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Current Opinion in Biomedical Engineering

Recent advances in antimicrobial surfaces for urinary catheters

Rita Teixeira-Santos[1,2], Luciana C. Gomes[1,2] and Filipe J. M. Mergulhão[1,2]

Abstract

Although urinary catheters (UCs) are one of the most used medical devices, they are related to a high incidence of urinary tract infections resulting from microbial colonization and consequent biofilm development on UC surfaces. Currently, a panoply of antimicrobial and antifouling surfaces is available to solve this longstanding problem. However, despite their high performance, these surfaces are still far from clinical application. In this current opinion article, we evaluate and critically discuss the antimicrobial performance and applicability of UC surfaces with different antibiofilm mechanisms. It is our opinion that either killing or anti-adhesive coatings are promising in controlling infection development. However, most of them are more effective in delaying microbial adhesion rather than preventing it.

Addresses

[1] LEPABE - Laboratory for Process Engineering, Environment, Biotechnology and Energy, Faculty of Engineering, University of Porto, Rua Dr. Roberto Frias, 4200-465, Porto, Portugal

[2] ALiCE - Associate Laboratory in Chemical Engineering, Faculty of Engineering, University of Porto, Rua Dr. Roberto Frias, 4200-465, Porto, Portugal

Corresponding author: Mergulhão, Filipe J. M (filipem@fe.up.pt)

Current Opinion in Biomedical Engineering 2022, **22:**100394

This review comes from a themed issue on **Biomaterials 2022: Antimicrobial Surfaces in Biomedical Engineering & Healthcare**

Edited by **Seeram Ramakrishna**, **Yarlagadda**, **Kristen Spann** and **Liliana Liverani**

For complete overview of the section, please refer the article collection - Biomaterials 2022: Antimicrobial Surfaces in Biomedical Engineering & Healthcare

Received 28 November 2021, revised 25 March 2022, accepted 4 April 2022

https://doi.org/10.1016/j.cobme.2022.100394

Keywords

Urinary catheter, Biomaterial, Infection, Biofilm, Antimicrobial activity.

Abbreviations

UC, urinary catheter; HAI, healthcare-associated infection; CAUTI, catheter-associated urinary tract infection; UTD, urinary tract devices; AMP, antimicrobial peptide; CHX, chlorhexidine.

Introduction

Urinary catheters (UCs) are flexible plastic tubes used to empty the bladder and collect urine in a drainage bag, being valuable devices in patient care and among the most frequently used medical tools in hospitals [1]. They are inserted in patients with urinary obstruction, before or after some types of surgery, and to help perform certain treatments [2]. Nevertheless, the prolonged use of these devices is associated with severe complications, including the occurrence of catheter-associated urinary tract infections (CAUTIs), which are the most common cause of healthcare-associated infections (HAIs) [1,3]. CAUTIs adversely impact morbidity and mortality and pose a considerable financial burden on healthcare systems [4]. Indeed, the repetitive inappropriate administration of antibiotics often leads to higher bacterial resistance and makes indwelling infections very difficult to eradicate [3].

In European intensive care units, urinary infections are associated with the use of catheters in 98% of the cases [5]. The agents liable for CAUTIs are usually bacteria (*Escherichia coli* followed by *Enterococcus* spp.) because of their capability to adhere and colonize the surface of urinary tract devices (UTDs); however, fungi (*Candida* spp.) and other microbes may also be involved in these infections [5,6]. Biofilm development on both the extraluminal and intraluminal catheter surfaces is of paramount importance to the pathogenesis of CAUTIs. Biofilms consist of communities of microorganisms typically attached to a surface and embedded in extracellular polymeric substances (EPS). This self-produced matrix holds the biofilm together and protects the microorganisms from host defenses, antimicrobial treatments, and shear forces [7]. The urinary catheter links the heavily colonized perineum with the sterile bladder, providing a route for bacterial entry along both its external and internal surfaces and consequent biofilm formation [8,9]. Urine often pools in the bladder or in the catheter itself, and the resulting urinary stasis (restricted urine flow) can promote bacterial growth. Additionally, catheter obstruction can damage the bladder mucosa, thus increasing its susceptibility to bacterial invasion. Once bacteria enter the urinary tract, low-level bacteriuria progresses within 24–48 h, increasing the risk of CAUTI development [10].

Another frequent issue related to the use of long-term UCs is the encrustation – an obstruction in the catheter lumen resulting from the existence of *Proteus* species and crystalline components in biofilms -, which can block the urine flow through the catheter, cause bladder

and urethral epithelial disturbance and lead to painful distension of the bladder or even pyelonephritis and septicaemia [11,12]. Hence, the discovery that bacteria and other microorganisms can cause CAUTIs by forming single- and multispecies biofilms and developing encrustation has boosted advances in the design of novel antifouling and antimicrobial urinary catheter materials [6,13].

