Universidade de Lisboa

Faculdade de Farmácia

Antimicrobial strategies to prevent catheters-associated medical infections

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Mestrado Integrado em Ciências Farmacêuticas

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Resumo

Atualmente, os cateteres urinários e intravasculares são dois dos dispositivos médicos invasivos mais utilizados, sendo responsáveis por uma grande fração das Infeções Associadas aos Cuidados de Saúde. A colonização microbiana da superfície dos cateteres é um dos processos causadores destas infeções, que tem como consequência o aumento dos custos, da morbilidade e da mortalidade dos doentes afetados. Em qualquer situação, o cateter escolhido deve ser biocompatível, sabendo-se que dos diferentes materiais disponíveis resultam distintas propriedades e predisposição para a formação de biofilmes. Os biofilmes são comunidades de microrganismos aglomerados, com tolerância/resistência aumentada não só ao sistema imunitário do hospedeiro como também a agentes antimicrobianos uma vez que formam uma barreira que dificulta a penetração pelos antibióticos. Adicionalmente, a ocorrência de mecanismos de degradação destas moléculas contribui para a falha da terapêutica e erradicação da infeção. Cateteres revestidos com substâncias antimicrobianas têm sido aprovados e comercializados ao longo dos anos como estratégia preventiva. Contudo, a prática inconsciente de terapêuticas com antibióticos poderá estar a reduzir a eficácia destes dispositivos na presença de estirpes bacterianas resistentes. Encontrar novas estratégias com compostos antimicrobianos alternativos torna-se agora essencial e, como tal, um crescente número de superfícies capazes de exercer atividade bactericida por contacto ou libertação do agente antimicrobiano tem sido reportado. Uma vez que a superfície antimicrobiana ideal ainda não foi desenvolvida, a presente revisão da literatura propõe-se não só a debater a eficácia dos cateteres já comercializados como também a descrever o progresso e perspetivas de novas estratégias antimicrobianas. Realça-se o uso de agentes como clorohexidina, triclosan, óxido nítrico, 5-fluorouracilo, compostos de amónio quaternário, quitosano, péptidos antimicrobianos e enzimas. Os inibidores do *Quorum Sensing*, ao interferir com a comunicação entre bactérias e com processos de adesão e crescimento, também merecem destaque, apresentando-se como potenciais substitutos dos agentes bactericidas ou bacteriostáticos normalmente utilizados. Todas estas estratégias apresentam provas de eficácia antimicrobiana, quer através da alteração da fisiologia dos agentes patogénicos, quer por transformações na sua integridade estrutural. Contudo, apesar dos resultados laboratoriais encorajadores, na maioria dos casos ainda persiste a necessidade de investigação adicional de forma a confirmar o valor de algumas estratégias na prática clínica.

Palavras-chave: Cateter; Infeção; Estratégias Antimicrobianas; Contacto; Libertação

Abstract

Nowadays, urinary and intravascular catheters are two of the most frequently inserted invasive medical devices and their extensive use is responsible for the major part of Healthcare-associated acquired infections. Microbial colonization of catheters surfaces is a contributing process to these infections and leads to increased costs, morbidity and mortality of the patients. Catheters should ensure biocompatibility and according to their material they present different properties and predisposition to develop biofilms. Biofilms are packed communities of microorganisms with increased tolerance/resistance to the host immune system and antimicrobial agents since they can act as a barrier resulting in decreased penetration of antibiotics. Degradation mechanisms of antibiotics is also a problematic event that leads to failure of infection eradication. A list of catheters coated with antimicrobial substances have been approved and commercialized as preventive strategy but the unconscious practice of antibiotic therapies may be decreasing their potential activity against bacterial resistance strains. Finding new strategies with alternative antimicrobial agents is now obligatory and a crescent number of designed surfaces based on releasing systems or contact-killing properties is being continuously reported. Since the ideal bactericidal surface has not been developed yet, the aim of this review is to question the effectiveness of previously developed catheters and describe the progress and promise of new antimicrobial approaches such as the use of chlorhexidine, triclosan, nitric oxide, 5-fluorouracil, quaternary ammonium compounds, chitosan, antimicrobial peptides and enzymes. Quorum Sensing inhibitors also deserves attention for being possible substitutes for bactericidal and bacteriostatic agents and interfering with bacteria-bacteria communication and social behaviours. All of these strategies have given proof of antimicrobial efficacy by modifying the physiology of pathogens or disrupting their structural integrity. However, despite the encouraging laboratorial results in most cases, there is still a great need for further investigation to confirm the real value of some approaches in clinical practise.

Keywords: Catheter; Infection Antimicrobial Strategies; Contact; Release

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To my parents and grandparents,

Who have always encouraged me to be the best I can be.

To my irreplaceable friendships,

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Abbreviations and Acronyms

Ag	Silver
AgNPs	Silver nanoparticles
AHLs	Acyl-homoserine lactones
BZK	Benzalkonium chloride
CAgNPs	Phytosynthesized silver nanoparticles
CAUTIs	Catheter-associated urinary tract infections
CHX	Chlorhexidine
CRBSI	Catheter-related bloodstream infections
CSS	Chlorhexidine-silver sulfadiazine
CVC	Central venous catheter
DBHD	Dibutylhexanediamine
DspB	DispersinB
EPS	Extracellular polymeric substances
HAI	Healthcare-associated infections
LDPE	Low Density Polyethylene
MAgNPs	Microbial silver nanoparticles
NONOate	Diazeniumdiolates
PD	Polydopamine
PEG	Polyethylene glycol
PHMB	Polyhexamethylene biguanide
PLGA	Poly(lactic-co-glycolic acid)
PUs	Polyurethanes
PVC	Polyvinyl chloride
QACs	Quaternary ammonium compounds
QAS	Quaternary ammonium silane
QS	Quorum Sensing
RSNOs	*S*-nitrosothiols
SNAP	S-nitroso-N-acetyl penicillamine
THF	Tetrahydrofuran
WBPU	Waterbone polyurethane

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1 Introduction

As consequence of using invasive devices during a medical or surgical treatment, a patient can acquire a Healthcare-associated infection (HAI) due to bacterial adhesion to the device's biomaterial surface.(1,2) Although the existent few data, it is known that 60-70% of HAIs are related to medical devices (1) and catheter-associated urinary tract infections (CAUTIs) are one of the main sources. (3) HAIs can lead to increased costs for the health system and patients, morbidity and mortality, with extended hospital stay.(2,4) The most frequent risk factors for HAIs include a age above 65 years, a hospital stay superior to seven days, placement of a central venous catheter (CVC) and urinary catheterization.(2) Consequently, in Intensive Care Units, urinary and bloodstream infections are catheter-associated in 96,7% and 43,3% of cases, respectively.(5)

In 1972 it was for the first time documented the connexion between biofilms and medical device-related infections (4) and the mechanism of biofilm formation is now understood. In catheterization, biofilm may be originated from the organisms that colonize the skin at the point of catheter insertion or by its migration through or around the device after implantation. Biofilms are packed communities of microorganisms, most frequently bacteria, but also fungi, viruses and parasites, with increased resistance to immune defence mechanisms and antimicrobial agents, causing tissue destruction and infection dissemination.(1,4) The most common infectious agents associated with urinary catheters and CVCs are listed in Table 1.

Table 1: Microorganisms most associated with biofilm formation on catheters

Type of device	Microorganism	Ref.
Urinary catheters	*Escherichia coli, Klebsiella pneumoniae, Enterococcus faecalis, Staphylococcus epidermidis, Proteus mirabilis*	(6)(7)
Intravascular catheters	Coagulase-negative Staphylococci, *Staphylococcus aureus, Klebsiella pneumoniae, Pseudomonas aeruginosa, Enterococcus faecalis, Candida* species	

Biofilm formation (Figure 1) starts with an initial attachment of the first cells to a surface, forming the conditioning film, where the planktonic forms continue to adhere in multi-layered clusters separated by interstitial spaces. Increased shear forces, microbial features such as pili, flagella, glycocalyx and fimbriae, and electrostatic interactions allow this stage to take place. During microorganisms colonization occurs the self-production of insoluble extracellular

polymeric substances (EPS) such as polysaccharides - the main component of this matrix - DNA and proteins. The polymeric mixture helps colonies to grow – growth - mediating their stabilization by cell-to-cell and cell-to-surface interactions allowing the maturation of biofilm. (1,4,8) Finally, the final cells can become specialized and able to colonize other sites by spreading and dissemination inside the host.(4)

