which was bonded before the insertion of the catheters by immersing in antibiotic solution. The procedure was proposed as method of reducing intravascular catheter infections in patients in intensive care units.

Different catheters with antimicrobial coating or bonding were proposed and their efficiency were analysed. The proposed catheters with cefazolin, teicoplanin, vancomycin, silver have not demonstrated a consistent decrease in the incidence of CRBIs (Pai et al., 2001).

Minocycline and rifampicin are the most studied combination of antibiotics available for modified catheter in order to reduce the risk infection through two distinct mechanisms of action. These vascular catheters impregnated with minocycline and rifampicin, a combination with synergic action, are one of the most used catheters commercially available (*Cook Spectrum*). The second generation of these catheters are coated both on the external and internal surfaces.

Trials evaluating different catheters noted varying results. Thus, according to Darouiche et colab. (1999), the use of central venous catheters impregnated with chlorhexidine and silver sulfadiazine are associated with a higher rate of catheter-related infections than the use of catheters impregnated with minocycline and rifampin. Therefore, several meta-analysis demonstrate that CVCs impregnated with rifampicin and minocycline are effective in reducing catheter-related bloodstream infection and the rate of catheter colonization (Falagas et al. 2007, Pai et al. 2001).

The 5-fluorouracil coated catheters, recently developed, had been shown to inhibit the growth of gram-positive and gram-negative bacteria and *Candida* species. In a single-blind, multicenter, randomized trial, catheters coated externally with fluorouracil were compared to catheters coated externally with chlorhexidine-silver-sulfadiazine. The results suggest that central venous catheters externally coated with 5-fluorouracil are a safe and effective alternative to catheters externally coated with chlorhexidine and silver sulfadiazine when used in critically ill patients (Walz et al. 2010).

- *Combinatorial approaches for impregnated catheters*

Recently, there were proposed different antimicrobial combination which could be used to reduce catheter-associated infections and catheter colonizations.

Combinatorial approaches using antiseptic and antibiotic-impregnated catheters could provide better protection against microbial contamination (Danese 2002). For example, one of the commercially available catheter, had been used a polyurethane catheter material which was first impregnated with a mixture of minocycline and rifampicin. After drying, the catheter was treated on the lumen and exterior surfaces with a chlorhexidine - polymer coating. (*Arrowgard BluePlus; Arrow International, Inc.*) Raad et colab (2012) proposed a modified method in which the catheters were impregnated first in chlorhexidine (CHX) solution and then continued to be impregnated with a mixture of minocycline

and rifampin (M/R). After impregnation, catheters were air flushed to remove any excess coating solution from the lumens of the catheters, dried, washed with water, and dried again. Their novel CHX-M/R- coated catheters have the extended-spectrum activity against resistant bacteria and fungi, superior to the standard M/R and CHX-treated catheters. In clinical trials, the use of these type of catheters has been associated with prolonged antimicrobial durability (between 4 and 7 weeks) (Darouiche et al. 2005) without excess adverse events, hypersensitivity, or emergence of antimicrobial antiseptic resistance (Rupp et. al 2005).

Schierholz et colab (2000) proposed the use of a combination of antibacterial and antifungal agent. The in vitro activity of catheters coated with rifampicin and miconazole (antifungal) was evaluated, and the results indicate that the increased antifungal activity of miconazole combined with rifampicin (antibacterial) could be an improvement for long-term central venous access.

Mansouri MD et colab. (2013) proposed a combination of an antibiofilm and an antibiotic against vascular catheter colonization. They proposed *N*-acetylcysteine (NAC) - as antibiofilm agent and levofloxacin - as a broad-spectrum antibiotic. The catheter was evaluated in vitro for antiadherence activity and reduced colonization and demonstrated the most active and durable efficacy against Gram-positive and Gram-negative bacteria.

3. CONCLUSION

The central venous catheters are indispensable for critically ill patients, but their use is generally associated with a local or systemic infections. Bacterial adherence to catheters depends, first of all, on the nature of the biomaterial. The development of technology utilizing biomaterial surface modification and antimicrobial coatings (with different antimicrobial agents) are the strategy for prevention of catheter-associated infections. There were reported many in vitro comparative studies concerning the antimicrobial catheters and also in vivo testing and clinical trials in order to evaluate their efficiency. The most effective antimicrobial CVCs that are recommended by clinical guidelines are those coated with antiseptics (chlorhexidine and silver sulfadiazine) or those coated with antibiotics (minocycline – rifampicin). The new catheters materials have been developed and the modified surface-treated central venous catheters are now commercially available, but the CVC related infections continue to be an important health problem.

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