Here, we discuss the most recent surface-modifying approaches for urinary catheters pursuing to decrease pathogen colonization and consequent biofilm formation. The progress made on UCs consisted of the development of novel coatings with antifouling and/or antimicrobial properties capable of modulating microbial adhesion and, by decreasing it, extending the durability of the implantable device and reducing clinical complications associated with its long-term use.

Antifouling coatings do not inactivate microorganisms directly but inhibit their attachment and thus biofilm growth. The most promising anti-adhesive mechanisms are (1) exclusion steric repulsion (polymers attached to surfaces that act as physical barriers to proteins and microbes), (2) electrostatic repulsion (charges on surfaces to prevent microbial adhesion), and (3) surface energy reduction (decrease of microbial adhesion through the use of low energy surfaces) [6]. The main kinds of antifouling coatings presently in research are based on the use of hydrophilic polymers [14], zwitterionic polymers [15,16], cationic polymers [17], amphiphilic polymers [18,19], and polymer brushes [20,21]. Alternatively, biocidal urinary catheter materials are developed to kill the microorganisms instead of decreasing their attachment [13]. They comprise release-based approaches using metals (such as silver and metal alloys), antibiotics, and disinfectants as active ingredients [22–24], as well as contact-killing strategies employing antimicrobial peptides (AMPs) [25] and carbon materials such as carbon nanotubes [26].

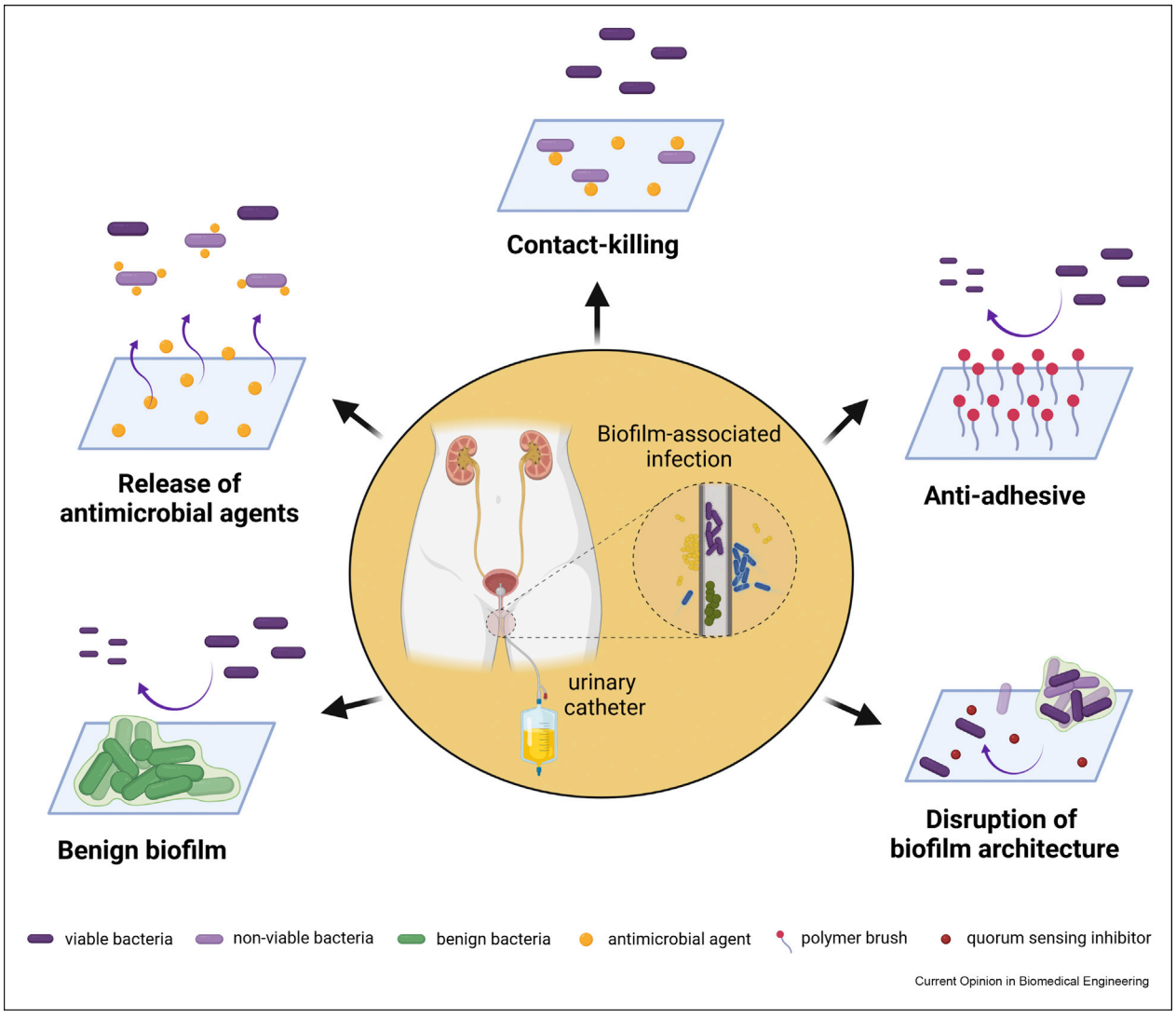
Current coatings were essentially designed based on biofilm formation mechanisms and can be grouped into five antibiofilm strategies which will be addressed in more detail in the next sections: (1) release of antimicrobial compounds, (2) contact-killing, (3) catheter surface modification for preventing microbial adhesion, (4) disruption of biofilm architecture, and (5) benign bacterial biofilms to inhibit pathogen colonization (Figure 1). Whereas release-based coatings exert their antimicrobial activity by leaching antimicrobial compounds over time, exposing and subsequently killing microbial cells (both adhered and planktonic) that gain access to the catheterised bladder through the intraluminal route, in the contact-killing surfaces, the antimicrobial agents are covalently anchored to the surface material and bacterial attachment and proliferation are inhibited by such compounds, usually as a result of cell membrane disruption via physical lysis or charge disruption. Anti-adhesive properties can be conferred to UCs through modification of the chemistry and/or topography of the surface, while disrupting biofilm architecture is another antibiofilm approach that consists in dispersing the biofilms formed on inert substrata and promoting a planktonic lifestyle with cells more susceptible to antimicrobial agents.