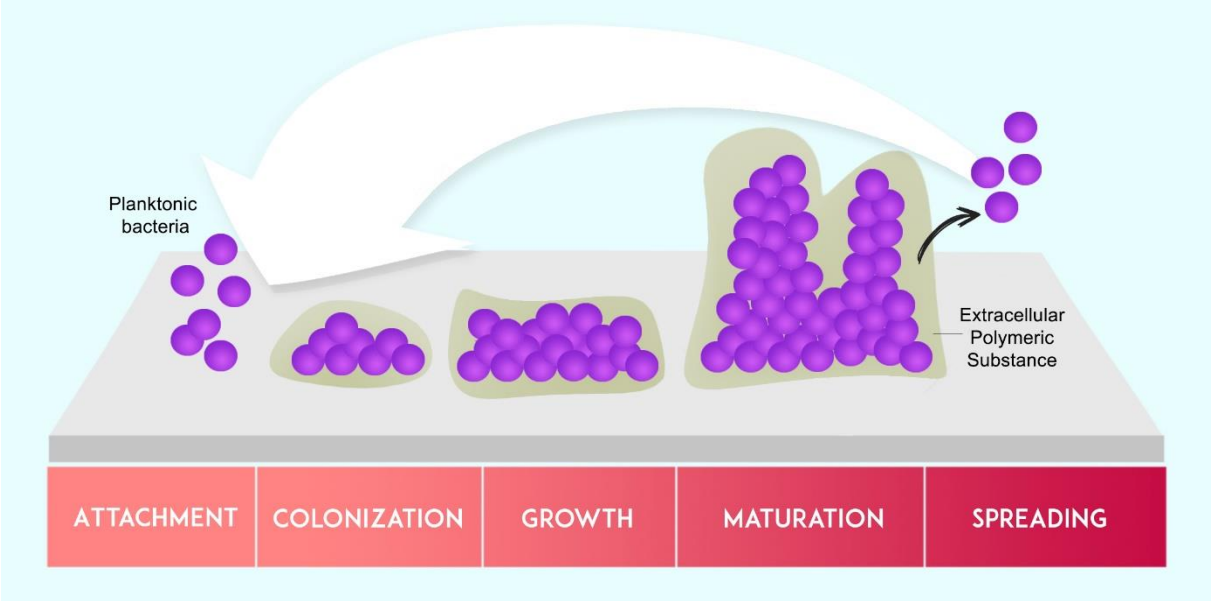

Figure 1 Process of biofilm formation

Degradation mechanisms of antibiotics, such as neutralization and dilution, may occur in some parts of the biofilm and the matrix can also act as a barrier resulting in decreased penetration of antimicrobial agents and failure of the therapy.(4,8) For this reason, strategies for biofilm development prevention must be achieved rather than applying all efforts in attempting to eradicate an infection once it is already established.

In order to prevent the biofilm formation anti-infective biomaterials have been developed and tested. These methodologies can be categorised according to their mechanism of action: (a) Antifouling strategies, which repel microbes through physical-chemical modifications, increasing surface hydrophilicity or introducing negatively charged groups; or (b) antimicrobial approaches that use coatings capable of interfering with their biological pathways. Either by modifying the physiology of pathogens or disrupting their structural integrity, it will be possible to kill the microbes in the surrounding areas and also destroy the complex organization of their biofilms. Antimicrobial coatings can also be divided in release-based and contact-based coatings as elucidated in Figure 2 (9–13) Independently, the ideal antimicrobial catheter should not reduce its activity when in contact with body fluids and the

activity should persist over the whole time of catheterization. Also the catheter should present a large antimicrobial spectrum and inhibit biofilm development, not contributing for resistance. (14)

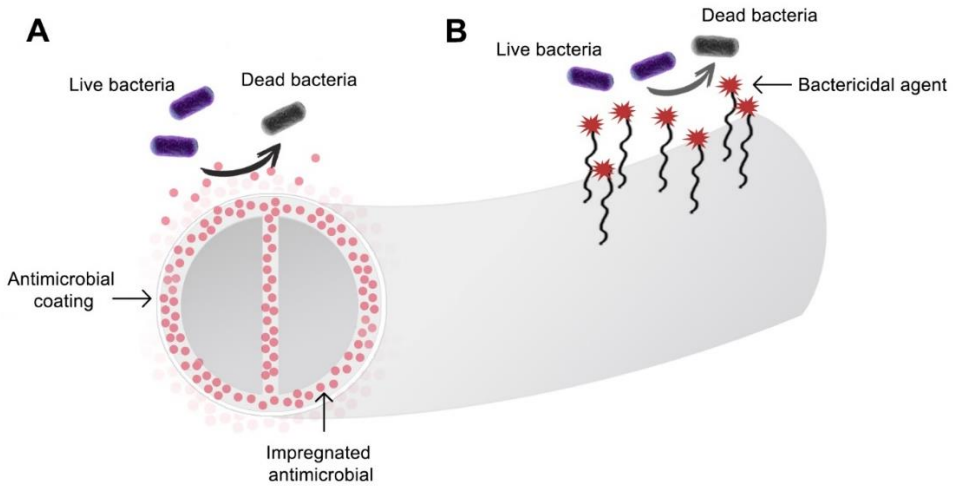

Figure 2 Antibacterial coatings for medical devices.

(A) Antimicrobial-releasing coating or impregnation; (B) Contact-killing coating.

The purpose of this work is to describe not only the approved anti-infective catheters existent in the market but also the current antimicrobial strategies in research or enrolling clinical trials to prevent catheters-associated medical infections. Another goal includes the characterization of contact-based and release-based methodologies, analysing presumable weaknesses and comparing their potential role in Medical care.

2 Materials and research methods

Information included into this work was obtained from scientific papers searched in four electronic databases (i.e. PubMed, ScienceDirect, Web of Science and Cochrane Library) while the epidemiological data was obtained from reports published by the European Centre for Disease Prevention and Control. Additionally, guidelines from the Healthcare Infection Control Practices Advisory Committee, last updated in February 2017, were also considered in this review. Priority was given to the most recent published articles, although several references previous to 5 years were also included due to their peerless data. The research included keywords such as «catheter», «antimicrobial», «bactericidal», «surface», «contact» and «release» and papers describing anti-infective strategies tested on materials commonly used to produce catheters were also considered.

3 Catheters: Uses, materials and complications

An ideal medical device should perform its function without causing adverse effects, ensuring biocompatibility and the user's safety. Biocompatibility depends on physical and chemical properties of catheters which are influenced by the material they are made of. (15)

3.1 Urinary catheters

Urinary catheters are used to collect urine from the body, control urinary incontinence and retention or after prostate/genital surgical procedures. (4,16) Giving the intended purpose, the suitable type of urinary catheter must be selected (Figure 3).

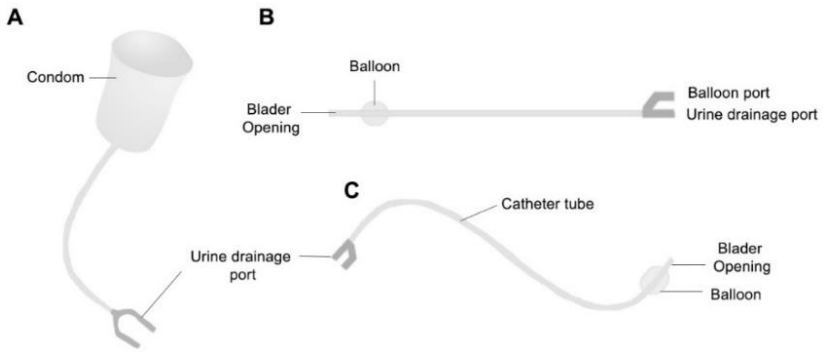

Figure 3 Types of urinary catheters. (A) Used in masculine catheterization for ~1 week (B) Intermittent or short-term catheterization (C) Foley or long-term use catheter.

It is recognised that the material´s properties and the device´s shape can influence biofilm formation. (1,3,17) The most commonly used urinary catheter materials include latex rubber, silicone, polyvinyl chloride (PVC), Teflon® and polyurethane. Due to its biocompatibility, good chemical and thermal stability, low surface tension and long lifetime before encrustation and occlusion, silicone has emerged as the material of choice in recent years. It has also been observed a superior bacterial adherence in latex compared to silicone and in PVC comparing with Teflon®. (16,18,19) Table 2 summarizes the characteristics of some base materials frequently used in urinary catheters production.

A common problem is related to the use of long-term urinary catheters which can experience encrustation due to the presence of crystalline components in biofilm – struvite and apatite - connected to a large number of urease-positive bacilli. Urea in the residual bladder hydrolyses urine into ammonia causing a rise in pH, aggregation of crystalline magnesium and calcium phosphates, blocking the urine flow through the catheter and inducing bladder and urethral epithelia trauma.(4,14)

Table 2: Frequently used base materials to produce urinary catheters. (16,20)

Latex rubber	Good flexibility but uncomfortable due to high surface friction; Low cost Leads to infection and rapid encrustation; Causes allergic reactions Restricted to short-term catheterization.
Silicone 100% silicone, uncoated, with a large lumen	Hypoallergenic; Reduced and delayed encrustation; Good chemical a thermal stability; Preferable to other materials in long-term catheterization
PTFE (polytetrafluoroethylene) or Teflon®	Reduced absorption of water; Fair biocompatibility; Low surface tension and flexibility; Smoother than simple latex therefore less encrustation
Silicone-coated	Latex catheters coated with silicone inside and out; Strength and flexibility of latex; Reduced encrustation like 100% silicone catheters
Hydrogel-coated	Soft and very biocompatible; Hydrophilic; Good absorption of fluid

3.2 Intravascular catheters

Intravascular catheters allow supplying nutritional solutions or medication, hemodynamic monitoring and the access in dialysis. (5,14) The design differs according to the use and duration (Figure 4), varying between short-term (3-10 days) and long-term (months or years) with a higher risk of infection each day the catheter is in place.(18,21) Due to its compatibility with the majority of drugs and low infection rates, polyurethane is the favourite material for vascular catheters. Silicone is also used but can suffer rupture more easily and be damaged by some solutions.(18)

When inserted, intravascular catheters will be coated with host-derived elements such as fibrin, fibrinogen, collagen, albumin and coagulation factors within 24 hours, promoting leukocyte adherence and platelets attraction. Bacteria can bind to attached proteins which can lead to thrombotic occlusion, bloodstream infection and further complications. (6)

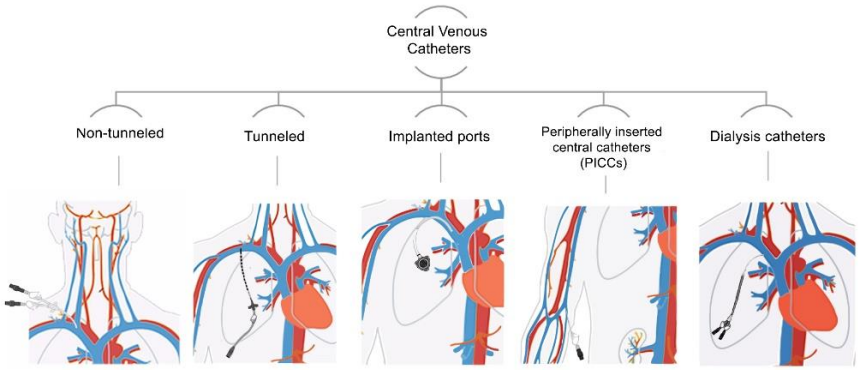

Figure 4 Types of Central Venous Catheters

4 Release-based antimicrobial strategies

Catheters with bactericidal properties can be obtained by coating the surface with an eluting antimicrobial agent which will be actively released over time, killing the microorganisms or restricting their growth on the surface or near by the device. (22,23) The released compounds usually originate an outer inhibition zone and an inner bactericidal zone. (24)

The easiest method of loading the agent includes impregnation of the bulk material with the bactericidal agent that will diffuse out after exposed to body fluids. This incorporation can be performed during the material preparation stage or by its dissolution in a solvent where the antimicrobial agent is added with subsequent evaporation of the solvent. (6) Local release provides delivering high doses at the potential site of infection, thus reducing the antibiotic resistance caused by exposure to low concentrations of antimicrobial agents. On the other side, the action of these surfaces is only temporary, showing a gradually decrease of the released compound to sub-inhibitory concentrations. (11,25,26) Ideally, the surface should offer a fast initial release to kill the bacteria nearby preventing the biofilm formation and maintain a slow and prolonged release during all the treatment. (27)

A list of catheters based on release strategies have been approved and commercialized, such as silver or antibiotic-coated, as observed in Table 3. However, strategies with novel antimicrobial agents are also being investigated and some of those research studies are described below and summarized in Table 6 and Table 7.

Table 3 Commercially available urinary and vascular catheters

Catheter type	Treatment	Ref.
Urinary	Nitrofurazone impregnation Silver alloy coating	(16) (28)
Vascular	Silver impregnation Minocycline-rifampicin impregnation Chlorhexidine silver-sulfadiazine coating Rifampicin-miconazole impregnation	(29) (30) (30) (31)

4.1 Silver

In the early 1860s, the first infection resistant biomaterials suggested were noble metals such as silver, gold and platinum due to their good compatibility with human tissues. (11) Since silver presents the highest toxicity for a broad spectrum of microorganisms and the least for animal cells, silver alloy coatings for urinary catheters have been approved. (14,23)

The bactericidal mechanism of silver is not yet completely understood. (32) It is known that silver ions released from silver-containing surfaces bind to sulfhydryl or thiol groups on bacteria's membranes, modifying their permeability and causing cell death. The inhibition of bacterial replication has also been described, once silver ions react with the negatively charged groups in the cellular proteins and DNA, leading to denaturation, and inducing hydroxyl radical formation. Another route that has been reported is the blockage of the respiratory chain of bacteria. (23,33) Due to the numerous antimicrobial mechanisms, the development of resistance to silver is less expectable. (33)

Silver-alloy coated catheters are available for urological use. This type of coating combines a layer of silver alloy with a hydrogel applied in the latex or silicone surface. (20,28) Despite their popularity, silver-alloy coatings have been found to present less microbial efficacy compared to antibiotics and no significant difference regarding to CAUTI development compared to silicone coated catheters, as reported by Jahn *et al*. (2012). (16,34)

Several reports indicate the lack of efficacy of this coating in reducing the incidence of CAUTI, however Aljohi *et al.* (2016) conducted a comparative study between the antimicrobial activities of noble metal alloy coated catheters and conventional siliconized latex Foley catheters and verified a 90% relative reduction of the CAUTI rate in the first group. (35,36) Table 4 and Table 5 summarize some efficacy studies with different types of urinary and vascular catheters, respectively.

Regarding to vascular catheters, Chen *et al.* (2014) led a meta-analysis for comparison of standard and silver-impregnated CVCs. The authors described no significant difference in bacterial colonization and incidence of catheter-related bloodstream infections (CRBSI) between both groups of devices. (29)

Nowadays, numerous strategies based on silver nanoparticles (AgNPs) are being studied since they show a high antimicrobial and antibiofilm potential. (37) (Table 7) This AgNPs can be produced by reduction of silver salts, such as silver nitrate, using a reducing agent or photoreduction with UV light. (23) Pollini *et al.* (2009) treated polyurethane catheters with a

photochemical deposition of AgNPs, obtaining a quite uniform distribution in both inner and outer surfaces, which were capable of inhibiting *E. coli* growth. Gram-negative bacteria are more susceptible to AgNPs than Gram-positive microorganisms. (38) Biogenic synthesis of AgNPs and cost effective methods are also being explored. Radhakrishnan *et al.* (2017) suggested microbial and phytofabrication of AgNPs using *Bacillus amyloliquifaciens* and *Curcuma aromatica* respectively, with very favourable results. Comparing to uncoated CVCs, coating with the synthesized microbial AgNPs (MAgNPs) showed 94,8% of *S. aureus* inhibition and 92,2% with phytosynthesized AgNPs (CAgNPs). (37)

Some assays demonstrated that the biocidal activity of AgNPs and their interaction with the biological system is influenced by characteristics as size, shape, surface charge and aggregation status. Thus a smaller size of nanoparticles facilitates the release of silver ions and causes superior oxidative stress in microbial cells, with consequently higher antibacterial activity. (33,38,39) However, the toxicity of AgNPs in hepatocytes, neuro-endocrine and germ-line cells, has also been reported for concentrations of 5-100 μg/mL, causing reduction of mitochondrial function, oxidative cellular damage, modifications in cell morphology and stimulation or suppression of pro-inflammatory factors production. (11,38)

Although the lack of information regarding to experimental studies in animal models and clinical trials and the unclear cytotoxicity, silver-based strategies continue to be the most popular preventing catheter-related infections. (33)

Table 4 Efficacy studies with approved Urinary Catheters

	Strategy	Study methodology	Results	Conclusions	Ref.
In patients	Silver alloy and hydrogel-coating vs. latex	1-year prospective study comparing the incidence of CAUTI between patients with a conventional latex Foley catheter and patients with a silver alloy and hydrogel-coated catheter.	31% reduction in the incidence of CAUTI per 1000 catheter-days in the silver-coated group, with *E. coli* as the most commonly involved agent (36.7%).	The protective effect of silver-coating was more evident in long-term catheterization and female patients.	(28)
	Noble metal alloy coating vs. siliconized latex	Single-blinded, randomized, prospective study of CAUTI-reducing efficacy in patients with catheters coated with a thin noble metal alloy of gold, silver and palladium compared to conventional siliconized latex Foley catheters.	90% relative reduction of the CAUTI rate in the noble metal alloy catheter group.	Data from this study confirmed that the coating is not toxic.	(36)
In vitro	Nitrofurazone vs. standard silicone	Incubation of Nitrofurazone impregnated and standard silicone catheters with strains obtained from the urine of a patient with CAUTI.	Adherence of *E. coli* and *E. faecalis* decreased using nitrofurazone catheters compared to silicone catheters.	Nitrofurazone impregnation showed a significant effect on bacterial adherence for the first 5 days.	(40)
	Silver alloy vs. Nitrofurazone vs. Nitric Oxide coatings	Silver alloy-coated, nitrofurazone-coated and nitric oxide-coated catheters tested against to an uncoated group for their antiseptic activity.	Equivalent antimicrobial activity for nitrofurazone- and NO-coated catheters and were capable of eradicating all bacteria. Silver-coating had no effect on *E. coli* growth compared with the control group.	Silver-coated catheters were not found to be effective.	(41)
	Minocycline-rifampicin impregnated	Silicone surfaces coated with pure silicone and impregnated with minocycline-rifampicin exposed to contaminated urine in an in vitro urinary model for 72 hrs.	Reported reproduction of *E. coli* and *P. aeruginosa*, but not of *Proteus mirabilis.*	The inhibition zones observed in the cell culture studies were not enough to prove antimicrobial efficacy against *E. coli* and *P. aeruginosa.*	(42)

Table 5 Efficacy studies with approved Vascular Catheters

	Strategy	Study methodology	Results	Conclusions	Ref.
In patients	Silver-impregnation vs. standard	Meta-analysis with 12 comparative studies enrolling: 1440 patients receiving a standard CVC; 1414 receiving a silver-impregnated CVC.	No significant difference in bacterial colonization between silver-impregnated and standard CVC was described in 10 studies. 9 studies indicated no significant difference in the risk of CRBSI between both types of catheters.	Silver-impregnated CVCs do not reduce the incidence of CRBSI and bacterial colonization compared to standard CVCs.	(29)
In patients	Chlorhexidine-silver sulfadiazine vs. standard	Systematic review of 18 controlled studies comparing both types of catheters.	Showed weak association between CSS-CVCs and reduced CRBSI. Still, CSS treatment reduced the risk of catheter colonization.	No statistically significant benefits of using this type of antiseptic catheter.	(43)
In patients	Chlorhexidine-silver sulfadiazine vs. Minocycline-Rifampicin	Placement of second generation CSS-CVCs in the pre-intervention group and Minocycline-Rifampicin CVCs in the post-intervention group.	Gram-positive bacteria predominated in both groups, including *Staphylococcus sp*. and *Enterococcus sp.*	Using Minocycline-Rifampicin coated catheters in patients requiring CVC insertion significantly decreased infection rates comparing to CSS-impregnated catheters.	(30)
In vitro		Comparing the weight% of Ag and in vitro culture test (*S. aureus*) in 90 CVC, using a bloodstream model: 2-lumen radiopaque polyurethane CVCs; 2-lumen CSS-CVCs; Minocycline/rifampicin-impregnated double-lumen polyurethane catheters.	Confirmed the decrease in Ag on the surface over time, with a CSS-CVSs' antibacterial function lost after 48 hours. Antibiotic-impregnated CVCs may be a better option when indwelling upper to 48 hours is needed.	CSS-CVCs may be safely used in veins for 48 hours.	(44)
In patients	5-Fluorouracil vs. Chlorhexidine-silver sulfadiazine	Group of patients randomized to 5-FU-CVC and other group to CSS-CVC.	The colonization rates were 2,9% in 5-FU catheters and 5,3% in the CSS-group. The CRBSI rates were 1,4% in the 5-FU group and 0,9% for CSS-CVCs.	5-FU-CVCs are equivalent to CSS-CVCs regarding to its ability in preventing microbial colonization.	(45)