Antimicrobial release coatings

The antimicrobial release strategy is based on the application of controlled-release coatings for site-specific delivery of antiseptics, antibiotics, or metals (e.g., silver and copper) (Table 1) [25]. This approach has been employed on diverse implantable medical devices to prevent or delay the onset of biofilm development. In recent years, the study of chlorhexidine (CHX)-based coatings using different delivery systems (varnishes, nanospheres, micelles, and nanoparticles) has deserved particular attention [27–30]. Results demonstrated that CHX-based coatings decrease bacteria and fungi growth on coated UCs 100-fold more than uncoated surfaces, while the controlled release of CHX inhibits 50% of bacterial growth for more than 6 days [28,29]. Furthermore, *in vivo* data indicated that CHX-based coatings are effective in delaying bacterial colonization and encrustation [30]. Since CHX has an extended spectrum of antibacterial and antifungal activities and high biocompatibility [27], its use seems to be a promising approach to inhibit microbial growth and biofilm development on coated surfaces. In addition, CHX is less likely prone to the acquisition of microbial resistance compared to conventional antibiotics due to its generalized mechanism of action. Lastly, the results pointed that polymeric matrices can efficiently release CHX, turning this type of coating into a good solution for UCs [28]. The release pattern of CHX differs significantly between formulations due to their matrix properties and is strongly dependent on hydrodynamic conditions (flow or static systems) [27]. However, data showed controlled release of CHX for 15 days, ensuring the effectiveness of surfaces over this period [28]. Similar to CHX, the combined action of rifampicin, triclosan, and sparfloxacin also provided the silicone UCs a long-term protective effect against resistant uropathogens [22].

Up to date, numerous studies have demonstrated the success of silver released from surfaces in reducing microbial adhesion and biofilm formation. The application of silver in UCs was already approved by the Food and Drug Administration and silver-coated catheters are one of the few antimicrobial catheters currently marketed

Figure 1



Strategies applied for the design of antimicrobial and antifouling surfaces on urinary catheters.

[31]. Silver and its formulations have been applied in different polymeric matrices, such as silicone and polyurethane, and evaluated against a wide range of pathogens. *In vitro* results indicated that silver-coated surfaces reduce bacterial attachment by 60–99.9% and inhibit biofilm formation by 85.8–97.4% [12,32–34]. In addition, silver-coated catheters resisted encrustation 2-fold more than uncoated catheters and displayed an extended working life (over 40 days) and high biocompatibility [12,33]. Similarly, results obtained by *in vivo* studies were also promising, showing that Ag-coated catheters significantly reduced bacterial colonization (50–99%) and conferred protection against biofilm formation for up to 7 days [33,35,36]. To improve the effectiveness of silver catheters, some authors developed antimicrobial coatings containing silver and zinc, which were effective in preventing bacterial biofilm development for 6 days [37,38]. Other authors coated silicone and polyurethane catheters with silver and norfloxacin (an antibiotic) and obtained a bacterial biofilm volume reduction of 75–80% compared to uncoated catheters [39]. The antibiofilm performance of coated catheters was kept for 14 days. Altogether these results highlight the potential of silver-based catheters in controlling the CAUTIs incidence. Likewise, silicone surfaces containing chelated copper ions also showed significant antimicrobial activity (50% bacterial inactivation) [16].

Lastly, the release of antimicrobial peptides from coated silicone catheters is here pointed to as a promising approach since *in vivo* results demonstrated that these catheters were able to decrease bacterial adhesion by

Table 1

Effectiveness of antimicrobial and antifouling surfaces designed for urinary catheters.