4.2 Antibiotics

Antibiotics can be entrapped into the surface of catheters by two different methods. In the first strategy, a layer of antibiotic can be applied covering the surface, with a consequently fast elution of the drug. On the other side, the antibiotic can be impregnated directly into the device polymer during its production with or without inclusion of excipients capable of retard or accelerate the drug release rate. Additionally, to accomplish superior solubility, anionic derivatives of antibiotics are synthetically created and the anionic charges bind them electrostatically to the surface. (27,46)

In the field of urinary devices, nitrofurazone impregnated Foley catheters have been approved and used, despite being uncomfortable for the patient. (16) Nitrofurazone impregnation showed a significant effect on *E. coli* adherence in the first 5 days when compared to untreated silicone catheters and a superior antimicrobial activity than silver-alloy coatings. (40,41) However, due to reports of nitrofurazone enhancing cell proliferation and leading to mammary and ovarian tumours in animals, its investigation and preference as a choice has decreased over the years. (16,47)

In the last two decades, CVCs impregnated with the conjugation of minocycline and rifampicin have been widely used due to their additive properties. These compounds act in different targets: (a) Minocycline is bacteriostatic, inhibiting bacterial protein synthesis by association with the 30S ribosomal subunit; (b) Rifampicin, also bacteriostatic, stops the bacterial RNA synthesis by interacting with RNA polymerase. (42,48) Both antibiotics are very powerful against Gram-positive and some Gram-negative pathogens (*Acinetobacter* species), but they are not potent against fungi. (48) It was demonstrated that using minocycline-rifampicin-coated catheters is more effective in decreasing the infection rates than other conjugation of antibiotics and antiseptics, such as chlorhexidine-silver sulfadiazine (CSS), as reported by Bonne *et al*. (2015). (30) However, despite the inhibition zones observed in *in vitro* studies, the reproduction of *E. coli* and *P. aeruginosa* cells is still observed in silicone surfaces impregnated with minocycline-rifampicin when exposed to contaminated urine. (42)

The incidence of catheter-related bloodstream infections (CRBSI) can also be reduced by placing the commercialized CSS or rifampicin-miconazole impregnated catheters. The first CSS-CVCs created were impregnated only in the external surface. Later, the second generation CSS-CVCs were treated in both external and internal surfaces, performing a reduction of

CRBSI and lower costs compared to standard catheters. (49) Sulfadiazine is a sulfonamide antibiotic that stops the folate pathway and DNA synthesis in bacteria, by being a structural analog of para-aminobenzoic acid (PABA) and inhibiting competitively its conversion. The combination of these three compounds provides a broad-spectrum of antimicrobial activity and according to a Cochrane's review, impregnated CSS-CVCs were also more effective than silver impregnation reducing bacterial colonization. (48,50,51) Conversely, Gilbert *et al.* (2008) found no evidence of significant benefits of using antiseptic CVCs, coated with CSS or silver impregnated, comparing with conventional catheters. (43) Although rare, some cases of anaphylactic reaction have also been reported. (52)

Rifampicin-miconazole impregnated CVCs are also a possible cost-effective alternative reducing the incidence of CRBSI and catheter related cost per day. (31,53) Miconazole is an antifungal agent with a fungistatic function by inhibition of ergosterol synthesis in the fungal cell membranes. (48) When rifampicin-miconazole CVCs were firstly proposed, Schierholz *et al.* (2000) concluded a superior activity against *Candida* spp, Gram-positive (*Staphylococcus* spp, *Enterococcus faecalis)* and Gram-negative organisms *(P. aeruginosa, E. coli* and *Enterobacter* spp.) compared with CSS-treated devices. The drug delivery exceeded 21 days in a nearly constant rate for both antibiotics. (54)

Regarding to research studies, Kowalczuk *et al.* (2012) treated heparin-coated silicone latex catheters with Sparfloxacin obtaining promising results. The immobilization process included oxidation with sodium periodate and linkage of sparfloxacin in an organic medium. The final catheters showed to be nontoxic and capable of reducing bacterial growth. (55)

Norfloxacin and gentamicin have also been under research towards the prevention of CAUTIs, with favourable potential, whereas some antibiotics including aminoglycosides, fosfomycin and ciprofloxacin have been pointed to be incompatible with polyurethane. (54,56,57)

Several conjugations of antibiotics have been evaluated to achieve synergic mechanisms with lower risk of creating resistance. *Pseudomonas* spp. show a high intrinsically resistance to many classes of antimicrobial compounds but Saini *et al.* (2015) combined azithromycin and ciprofloxacin and found it to be effective against *P. aeruginosa* biofilm cells with a 92% decrease compared with the control. (58,59) Combinations with antiseptics, such as triclosan, are also being studied too, in order to reduce infection and complications in long-term urinary catheterization. (60) (Table 6)

Antibiotic-impregnated catheters are a good alternative to Ag-alloy coatings and their potential toxicity. However, they can be the trigger for antimicrobial resistance and do not work in resistant mutants. Additionally, limited concentrations and types of antibiotics can be loaded, which restrains the antimicrobial spectrum. (61) Still, the existing guidelines for CRBSI prevention recommend the use of a CSS or a minocycline-rifampicin impregnated catheter in patients with catheterization upper to 5 days, with no data for pediatric patients. (49,62)

4.3 Chlorhexidine

Chlorhexidine (CHX) is a topical antimicrobial agent commonly used for wound irrigation, cutaneous disinfection and prevention of oral biofilm, and it has been recently studied as a coating for urinary catheters. (44,63) Since this compound is positively charged, it shows affinity to the negatively charged bacterial cell surface, causing the disruption of the cell membrane and leakage of intracellular constituents. Thus, this mechanism of action reduces the development of bactericidal resistance. (16)

The application of CHX to CVCs by impregnation with antibiotics, as mentioned in section 4.2, has been introduced and commercialized since the late 1980s. However, according to Choi YJ *et al.* (2017) there is still a decrease of silver concentration on the surface over time with an antibacterial function lost after 48 hours. This author also supports using minocycline-rifampicin impregnated CVCs instead when indwelling is upper to two days. (51)

CHX has been mostly studied as nanoparticles. (16) (Table 6) Phuengkham *et al.* (2015) spray-coated silicone surfaces with CHX-loaded nanospheres, verifing their capability of reducing the initial attachment of bacteria under urinary conditions and mantaining a sustained release and antimicrobial activity for two weeks. (64)

As gold presents low toxicity against human cells, Ahmed *et al*. (2016) tested the nanoconjugation between gold and CHX by mixing solutions. The results showed that this approach can provide both antibacterial and antibiofilm activity in a dose-dependent way. (65) The antimicrobial activity of some gold nanoparticle-based agents against resistant bacteria including MRSA, *E. coli*, *P. aeruginosa* and others has already been described by some authors. (33)

Besides nanotechnology strategies, CHX can also be embedded on bulk polymers with subsequent controlled release. Gaonkar *et al.* (2007) found a sinergic effect using the

impregnation of silicone Foley catheters with CHX and Triclosan with a prolonged efficacy against numerous uropathogens including *P. mirabilis.* As this method prevented colonization for 20-30 days (66) it could be a favourable strategy for long-term catheterization.

Many combinations are being studied in order to find a superior antimicrobial and antibiofilm activities. For example, a chlorhexidine and protamine sulphate coating provided a significant inhibition of biofilm formation due to *E. coli*, *P. aeruginosa* and *S. epidermidis* compared to silver-hydrogel coated and uncoated catheters, as showed by Darouiche *et al.* (2008). The procedure consisted of immersing silicone bladder catheters in a solution containing both compounds. (67)

Several authors defend that chlorhexidine used single is perhaps not a recommendable choice for preventing CAUTIs due to its limited activity against *P. mirabilis* (14) therefore this approach still remains controversial.

4.4 Triclosan

The antimicrobial activity of this compound is recognised for almost 50 years and it has been extensively used since it has a low potential for allergic reactions. Its bacteriostatic effect acts by inhibition of enoyl-acyl carrier protein reductase enzyme (necessary for fatty acid synthesis) and by disrupting bacterial membranes. (68,69) The ability for killing microorganisms protected by crystalline biofilm has also been reported, revealing the potential of using triclosan when encrustation has occurred. (70) At low concentrations, the broad-spectrum activity of triclosan includes Gram positive and Gram negative bacteria, several virus and fungus, without evidence of causing bacterial resistance in humans. (68) Jones *et al.* (2006) have previously shown catheters with balloons inflated with triclosan resisted to encrustation for 48 hours and only little crystalline biofilm was seen in 7 days, compared to 24h from the control catheters. (71)

Due to being very soluble in organic solvents, the coating process can be achieved by dip and evaporation. (68) Fisher *et al*. (2015) developed Foley impregnated catheters by immersion in a solution with chloroform, (w/v) 1% triclosan, 1% sparfloxacin and 0.2% rifampicin. After, the devices were rinsed in absolute ethanol and dried overnight to finish the evaporation. The results of this combination were encouraging, showing capability to prevent colonization by *Proteus mirabilis, S. aureus* and *E. coli* for 7 to 12 weeks and a 30% and 20% release of the initial triclosan and sparfloxacin, respectively, after 28 days. The authors propose that this

combination could reduce infection and complications in long-term urinary catheterization, as previously mentioned. (60)

Low Density Polyethylene (LDPE) is also compatible with triclosan as proved by Thomé *et al.* (2012). The researchers produced urinary catheters adding crescent amounts of triclosan to LDPE and found an increasing antimicrobial activity with increased triclosan concentrations. (72)

In an attempt to diminish the occurrence of encrustation caused by *Proteus mirabilis*, triclosan-loaded waterbone polyurethane (WBPU) samples were developed. Triclosan was dissolved with acetone and the mixture was added to the prepolymer emulsifying solution, obtaining samples with a superior antimicrobial activity against *Proteus mirabilis*. The inhibition zones were formed in a dose-response manner and happened a reduction of the artificial urine pH, decreasing the catheters encrustation. (70)

The combination of Dispersin B (DspB), a glycoside hydrolase, and triclosan has also revealed antimicrobial activity in a rabbit model, significantly reducing vascular catheters colonization by *S. aureus*, *S. epidermidis*, *E. coli* and *C. albicans*. DspB is capable of dispersing biofilm formation by causing a polysaccharide depolymerisation implicated in the process. (73) Darouiche *et al*. (2009) tested the *in vivo* efficacy of triclosan + DspB-coated CVCs and obtained an antimicrobial activity for > 8 days with a presumably slow release mechanism. (73)

Still in the field of new CVC coatings, a combination of xylitol, triclosan and polyhexamethylene biguanide (PHMB) has been proposed. (Table 7) Xylitol is a polyalcohol with anti-adhesive effects against some microorganisms and PHMB interacts with membrane phospholipids and modifies its integrity in Gram-negative bacteria. *In vitro*, this formulation revealed antimicrobial activity against *C. albicans*, *K. pneumoniae*, *S. aureus*, *P. aeruginosa* and *E. coli*, and a significant reduction in bacterial adherence. Additionally, *in vivo* studies in rats showed no episodes of bloodstream infection, indicating a good biocompatibility for this catheter material. (74)

Despite of its main use as a liquid filled into the retention balloon of urinary catheters, the results of impregnation and coating seem favourable too. Nevertheless, these approaches remain in discussion due to reports of triclosan causing hormonal deregulation in some animal studies. (16)

4.5 Nitric Oxide

Nitric Oxide (NO) is a gas molecule naturally involved in cellular pathways, vascular modulation, homeostasis and immune function. (75) Besides its role as a vasodilator, NO also exhibits antithrombotic and antimicrobial properties. Its bactericidal effect involves crossing the bacterial membranes and nitrosation of DNA, proteins and lipids, or when in combination with oxygen reactive species the oxidation of the same components. (23) Due to its studied compatibility with silicone rubber and polyurethanes, NO releasing approaches applied to catheters are being widely searched. (76,77)

Margel *et al*. (2017) charged urinary catheters with NO by exposure in a camber filled with a gaseous NO-containing environment and reduced pressure. With a released concentration of between 1.75-2.8 ppm per catheter after 24 hours, the attachment and colonization of *P. aeruginosa*, *E. coli* and *C. albicans* were prevented. (Table 6) Through this methodology, the authors achieved a NO release from urinary catheters for 14 days, with no significant physiological, haematological and biochemical alterations in the clinical studies. (78)

Given the high reactivity of the NO molecule, assuring a controlled delivery when using the gas in its natural form is very difficult. To fight this issue, NO donor molecules have been studied and used covalently attached to the surface or noncovalently integrated within polymers. (76,77) Diazeniumdiolates (NONOates), *S*-nitrosothiols (RSNOs), metal nitosyl compounds and other nitrogen oxides have emerged as NO donor molecules and have been used for controlled delivery. (77) Their high stability and aptitude to release NO under physiological conditions with no required enzymes, make NONOates and RSNOs promising candidates. (79)

Brisbois *et al.* (2016) fabricated a NO-releasing polyurethane CVC with both NONOate dibutylhexanediamine (DBHD) and poly(lactic-co-glycolic acid) (PLGA) additives, showing a 95% reduction in bacterial adhesion. (Table 7) The catheters were prepared by dip coating polymer solutions and dried. *In vitro* and *in vivo* assays presented good biocompatibility with no evidence of causing cell lysis or toxicity in 48 hours. (80)

S-nitroso-*N*-acetylpenicillamine (SNAP) is a promising RSNO molecule with the ability of releasing NO upper to 3 weeks. (77) Recently, Wo *et al*. (2017) reported a solvent SNAP impregnation technique into a polyurethane polymer, obtaining a controlled release for at least 14 days and a significant reduction of *S. epidermidis* and *P. aeruginosa* biofilms. (81) Colletta

et al. (2015) have already described a SNAP impregnation procedure applied to silicone Foley catheters with a long-term NO release for 30 days. In their method, SNAP was firstly dissolved in tetrahydrofuran (THF), an organic solvent, and the catheters were completely immersed into this solution for 24 hours. After the swelling and impregnation process, the devices dried for 72 hours to remove the residual solvent by evaporation. (82)

Since Methicillin-resistant *S. aureus* (MRSA) causes 7.4% of the central line-associated bloodstream infections, a sustained NO-releasing based on nanoparticles (NO-np) to treat CVCs is being developed and evaluated against this pathogen. Briefly, the process includes a redox reaction of sodium nitrite with NO production and a drying phase with a lyophilizer to form a fine powder containing NO-np. The results show a bacterial growth decrease of 40% and 50% when treated with 2-5 mg/mL and $\geq$ 5 mg/mL of NO-np, respectively. Mihu *et al.* (2017) also agree that nanoparticles present a good stability and minimal cytotoxicity, enlightening this approach as an alternative to the potential cytotoxicity by diazeniumdiolates already reported. (75,79)

NO-coated catheters were found to have an equivalent antimicrobial activity compared with nitrofurazone coated catheters and more effectiveness than Ag-alloy coatings. (41) The positive data provides NO a favourable role inducing biofilm dispersal, however several reports indicated some adverse effects of NO such as inhibition of platelet aggregation, reduction in blood pressure, priapism, skin edema and erythema. (78)

4.6 5-Fluorouracil

The antimetabolite 5-Fluorouracil (5-FU) is frequently used as a cancer chemotherapy agent since it interferes with thymidine synthesis, inhibiting the production of DNA. Thymine deficiency on growing bacteria inhibiting their multiplication has been reported but the antimicrobial effects of 5-FU are not completely understood. Still, this compound is capable of inhibiting the growth of Gram-positive and Gram-negative bacteria and *Candida* species. (45,48,83)

Avelar *et al*. (2010) developed a coated CVC with a polymer containing 1 mg of 5-FU in order to achieve the slowly release of the compound. After day 28, 90% of the loaded 5-FU dose was released from the device, with a portion entering the systemic circulation and being excreted untouched in urine, while other suffers metabolism to inactive compounds in the liver. (83) The preclinical testing showed a greater antimicrobial activity against *S. epidermidis* and

S. aureus comparing with CSS-CVCs and lower biofilm densities. Later, based on this findings Walz and co-workers (2010) conducted a clinical trial comparing the activity of 5-FU externally coated CVCs with CSS-treated catheters and the obtained data showed no toxicity and equivalent ability to prevent microbial colonization, being a safe and effective alternative when used in critically ill patients.

Given the no existent reports regarding bacterial or fungal resistance and no evidence of tissue toxicity, 5-FU remains an alternative to create anti-infective coatings to CVCs and other implantable medical devices. (45,83)

5 Contact-based antimicrobial strategies

A different antimicrobial strategy for biofilm prevention can be the use of non-eluting surfaces counteracting bacterial attachment and killing the bacterial cells on contact with the advantage of showing a longer antimicrobial durability and less toxicity. The major drawback is that, this kind of bioactive surface can suffer inactivation when coated with proteins from the physiological fluids. (23,48) Antimicrobial agents – mainly cationic molecules or enzymes - are bind covalently to the surface by hydrophobic polymeric chains and have demonstrated a mechanism of contact killing based on membrane interactions. (25)

Comparing with release-based strategies, contact-based surfaces can prolong their antimicrobial action without interfering with the host immune responses since the cationic functional groups are stable on the surfaces. In addition, these compounds show a good compatibility with the loading materials and are unlikely to cause bacterial resistance due to their action mechanisms. (84,85) Conversely, to kill the bacteria is necessary that they reach the surface closely. (86)

5.1 Cationic compounds

5.1.1 Quaternary ammonium compounds

Quaternary ammonium compounds (QACs) have emerged as one of the most promising alternative approaches through incorporation into polymers. QACs are positively charged molecules with a central nitrogen atom covalently linked to four alkyl groups (87) and some reports show a directly proportional relation between the efficacy of these cationic polymers and the length of the alkyl chain. (88) Despite not being completely understood, their mechanism of action seems to be associated with the disruption of the cell membrane, cellular lysis and modification of cell surface charges. In viruses, QACs act by disruption of the envelope with the nucleocapsid release. (84) Cytotoxicity can be caused through the same pathways but does not seem to be significant. (86,89)

The antibacterial, antifungal and antiviral non-leaching surface can be designed using several grafting techniques, remaining permanently biocidal. (90) The grafting process can either include direct immobilization of molecules on the surface or polymerization reactions to increase the polymer’s density. (84)