Strategy	Coating	Material	Microorganism	Major conclusions	Ref.
Release of antimicrobial compounds	**Antibiotics/Antiseptics**				
	Chlorhexidine (CHX) varnishes	Siliconized latex	*P. aeruginosa*[1]	Chlorohexidine-coated catheters almost completely inhibited biofilm formation compared to uncoated samples ($p < 0.05$) due to the controlled CHX release.	[27][a]
	Chlorhexidine-loaded poly(ε-caprolactone) nanospheres (CHX-NS)	n.d.	*E. coli*[2] *S. aureus*[3] *C. albicans*[4]	CHX−NS−coated UCs decreased microbial growth 100-fold compared to the control. Moreover, microbial growth was inhibited by 50% for 15 days due to the controlled release of CHX.	[28][a,*]
	Chlorhexidine-loaded poly(ethylene glycol)-block-poly(ε-caprolactone) micelles	n.d.	*E. coli*[2] *S. aureus*[3] *C. albicans*[4]	After 1 day, coated catheters inhibited microbial growth 100-fold more compared to the control. CHX-micelles-coated UCs decreased by 50% bacterial growth for 6 days and delayed *C. albicans* biofilm formation until day 4. Moreover, coated catheters demonstrated biocompatibility properties.	[29][a,*]
	Chlorhexidine-loaded nanoparticles (CHX-NPs)	n.d.	–	Uncoated catheters revealed, on average, more encrustation thickness than coated catheters (84.4 vs. 11.2 μm), indicating that CHX-NPs were effective in delaying encrustation and bacterial colonization. In addition, *in vivo* biocompatibility tests indicated that there was no dermal toxicity associated with coated catheters.	[30][b]
	Rifampicin, triclosan, and sparfloxacin	Silicone	MRSA[3] MRSE[3] ESBL *E. coli*[2] NDM-1 *E. coli*[2]	Coated catheters prevented colonization by MRSA, MRSE, ESBL *E. coli*, and NDM-1 *E. coli* for 12 consecutive weeks.	[22][a,*]
	Silver and other metals				
	Alternate layers of silver nanoparticle (AgNP) and polydopamine	Silicone	*E. coli*[2]	*In vivo* results showed that AgNP-coated catheters significantly reduced bacterial colonization (50−99%) and did not cause significant toxicity for 2−3 weeks. Coated catheters inhibited encrustation more effectively than the control catheters.	[36][b]
	Phytomolecules-capped silver nanoparticles using *Carissa carandas* leaf extract	n.d.	*E. coli*[2] *P. aeruginosa*[1] *S. aureus*[3]	AgNPs-coated catheters inhibited biofilm formation in 85.8 ± 1.5%, 82.8 ± 1.8%, and 71.4 ± 1.3% for *P. aeruginosa*, *S. aureus*, and *E. coli*, respectively.	[32][a]
	Silver-polytetrafluoroethylene (Ag-PTFE) nanocomposite	Silicone	*E. coli*[2] *P. mirabilis*[5]	The Ag-PTFE-coated catheters reduced adhesion, and demonstrated a high antibiofilm effect (97.4%) and excellent biocompatibility. Coated catheters were resistant to encrustation for 78 ± 6 h and 89.5 ± 3.5 h vs. 33.3 ± 1.1 h and 36.2 ± 1.1 h achieved by control catheters, with an initial cell concentration of 10^6 and 10^3 cells/mL in the bladder, respectively.	[12][a,*]

	Silver-polytetrafluoroethylene (Ag-PTFE) nanocomposite	Silicone	*E. coli*[2] *S. aureus*[3]	Ag-PTFE-coated catheters reduced bacterial attachment by 60.3% and 55.2% compared to uncoated and Ag-coated catheters, respectively. In addition, 74.5% and 25.6% of *E. coli* and *S. aureus* cells adhered to coated catheters were killed. Ag-PTFE-coated catheters decreased biofilm coverage by 97.4% and displayed an extended lifetime over 40 days and good biocompatibility.	[33][a,*]
	3,4-dihydroxyphenylalanine (DOPA)-based copolymers in combination with silver nitrate particles	Polyurethane	Gram-negative and Gram-positive bacteria	DOPA-based copolymers with silver particles killed more than 99.9% of planktonic bacteria and reduced bacterial attachment by 99.9% while maintaining biocompatibility with mammalian cells.	[34][a]
	Silver-polyethylene glycol (Ag-mPEG-$DOPA_3$)	Polyurethane	*E. coli*[2]	The number of CFU was lower among rabbits implanted with the Ag-mPEG-$DOPA_3$ vs. controls (4/11 vs 10/12, respectively; $p = 0.029$). This coating decreased the number of rabbits with invasive infection compared to control ($p = 0.02$) and did not cause adverse animal tissue effects.	[35][b]
	Silver and zinc	Silicone	*E. coli*[2]	Zn/Ag_2O-PDMS films inhibited biofilms, whereas Ag/Ag_2O-PDMS films had a residual biofilm growth after 6 days.	[37][a]
	Silver and zinc	Silicone	*E. coli*[2]	All coated catheters (Ag/Ag_2O, Zn/Ag_2O, and Ag_2O) inhibited planktonic growth and delayed biofilm development for 6 days compared to controls.	[38][a]
	Chelated copper ions on polydopamine films (pDA)	Silicone	*E. coli*[2] *S. epidermidis*[3]	pDA films showed significant antimicrobial activity (death fraction = 0.5) and high biocompatibility.	[16][a]
	Antimicrobial peptides				
	HHC36 into anhydrous polycaprolactone polymer-based dual-layer coating (PCL(P)-POPC(P))	Silicone	*E. coli*[2] *P. aeruginosa*[1] *S. aureus*[3]	PCL(P)-POPC(P)-coated catheters significantly reduced planktonic growth compared to uncoated silicone catheters ($p < 0.05$). The antibiofilm efficacy of coated catheters was kept for 7 days. *In vivo* results demonstrated that PCL(P)-POPC(P) coatings significantly decreased adhesion (2×10^2 CFU) compared to control (2.4×10^7 CFU). In addition, this coating demonstrated high biocompatibility with mammalian cells.	[25][a,b]
	Other compounds				
	Tetraetherlipid-Silver-Norfloxacin-Polylactid (TANP)	Silicone Polyurethane	Gram-negative and Gram-positive bacteria	The biofilm volume significantly decreased by 75–80% on the TANP coated catheters. Also, the presence of crystalline deposits was reduced by 10–20% on coated surfaces.	[39][a,*]
Contact-killing	**Antibiotics**				
	Liposomal amphotericin B (L-AMB)	Silicone	*C. albicans*[4]	Immobilized L-AMB reduced fungal attachment by 10^3-fold reduction and displayed low toxicity.	[23][a,*]
	Metals				
	Noble metal alloy (gold, silver, and palladium)	n.d.	–	There was a positive correlation between the long-term use of a noble metal alloy-coated	[43][c]

(*continued on next page*)

Table 1. (*continued*)

				catheter and the cessation of frequent CAUTIs. The coating was stable, with no significant metal release.	
				The occurrence of symptomatic CAUTIs decreased by 69% in the coated BIP Foley Catheter concerning the control group (6.5 vs. 20.8 CAUTI/1000 catheter-days).	[44][d]
	Zinc oxide	Silicone	*S. epidermidis*[3]	No biofilm was formed on coated surfaces.	[45][a]
	Antimicrobial peptides				
	Antimicrobial peptides from crowberry endophytes (Chain201D)	Gold substrate	*E. coli*[2] *S. aureus*[3]	Chain201D surfaces killed 99% of adherent bacteria by contact.	[46][a]
	Carbon materials				
	Pristine and ball-milled multi-walled carbon nanotubes (CNTs)	Silicone	*E. coli*[2]	The 3 wt% CNT-PDMS coatings significantly reduced cell culturability (39%) compared to the control. Also, ball-milling treatment generated textural modifications on CNT surfaces which inhibited biofilm formation, reducing the amount of biofilm per surface area, biofilm thickness, and surface coverage in 31, 47, and 27%, respectively, concerning surfaces where CNTs were not ball-milled.	[26][a,*]
	Diamond-like carbon (DLC)	Silicone	*E. coli*[2] *P. aeruginosa*[1] *S. aureus*[3]	DLC-coated films significantly reduced the culturability of *P. aeruginosa* (9.2×10^2, $p < 0.001$) and *E. coli* (9.2×10^5, $p = 0.036$) compared to the control. In addition, biofilms formed on the uncoated silicone films were larger than those on the DLC-coated films.	[47][a,*]
	Biopolymers				
	Nanostructured lipid carriers (NLC) coated with chitosan	Silicone	*E. coli*[2]	NLC-chitosan impaired the bacterial viability of biofilms at all stages ($p < 0.05$) and suppressed bacterial growth in 48 h-biofilms.	[48][a]
Anti-adhesive	**Amphiphilic polymers**				
	p(MMP-co-HEMA) and p(DMP-co-HEMA) copolymers	n.d.	*E. coli*[2]	Copolymers showed lower bacterial adherence with a reduction greater than 90% compared to control.	[19][a,*]
	Poloxamer 338	Silicone	*E. coli*[2]	P388-coated catheters reduced up to 0.83 Log the *E. coli* biofilm. In dynamic conditions, *E. coli* was undetected on P388-coated silicone films.	[18][a,*]
	Superhydrophobic polymers				
	Trifluoropropyl (TFP) spray-coated PDMS	Silicone	*P. mirabilis*[5]	Compared to the commercially silver-coated latex and silicone catheter surfaces, TFP−PDMS showed a lower amount of adhered bacteria over 14 days.	[49][a,*]
	Hydrophilic polymers				
	Polydopamine and poly(N,N-dimethylacrylamide) (PDA/uhPDMA)	Polyurethane	Gram-negative and Gram-positive bacteria	PDA/uhPDMA coating inhibited bacteria colonization by 78−95% after 24 h, depending on bacterial species. After 30 days, coated catheters reduced the number of adhered bacteria by	[14][a,*,b]