Since the discovery of benzalkonium chloride's (BZK) bactericidal properties in 1935, several quaternary ammonium salts have been investigated. (91) Some CVCs impregnated with BZK alone or heparin-bonded have been commercially available but the lack of clinical trials on their effectiveness is noticeable (92) In 2000, Moss *et al.* conducted a controlled randomized study, obtaining a significantly reduction of colonization in BZK-CVC catheters when comparing with polyurethane non-treated catheters. (93) Later in 2001, a study of Jaeger and colleagues, evaluated the efficacy of BZK impregnated CVC in preventing catheter-related infections in patients undergoing chemotherapy. Nevertheless, the obtained data demonstrated no significant benefit of using BZK treated devices in patients with a high risk of infectious complications. (94) Given the controversial information and some reports of severe allergic reactions, the use of BZK eluting catheters is not very well supported today. (48,95)

Despite the limited number of published articles describing QAC-based strategies specifically applied to catheters, numerous studies have been described on polyurethane or silicone surfaces given the easy synthesis and low cost of QACs (96). Pant *et al*. (2017) thought of a new multi-defense strategy by combining the incorporation of SNAP as a NO donor in a CarboSil® polymeric composite with a benzophenone based quaternary ammonium molecule coating. The QAC's immobilization was achieved using spray coating with subsequently irradiation with UV light. This approach allowed to reduce adhered bacteria by 99,0% and 99.98% for *P. aeruginosa* and *S. aureus* respectively, demonstrating better results than using both strategies separately. Therefore, the authors believe this combination offers a new route to produce antimicrobial surfaces for many medical devices. (96)

Recently, some other innovative strategies have been published. Zanini *et al.* (2015) studied a novel plasma-based methodology for the development of quaternary ammonium silane (QAS) coatings for polyurethane catheters. (Table 6) The obtained results allowed to conclude a superior antimicrobial activity against *E. coli* (for the highest amount of QAS adsorbed on the surfaces). (97) On the other hand, Bakhshi *et al.* (2013) developed a bactericidal coating based on functionalization of soybean oil with quaternary ammonium salts and hydroxyl groups. Using this vegetable resource, the authors obtained an inexpensive biocompatible coated polyurethane and suggested its application in biomedical devices. (98)

Many *in vitro* studies already proved that immobilized QACs are excellent candidates in preventing bacterial infections. However, additional *in vivo* data is necessary to confirm the efficacy of these approaches applied to medical devices and specifically to catheters. (86)

5.1.2 Chitosan

Chitosan is a natural linear cationic polysaccharide with non-toxic, antitumoral, antibacterial and antifouling properties already described. (99) Although being widely used as drug carrier, chitosan is also being studied for contact-killing coatings. (25) While low-molecular-weight chitosan penetrates the bacterial cell walls and binds with DNA, high-molecular-weight chitosan apparently acts through electrostatic interactions between its positive charge and the negatively charged components on microbial membranes, changing cell permeability and transport into the cell. (88,99,100)

The potential of chitosan to reduce the adhesion and re-growth of Gram negative uropathogens on urinary Foley catheters was well demonstrated by Campana *et al.* (2017), encouraging its application to prevent catheters-associated infections. The authors found a reduction in *K. pneumoniae* and *E. coli*'s viability and an increasing antimicrobial activity of chitosan solutions with lower molecular weight and pH values of the medium. (101)

Chitosan should also be considered on central venous catheters for preventing fungal biofilms. Catheters-related infections due to *Candida* spp. present a high mortality rate and chitosan seems to be a candidate as therapeutic agent not only against bacteria but also fungi. Martinez *et al.* (2010) incubated polyethylene CVCs with 5 mg/mL chitosan for 1h at room temperature and subsequently, the treated catheters were inserted in rats. The *in vivo* data allowed to conclude that chitosan-coated catheters are capable of inhibiting *C. albicans* biofilm formation. Moreover, the authors also mentioned that the modification of fungal cellular membranes charge can either lead to a superior killing rate of these cells by macrophages. (102)

Besides the application of chitosan in polyethylene-based devices, studies regarding polyurethane surfaces have also been published. Kara *et al.* (2015) combined the antimicrobial properties of chitosan with the anti-adhesive skills from heparin to modify synthesized polyurethanes. (Table 7) Due to being negatively charged, heparin is capable of repelling bacteria and thus, preventing biofilm formation. Briefly, the immobilization process involved immersion of PU samples in chitosan solutions and the obtained results showed an antimicrobial activity not affected by the chitosan concentration used. (100)

On the other hand, chitosan is also able to bind anionic antibiotic molecules such as rifampicin to form a system capable of slowly release of the linked drugs with high efficiency. (23,88) Lv *et al*. (2013) immobilized chitosan onto the surface of polyurethane samples by immersion in chitosan aqueous solutions, in order to create a drug delivery system to achieve a

long-term antimicrobial effect. The following drug binding process also included immersion of the chitosan-polyurethane samples in saturated rifampicin aqueous solutions, resulting in a proved strong absorption of the antibiotic. The study showed 82% release of the antibiotic after 30 days and a long antimicrobial activity against *S. epidermidis*, *S. aureus* and *E. coli.* The authors emphaticize the need of further studies to clearly evaluate the potential of the chitosan-immobilized PUs in biomedical applications including catheters and other medical devices. (103)

Since its discovery in 1859, chitosan has been the most explored polymer in biomedical sciences. (104) All these numerous findings undoubtedly support that chitosan might be used for designing coatings to protect medical devices including catheters, but further specific *in vitro* and *in vivo* studies are still necessary.

5.1.3 Antimicrobial peptides

Antimicrobial peptides (AMPs) are short peptides with 15-50 amino acid residues that can be found in many prokaryotic and eukaryotic organisms as host defence natural molecules involved in the innate immune response. Given their ability for killing microorganisms by disrupting their anionic membranes, antimicrobial coatings based on AMPs hold promise preventing catheters-related infections with demonstrated biocompatibility and broad-spectrum activity against several bacterial species, including those with resistance to antibiotics, viruses, parasites and fungi. (105–107) Besides membrane disruption, other reported antimicrobial mechanisms of AMPs include disturbance of DNA, RNA or protein synthesis when translocated through the membrane. (108)

Analyses of the already known AMPs indicate that nearly 90% are cationic. (109) Narayana *et al.* (2015) proposed a peptide classification based on amino acid composition, dividing AMPs into linear, cysteine-rich or rich in specific amino acids like glycine, arginine, histidine or proline.

AMPs can either be directly grafted to surfaces, with higher concentration and superior effectiveness, or conjugated through polymer brushes. (107) Yu *et al.* (2017) developed an antimicrobial coating combining the use of AMPs with an anti-adhesive polymer brush coating on polyurethane catheters and demonstrated an excellent antimicrobial activity against *P. aeruginosa* and *S. aureus.* (Table 6) Assuming these positive outcomes, AMP-immobilized catheters with further developments could prevent the incidence of CAUTIs. (105)

To act as strong coating agents, AMPs must maintain the antimicrobial activity, salt resistance when tethered and biocompatibility. As several natural AMPs do not preserve these characteristics, synthetic peptides with the desired properties are being developed. (110) Based on this impression, Lim *et al.* (2013) produced an arginine- and tryptophan-rich peptide using silicone-based surfaces as immobilization platforms. The peptide was crosslinked to the polyethylene glycol (PEG) spacer used in the surface functionalization procedure conducted earlier. Given the promising results, in 2015 the authors suggested the novel AMP plus polydopamine (PD) to coat Foley catheters. (Table 6) Dopamine molecules are capable of forming a layer on a variety of surfaces via dip-coating and then can be covalently linked to several functional groups such as amines. After the surface activation step with PD, the grafting of AMP onto the modified polymer surface was performed by immersion and the results showed bactericidal effect against *S. aureus*, *P. aeruginosa* and *E. coli*. The authors affirm the potential of this new technique due to being economical advantageous and biocompatible. (111)

AMPs have arisen as attractive compounds because resistance mechanisms to these compounds are limited given the diversity of peptide sequences and their multiple targets. As the majority of AMPs undergoing clinical trials has been developed for topical purposes, additional studies in relevant *in vivo* models to evaluate the efficacy of AMP-based coatings on materials commonly used in catheters are still essential. (105,112)

5.2 Enzymes

The use of enzymes capable of destroying biofilms and preventing their initial attachment have been proposed as an alternative to antibiotics given their prolonged stability and antimicrobial effect against a broad-spectrum of microorganisms. Enzymes can be incorporated on surfaces either by reversible immobilization with subsequent release from the material or by irreversible immobilization that hardly detaches the enzyme. (113) They can be divided according to their mechanism of action: (a) hydrolytic enzymes, acting by degradation of bacterial structural components; (b) oxidative enzymes, leading to production of other antimicrobial substances; (c) and quorum quenching enzymes. (16)

Lysozyme is a natural component of the innate immune system and its application to medical devices has been widely investigated. It can be found in several human secretions such as saliva and tears and acts by catalysing the hydrolysis of the bond between N-acetylglucosamine and N-acetylmuramic acid, constituents of the peptidoglycan. (113,114) Guadarrama-Zempoalteca *et al*. (2016) produced functionalized PVC urinary catheters by immersion in a solution containing lysozyme after several activation steps. (Table 6) The covalent immobilization on copolymer brushes was successfully achieved and the final catheters showed a notable decrease in the amount of *S. aureus* adhered to their surfaces. On the other hand, Flores-Rojas *et al.* (2017) recently immobilized the same biologic enzyme on silicone surfaces conjugated with previously created brushes and the results showed that this methodology was similarly concluded with success. (115)