				73.5% compared to uncoated catheters. *In vivo* studies showed that coated catheters decreased biofilm formation by 99.7% after 3 days of implantation in mice and by 96.5% after 14 days of implantation in pigs. Moreover, PDA/uhPDMA coating displayed high biocompatibility.	
	Hydrogel				
	N-halamine-impregnated hydrogel	Silicone	*E. coli*[2] *S. aureus*[3]	Coated catheters inactivated bacteria in 6 Log within 30 min and decreased biofilm growth by 90% compared to uncoated catheters after being challenged with *S. aureus* for 3 days.	[50][a,*]
	Polymer brushes				
	Poly[N-(2-hydroxypropyl) methacrylamide] (poly(HPMA)) brush	Glass	*E. coli*[2]	Poly(HPMA) brushes yielded 40% less surface area covered than the PDMS at 24 h and 30% less at post-infection period. Coating reduced the total cell numbers by 61% at 24 h and 87% at post-infection period compared to control. In addition, brushes reduced VBNC cells by 94% compared to control at 24 h and eliminate them in the post-infection period.	[21][a,*]
	Poly[oligo(ethylene glycol) methyl ether methacrylate] (poly(MeOEGMA)) brush	Glass	*E. coli*[2]	After 24 h, polymer brush coating decreased the biofilm surface coverage area by 60% concerning PDMS. The biofilm viability was 35% less for polymer brush compared to control.	[20][a,*]
	Polyzwitterions				
	Chelated copper ions on polydopamine films conjugated with sulfobetaine acrylamide (pDA-SBAA)	Silicone	*E. coli*[2] *S. epidermidis*[3]	pDA-SBAA films were able to resist bacterial adsorption by 96% compared to control and presented a high death fraction (0.8). Moreover, this coating displayed excellent biocompatibility.	[16][a]
	Other compounds				
	Calixarene polymer	Silicone	*E. coli*[2] *P. mirabilis*[5]	Coated substrates reduced biofilm development and crystal formation by *P. mirabilis*. Samples did not leach toxic compounds over the tested period.	[51][a]
	Natural polymer released by a marine *Cyanobacterium* - CyanoCoating	Gold substrate	*E. coli*[2] *K. pneumoniae*[6] *P. mirabilis*[5] MRSA[3] *C. albicans*[4]	CyanoCoating exhibited a high anti-adhesive efficacy towards the tested uropathogens (68–95%). In addition, CyanoCoating decreased biofilm formation by *E. coli*, *P. mirabilis* and *C. albicans* (30–60%) under conditions representative of the urinary tract.	[52][a]
	Natural polymer released by a marine *Cyanobacterium* - CyanoCoating	Polyurethane	*E. coli*[2] *S. aureus*[3]	CyanoCoating obtained by ozone activation reduced *S. aureus* and *E. coli* attachment by 98 and 99%, respectively. Moreover, it decreased *E. coli* biofilm coverage area by 95% compared to the control.	[53][a,*]
Disruption of biofilm architecture	**Quorum sensing inhibitors**				
	2,5-dimethyl-4-hydroxy-3(2H)-furanone	Latex Polyurethane Silicone	*C. krusei*[4] *C. glabrata*[4] *C. tropicalis*[4]	Coated catheters completely inhibited biofilm growth of non-*Candida albicans* species.	[54][a]

(*continued on next page*)

Table 1. (*continued*)

	Chrysophanol (CP)-functionalized silver nanoparticles	Latex Silicone	*E. coli*[2] *P. aeruginosa*[1]	CP-AgNPs coated surfaces decreased the attachment of *P. aeruginosa* and *E. coli* cells to 12 and 6%, respectively. After 7 days, coated silicone catheters decreased biofilm formation by 93 and 97% for *P. aeruginosa* and *E. coli*, respectively, under flow conditions. *In vivo* studies demonstrated that implanted coated catheters showed very few cells and did not cause side effects in human bladder fibroblast cells.	[55][a,*,b]
Benign biofilms to inhibit pathogen colonization	Pre-established *Lactobacillus plantarum* biofilms	Silicone	*E. coli*[2]	Coated surfaces reduced by 76, 77 and 99% *E. coli* culturability following exposure to *L. plantarum* biofilms for 3, 6, and 12 h, respectively.	[56][a,*]

[a], *in vitro* study; [b], animal study; [c], human study; [d], clinical trial; *, *in vitro* study performed under flow conditions; [1] *Pseudomonas* sp.; [2] *Escherichia* sp.; [3] *Staphylococcus* sp.; [4] *Candida* sp.; [5] *Proteus* sp.; [6] *Klebsiella* sp.

CFUs, colony-forming units; CHX, chlorhexidine; DLC, diamons-like carbon; CNTs, carbon nanotubes; ESBL, extended-spectrum beta-lactamase producing *E. coli*; MRSA, methicillin-resistant *Staphylococcus aureus*; MRSE, methicillin-resistant *Staphylococcus epidermidis*; n.d., not defined; NDM-1, carbapenemase-producing *E. coli*; NPs, nanoparticles; p(DMP-co-HEMA), poly(dimethacrylated poloxamer-co-hydroxyethyl methacrylate); PDMS, poly(dimethylsiloxane); PEG, polyethylene glycol; p(MMP-co-HEMA), poly(monomethacrylated poloxamer-co-hydroxyethyl methacrylate); VBNC, viable but non-culturable.

10^5-fold reduction, provided antibiofilm protection for 7 days, and presented biocompatibility with mammalian cells [25].

The effectiveness of antimicrobial release coatings is due to the high concentration of antimicrobial compounds free at the site of infection and their broad spectrum of action [31]. Release surfaces based on antibiotics, metals, or antiseptics, such as quinolones, silver, and chlorohexidine, respectively, have been the subject of intense research. However, we believe that issues related to the acquisition of microbial resistance [19], the limited durability of antimicrobial surfaces [12], and the reduced number of *in vivo* studies (25%) or *in vitro* studies performed under dynamic conditions representative of the urinary tract environment (25 and 38% of the reviewed studies, respectively), may restrict the clinical application of these coatings as hydrodynamics proved to modulate microbial attachment and biofilm development in different settings [40–42].

Contact-killing coatings

A convenient approach to minimize cytotoxic effects associated with antimicrobial coatings is to produce catheter surfaces with the capability to inactivate microbial cells without releasing active agents. In this way, antibiotic agents like liposomal amphotericin B may be efficiently immobilized on silicone catheter surfaces, significantly reducing fungal attachment [23]. Likewise, the use of noble metal alloys (silver, gold, and palladium) to coat urinary catheters demonstrated to be an efficient and safe approach that can decrease the incidence of CAUTIs by 69% compared to uncoated catheters [43,44]. The immobilization of zinc oxide nanoparticles on silicone UCs was also efficient in controlling biofilm formation by Gram-positive bacteria [45].

In the last decade, AMPs have been successfully applied in contact-killing surfaces, representing a promising alternative to conventional antimicrobial compounds. Recent data demonstrated that AMPs can kill by contact about 99% of adhered uropathogens [46]. In fact, AMPs exhibit a wide spectrum of antimicrobial activity and target microorganisms by multiple mechanisms of action, therefore they are less likely to induce microbial resistance.

Carbon-based materials, including carbon nanotubes and diamond-like carbon, have also succeeded in inhibiting bacterial colonization and the consequent biofilm formation on medical surfaces for up to 14 days. Because they cause severe cell membrane damage by direct contact, carbon-based silicone surfaces can significantly reduce bacterial culturability [26,47].

Lastly, biopolymers such as chitosans have been successfully tested as a coating for UCs, being able to suppress bacterial growth in 48 h-biofilms [48].

Although the contact-killing coatings discussed above (Table 1) may be effective in reducing the viability of adhered bacteria and thus be promising in controlling the incidence of CAUTIs, they are far from the clinical application, with the exception of metal alloy-coated catheters. Most of these coatings have not been studied in conditions representative of the urinary tract, and little is known concerning their biocompatibility and long-term applicability.

Anti-adhesive coatings

Contrary to antimicrobial release or contact-killing coatings, anti-adhesive coatings resist microbial attachment and biofilm formation by repelling pathogens from the catheter surfaces [6]. This approach has the advantage of minimizing the risk of emerging resistant strains associated with the use of antimicrobial compounds and offering high biocompatibility. Thus, by optimizing the physicochemical properties of catheter surfaces, including the charge, roughness, and topography, it is possible to modulate initial microbial adhesion. In this context, several polymers such as amphiphilic polymers, superhydrophobic polymers, hydrophilic polymers, hydrogels, polymer brushes, and polyzwitterionic polymers are currently being explored as anti-adhesive coatings for UCs (Table 1).