In addition to bactericidal enzymes, alternatives centred on Quorum Sensing (QS) pathways are also emerging. They focus on disturbing the communication between bacteria and desynchronizing their behaviour through the use of QS disrupting enzymes such as acylase. (116,117) Autoinducers (AIs) are small signalling molecules secreted by bacteria which activate specific receptors, consequently leading to biofilm formation. The most common AIs observed in Gram-negative and positive bacteria are acyl-homoserine lactones (AHLs) whose QS action can be interrupted by bond cleavage using acylase enzyme. (108) Ivanova *et al.* (2015) thought of acylase-based coatings for silicone urinary catheters using a layer-by-layer method. (Table 6) Although not acting by contact-kill, this enzyme successfully interrupts the QS pathways and strongly inhibits the initial attachment of *P. aeruginosa* compared to uncoated silicone. Further studies regarding the influence of artificial urine on enzymatic coatings are still required to confirm their role as CAUTI-preventing agents. (117)

Table 6 Research studies with potential application in Urinary Catheters

	Strategy	Methodology	Concentrations	Results	Biocompatibility	Ref.
Antibiotics	Sparfloxacin coating	Silicone latex catheters, firstly coated with heparin, were with Sparfloxacin (SPA) by two immobilization methods. Both included oxidation with sodium periodate and linkage of SPA in an organic medium.	The medium contained 1 mg SPA/mL	Lack of bacterial growth (*S. aureus*, *S. epidermidis* and *E. coli*) with SPA-treated catheters in the Mueller-Hinton (MH) broth medium and inhibition zones on the MH agar medium.	SPA-treated catheter showed nontoxic properties.	(55)
	Triclosan, sparfloxacin and rifampicin impregnation	The compounds were dissolved together in chloroform and the Foley catheters and silicone discs were immersed in the solution for 1h. After, they were rinsed in absolute ethanol and dried overnight.	Concentrations w/v of 0,2% rifampicin, 1% triclosan and 1% sparfloxacin in the solution used.	After 28 days, 30% of the initial triclosan and 20% of sparfloxacin had been released. Prevented colonization by *Proteus mirabilis, S. aureus* and *E. coli* for 7 to 12 weeks.	Not tested.	(60)
Chlorhexidine (CHX)	Chlorhexidine-loaded nanospheres	Preparation and optimization of chlorhexidine-loaded nanospheres (CHX-NPs) using high-pressure emulsification-solvent evaporation technique, with spray-coating on a silicone surface.	2 mg/mL CHX-NPs for 20 cycles of spray-coating. Initial burst release of CHX approximately 20 % in the first day. Amount of CHX released per day during 2 weeks: 3.35 ± 0.16 µg	CHX-NPs coated silicone tubes were capable of reducing initial attachment of bacteria under urinary environment. CHX-NPs coated substrates showed antibacterial activity against *S. aureus, S. epidermidis* and *E. coli* up to 15 days.	CHX-NPs coated substrates could provide the burst release at potentially non-cytotoxic levels of CHX followed by sustained release for the next 2 weeks.	(64)
	Gold nanoparticles conjugated with chlorhexidine	Preparation of the nanoconjugates of CHX by mixing CHX with $AuCl_4$ solution and stirring for 10 min. Addition of sodium borohydride to indicate the reduction and formation of colloidal gold. Further stirring and separation of the sediment.	5mL of 1mM CHX mixed with 5mL of 1 mM $AuCl_4$ solution. 30 µL of 5mM sodium borohydride added.	Au-CHX nanoparticles inhibited the isolates of *K. pneumoniae* at 112 µM concentration. At 100 µM concentration it significantly disrupted the biofilm of all isolates. Showed both antibacterial and antibiofilm effect in a dose-dependent manner	Gold nanoparticles show low toxicity towards human cells.	(65)
	Chlorhexidine and triclosan impregnation	Uncoated silicone Foley catheters impregnated with CHX and triclosan using a proprietary 2-step method.	Initial release of 607 µg/cm of CHX and 415 µg/cm of triclosan. Average release rates of 14,5 µg/day of CHX and 3,7 µg/day of triclosan.	Prevented colonization with *K. pneumoniae. E. aerogenes, P. mirabilis, MRSA*, vancomycin-resistant *E. faecium, E. faecalis, E. coli and C. albicans* for 20-30 days or longer. Uncoated catheters were colonized in 1-2 days.	Might not cause mucosal irritation or toxicity based on animal studies.	(66)
	Combination of chlorhexidine and protamine sulphate (PS)	Silicone bladder catheters coated with CHX + PS by dipping in a solution containing both compounds, with a final gas sterilization with ethylene oxide.	The immersion solution contained 400 mg/mL of CHX and 100 mg/mL of PS.	Significant inhibition of biofilm formation due to *E. coli*, *P. aeruginosa* and *S. epidermidis.* After soaking the catheter in sterile artificial urine medium for 1, 3, 5 and 7 days, CHX+PS coating prevented 80% of *E. coli* and *S. epidermidis* colonization.	Efficacy assays were performed in rabbit model.	(67)

Triclosan	Triclosan impregnation	Triclosan was dissolved with acetone and added to an emulsifying solution for its loading in waterborne polyurethanes (WBPU).	Catheter samples with 1, 0.1 and 0.001 mg triclosan	*Proteus mirabilis* growth was significantly inhibited as well as the artificial urine pH of the bladder model. Encrustation decreased.	The synthesis method of WBPU was proved non-toxic.	(70)
Nitric oxide	Nitric oxide (NO)	Urinary catheters were charged with NO by exposure in a chamber filled with a gaseous nitric oxide-containing environment.	NO released from catheters at concentration of between 1.75-2.8 ppm per catheter after 24 hours	*P.aeruginosa*, *E. coli* and *C. albicans* attachment and colonization prevented by NO-charged urinary catheters. Urinary catheters release NO for 14 days.	Physical changes not detected. Physiological, haematological and biochemical parameters without significant differences.	(78)
	SNAP impregnation	S-nitroso-*N*-acetylpenicillamine (SNAP) dissolved in THF and the catheters were completely immersed into this solution for 24 hours. After, catheters dried for 72 hours.	SNAP was dissolved in THF at a concentration 125 mg/mL of solvent.	Release for 30 days. Significant antibiofilm effect against *S. epidermidis* and *P. mirabilis.*	Previous studies proved the catheter tubing was the safest as possible.	(82)
QACs	Quaternary ammonium compounds coating	Plasma-based approach for coating onto polyurethane catheters with a plasma-induced graft-polymerization and a liquid phase adsorption.	The immersion solution contained 0.05%wt of 3-(trimethoxysilyl)-propyldimethyloctadecylammonium chloride	Coated catheters showed in vitro antimicrobial activity against *E. coli.*	Catheters were successfully functionalized with the plasma-based methodology used.	(97)
AMP	Antimicrobial Peptides coating	Modified polyurethane catheters brush coated with AMPs using a tethering strategy.	Peptide solution contained 0.6 mg/mL	Excellent antimicrobial activity toward *P. aeruginosa*, *S. aureus* and *S. saprophyticus.* Reduction in bacterial adhesion also showed in a mouse CAUTI model.	Biocompatible.	(105)
	Antimicrobial peptide + Polydopamine	Foley catheters treated with a synthetic AMP after being dip-coated with polydopamine.	Peptide solution contained 2.0 mg/mL	Bactericidal effect against *S. aureus*, *P. aeruginosa* and *E. coli.*	Acceptable cytotoxicity levels for AMP-immobilized samples.	(111)
Enzymes	Lysosyme	PVC urinary catheters conjugated with copolymer brushes and lysozyme.	2.5 mg/mL lysozyme in PBS	Decreased amount of *S. aureus* adhered to the surfaces.	The polymer used is biocompatible.	(113)
	Acylase	Coatings on silicone urinary catheters using a layer-by-layer technique.	Acylase solution 1 mg/mL	Enzymatic inactivation of que QS molecules. Initial attachment of *P. aeruginosa* strongly inhibited.	No cytotoxicity.	(117)

Table 7 Research studies with potential application in Vascular Catheters

	Strategy	Methodology	Concentrations	Results	Biocompatibility	Ref.
Silver (Ag)	Photochemical deposition of Ag nanoparticles (NPs)	Treatment of both inner and outer surface of polyurethane catheters by dipping into a solution with a silver salt dissolved in methanol. The inner surface was treated with the solution using a syringe. Wet catheters were exposed to UV irradiation to induce Ag photo-reduction and nanoparticles formation.	The process was conducted according to a patented technique (118)	Antibacterial tests performed against *E. coli* revealed inhibition of bacterial growth induced by Ag ions. The untreated catheter did not show any inhibition effect.	No information.	(12)
	Microbially and phytofabricated AgNPs	**1)** Biomass of *Bacillus amyloliquifaciens* treated with aqueous solution of $AgNO_3$. Purification of the synthesized microbial AgNPs. **2)** Phytoshynthesis of AgNPs using tubers of *Curcuma aromatica* crushed with a mortar and pestle. After filtration, the extract was added to aqueous $AgNO_3$, producing AgNPs.	**1)** Aqueous solution of filter sterilized 1mM $AgNO_3$ (100mL) **2)** 20g of *Curcuma aromatica* Aqueous 1mM $agNO_3$ (10mL/100mL)	MAgNPs exhibited superior antibacterial activity compared to CAgNPs. Compared to uncoated CVCs, MAgNPs coating reduced biofilm in 94.8% and CAgNPs in 92.2%.	No information.	(37)
Triclosan	Triclosan + DispersinB impregnation	CVCs were coated by dipping in a solution with triclosan and DspB	The solution contained 10 mg/mL of triclosan and 100 µg/mL of DspB	Synergistic effect against *S. aureus*, *S. epidermidis* and *E. coli* with a significantly reduced colonization. Antimicrobial activity maintained for > 8 days.	Triclosan DspB are clinically safe.	(73)
	Triclosan, xylitol and PHMB impregnation	CVC fragments impregnated with xylitol, triclosan and polyhexamethylene biguanide (PHMB) by immersion in a antimicrobial solution.	3.0% silicone, 5.0% xylitol and 10.0% pre-formulated antimicrobial solution containing 0.15% triclosan, 0.2% PHMB and other components.	Antimicrobial activity against *C. albicans*, *K. pneumoniae*, *S. aureus*, *P. aeruginosa* and *E. coli* in vitro and reduced bacterial adherence.	In vivo assays were done in rats and no significant tissue reaction was observed.	(74)
Nitric Oxide	Nitric Oxide nanoparticles (NO-np)	The process included a redox reaction of sodium nitrite with NO production and a drying phase with a lyophilizer to form a fine powder containing NO-np.	*S. aureus* biofilms were incubated with 200 µl of BHI medium containing 1.25, 2.5, or 5 mg/ml of NO-np in susceptibility assays.	Bacterial growth decreased by 40% treating with 2-5 mg/mL of NO-np and by 50% with ≥ 5 mg/mL.	Minimal cytotoxicity	(75)
	Diazeniumdiolate coating	Polyurethane CVC fabricated by dip coating in solutions containing dibutylhexanediamine (DBHD) and poly(lactic-co-glycolic acid) (PLGA)	The active solutions contained 25 wt% DBHD with various ratios of PLGA	95% reduction in bacterial adhesion.	No evidence of causing cell lysis or toxicity.	(80)
	SNAP impregnation	Impregnation of a polyurethane catheters by soaking in a S-nitroso-*N*-acetylpenicillamine (SNAP) solution. After, the catheters were treated with MeOH and dried overnight for the evaporation process.	The solution contained 120 mg/mL of SNAP.	The SNAP-impregnated catheters release NO for at least 14 days. This release reduced the adhesion of *S. epidermidis* and *P. aeruginosa* after 14 days.	SNAP is a non-toxic NO donor and the polymer is biocompatible.	(81)
Chitosan	Chitosan and Heparin	Modification of polyurethane samples by immobilization of Chitosan and Heparin.	Two concentrations of CH solutions used: 5 mg/mL and 20 mg/mL	CH concentration used did not affect the level of antimicrobial activity. Weak proliferation of modified PUs with *E. coli*, *P. aeruginosa*, *S. aureus* and *S. epidermidis.*	CH and Heparin already reported as biocompatible.	(100)

6 Dual and other approaches

The pursuit for novel and more economic biological agents capable of preventing the formation of biofilms has conducted to many interesting findings. Bacteriophages and development of phage cocktails are being explored with attention for medical device coatings, but further information is still necessary to confirm the reliability of these approaches. Still, due to their proved capacity to infect bacteria and cause their lyses rapidly, Milo *et al.* (2017) created and described a novel infection-responsive coating for urinary catheters. The coating was composed by two layers, a lower hydrogel film impregnated with bacteriophage and an upper 'trigger' layer with a pH-sensitive polymer. Therefore, the designed surface released a therapeutic concentration of bacteriophage as an answer to raised urinary pH, delaying the encrustation process. After the triggered phage release from the catheter, a significant reduction in *P. mirabilis* concentration in the bladder model was observed, proving the potential of phage therapy against CAUTI. (119)

Honey has also been reported as a potent antimicrobial agent exerting an inhibitory effect to several pathogens. The major source of its activity was proved to be the hydrogen peroxide, whose concentrations differs with the type of honey and floral source. (120) Since Sahara honey (SH) shows the higher potency, Aissat *et al.* (2016) explored the antimicrobial activity of this compound conjugated with propolis against already formed biofilms on urinary catheters. The tested bee products exhibited an excellent anti-adhesive and antibacterial effect against *S. aureus*, *P. aeruginosa* and *E. coli*. (121)

It is also possible that the same surface exhibits combined contact and release-based mechanisms. Many years ago, Li *et al.* (2006) reported the possibility of creating dual-acting surfaces through the use of a layer-by-layer technique. The suggested coating comprised a first layer with embedded silver ions to be released and a second region with quaternary ammonium salts immobilized to polystyrene. The authors believed this scheme could also be extended to antibiotics. (122) However, maybe due to their superior complexity, today there is still a deficiency in data regarding dual strategies specifically applied to catheters. Nevertheless, the possibility of having two different biocides incorporated into the same device, acting simultaneously by contact-kill and release mechanisms, seems a promising alternative to be explored.

7 Discussion

Today, urinary and intravascular catheters persist in being two of the major sources of nosocomial infections due to their extensively usage in Medical care. During the past years, efforts to find new preventive approaches conducted to a variety of new coatings for catheters. Summing up, the preparation of antimicrobial surfaces can be achieved either by physical treatment or by immobilization with grafting techniques. The physical treatment strategy does not change the bulk properties of the polymer and it can be reached via: (a) immersion in antimicrobial solutions with evaporation of the residual solvent; (b) spray-coating; (c) incorporation of the antimicrobial agent into the polymeric matrix during the base material production; (d) or by a swell-encapsulation technique, which consists in putting the already fabricated polymer in an antimicrobial solution capable of swelling it, with a posterior evaporation step to leave the biocidal in the material. On the other hand, immobilization with grafting techniques is mainly applied to catheters coating when the aim is to create a rougher surface with anti-adhesive and anti-biofilm properties. (123)

In this work, several methodologies to design antibacterial catheters were summarized. Even though all of them show both negative and positive aspects, some are already approved and commercialized. Despite being widely used, silver impregnated catheters did not show conclusive effectiveness in clinical trials and several reports still indicate superior efficacy against microbial colonization for antibiotics-based coatings. Silver is not expectable to cause resistance of microorganisms, but its unclear cytotoxicity and controversial efficacy is making this alternative quite questionable. Treating catheters with antibiotics also persists as a cost-effective approach, but should be used rationally due to the resistance issue. With the increasing practice of irrational antibiotic treatments, the emergence of microbial resistant strains and failure of therapy has become a serious Public Health problem. For example, cultures of urine collected from catheters inserted in a group patients showed that 100% of strains were resistant to ampicillin, 91.7% to ciprofloxacin, 29.2% to carbapenems and 17.2% to fosfomycin. (124)

Approaches using antiseptics as alternative to antibiotics were also described and those include the single use of chlorhexidine or triclosan, or in combination, given their ability to produce synergic effects with other antimicrobial agents. However, chlorhexidine presents the weakness of possessing limited activity against *P. mirabilis*, an important pathogen in urinary infections. On the other hand, nitric oxide showed superior efficacy compared with the Ag-alloy coatings frequently used, but since its safety is not completely clarified this approach

remains in the line for additional clinical studies. Still in the group of release-based strategies, 5-fluorouracil exhibits an effective antimicrobial activity and no evidence of fungal and bacterial resistance or tissue toxicity, becoming an interesting approach to be further explored given the good results in clinical trials. Concerning to contact-killing strategies, the antimicrobial properties of QACs, chitosan and antimicrobial peptides have been demonstrated but the deficiency of *in vivo* and clinical data, as well as studies specifically on catheters, is still critical.

Phage-based approaches can bring satisfactory results given their superior bacterial specificity compared to antibiotics. Additionally, their easy manipulation and fair stability make them promising candidates to create alternative antibacterial coatings for catheters.

One of the most encouraging approach to minimize the resistance matter seems to be the use of quorum-sensing inhibitors since they can battle the causes of bacterial virulence. Interfering with the bacterial communication process through quorum-sensing inhibitors can be another route to block biofilm formation and growth, instead of using bactericidal or bacteriostatic agents. Besides, as they can be obtained from natural sources, these molecules stand as an exciting way to follow.

Some unresolved issues about the best antimicrobial strategies to combat catheters-associated medical infections are still evident but there is an agreement about the importance of hygiene practices and fighting against the poor compliance of healthcare guidelines. According to the Centers for Disease Control and Prevention guidelines (125,126), safety practices should include sterile precautions during insertion, appropriately selection of catheters regarding their duration of use and their removal in case of infectious complications. Recommendations disapprove systemic antimicrobial prophylaxis to prevent catheter colonization and only mention using a CSS or minocycline-rifampicin impregnated CVC in patients whose catheterization is expected to last for > 5 days. The duration of urinary catheterization should be minimized and using an antimicrobial-impregnated catheter should be considered. Additional research about the influence of using antimicrobial modified urinary catheters, such as silver-coated, is still necessary, as well as the group of patients who will benefit from these strategies.

8 Conclusion

Once biofilms are already established, antibiotics therapies alone frequently fail in overcoming these infections. Thus, their eradication is a complex challenge and that is why antibacterial coatings became the focus of the research community.

This work reviewed different strategies with the common goal of preventing biofilm formation on catheters, including release-based approaches using silver, antibiotics, antiseptics, nitric oxide or 5-fluorouracil, and contact-based approaches with QACs, chitosan, AMPs and enzymes as antimicrobial agents. All of these strategies have given proof of antimicrobial efficacy but further investigation is essential to clarify the clinical value of some of them.

Despite this intensification of research to find novel preventive strategies, laboratorial studies still present some limitations since the conditions are not exactly equivalent in all of them and to those we find when a catheter is inserted in a human body. Consequently, the efficacy data obtained from *in vitro* studies cannot reflect properly the results obtained in a clinical application in most cases. Only a few laboratorial studies have made their way to clinical studies and for that reason there is still a need for further well-designed clinical trials as well as more cytotoxicity studies to find additional side effects.

In conclusion, the aiming for synergistic approaches using multi-target processes and the combination of antifouling and bactericidal properties seem to be the focus in the future, as well as clarifying the mechanism of action of some already known antimicrobial agents.

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