Amphiphilic polymers showed to be effective by significantly reducing the adsorption of nonspecific proteins and bacterial adhesion (>90%) [18,19]. Also, silicone surfaces coated with superhydrophobic polymers showed reduced bacterial attachment over 14 days [49]. Alternatively, hydrophilic polymers demonstrated high *in vivo* antibiofilm performance, inhibiting bacterial biofilm formation by 96.5% after 14 days of catheter implantation and good biocompatibility [14]. Hydrogel-coated silicone catheters were also able to decrease the biofilm growth of Gram-positive and Gram-negative bacteria by 90% concerning uncoated catheters [50]. Alternatively, polymer brushes were able to reduce the surface coverage area by more than 60% and, at the same time, decrease biofilm viability by restricting the contact of substratum with microbial cells [20,21]. Also, polyzwitterionic polymers exhibited high performance in inhibiting bacterial adhesion (about 96%) because of their resistance to nonspecific protein adsorption by electrostatic and steric repulsion [16]. Other compounds such as calixarene and natural polymers released by marine organisms have also been studied against bacteria and fungi and offer a broad anti-adhesive activity for UCs surfaces [51–53].

Although most anti-adhesive coatings are effective in reducing initial microbial adhesion, their effect on the viability of adhered cells is rarely reported. Moreover, there is a lack of knowledge concerning the long-term biofilm prevention activity of anti-adhesive coatings.

Biofilm-disrupting coatings

Currently, several approaches have been used to disturb the architecture of biofilms, including the use of quorum sensing inhibitors. In fact, compounds like 2,5-dimethyl-4-hydroxy-3(2H)-furanone and chrysophanol (Table 1) were shown effective in inhibiting the biofilm formation of fungi and Gram-positive bacteria, even for long periods (more than 7 days) under flow conditions, and did not induce toxicity in human cells [54,55]. However, the major limitation of this strategy consists in the narrow spectrum of action of quorum sensing inhibitors [31], which may impair its applicability in UCs coatings. Consequently, few studies are addressing the performance of these coatings for urinary tract applications.

Benign biofilm coatings

A new strategy that is emerging to combat biofilm development on UCs surfaces consists of the use of pre-established biofilms of benign bacteria. Indeed, silicone surfaces coated with *Lactobacillus plantarum* biofilms were able to reduce the *E. coli* culturability by 99% after 12 h of contact (Table 1). In addition, results suggested that *E. coli* cells are thermodynamically less predisposed to attach to *L. plantarum* biofilms compared to silicone [56]. Also, urinary catheters which have been pre-inoculated with benign *E. coli* 83972 may prevent UTI by interfering with either catheter colonization or bladder invasion by uropathogens. Trautner and colleagues [57,58] found that coating UCs with this non-pathogenic *E. coli* strain impeded catheter colonization by a wide variety of pathogens. Although these results are promising, side effects associated with the use of viable bacterial cells to coat medical devices, including the emergence of microbial resistance or virulence traits acquisition, are not well established, which can hinder its acceptance in clinical settings. Besides, its long-term activity to prevent biofilm formation is still unknown.

Toxicity of antimicrobial coatings newly designed for UCs

Urinary catheters require biocompatible coatings to ensure appropriate performance and patient safety. Among the studies included in this current opinion article, only 35% of them evaluated the cytotoxicity of antimicrobial and antifouling coatings against mammalian cells. Data demonstrated that antimicrobial coatings based on the release of chlorohexidine [29,30], metals

like silver or copper [12,16,33–35], and antimicrobial peptides [25] are non-toxic, exhibit good biocompatibility, and are suitable for coating UCs. Regarding contact-killing coatings, only the toxicity of liposomal amphotericin B-coated silicone surfaces was assessed displaying reduced toxicity [23]. Anti-adhesive polymers, including hydrophilic and polyzwitterionic polymers, also demonstrated low toxicity and excellent biocompatibility for animal and human cells [14,16]. Lastly, antimicrobial coatings using chrysophanol to disrupt biofilm architecture did not induce side effects in human bladder fibroblast cells [55].

As regards the development and selection of antimicrobial resistance, only one study evaluated the effect of antimicrobial release coatings on the acquisition of bacterial resistance [37]. Results demonstrated that PDMS films containing silver and zinc did not induce *E. coli* resistance for the tested period (6 days).

Therefore, considering the clinical limitations posed by the toxicity of catheter-modified surfaces, the aforementioned antimicrobial coatings hold great potential to be applied for the design of urinary catheters.

Conclusions

Despite the progress in this field, the problems related to the use of urinary catheters still exist and the challenge increases with the emergence of microbial resistance. Consequently, the development of effective antimicrobial surfaces is needed to address this issue. This review addressed the antimicrobial and anti-adhesive efficacy of coatings newly designed to combat microbial attachment and biofilm formation on UC surfaces. In the last years, there has been growing interest in the study of antimicrobial surfaces to coat UCs. However, the currently available data indicate that the applicability of these surfaces is limited, probably due to the lack of information about their performance under conditions representative of the urinary tract environment, biocompatibility, and long-term effectiveness to prevent catheter-associated biofilms. Among the described antimicrobial surfaces, the antimicrobial release and contact-killing coatings seem to be promising approaches since results revealed their high potential to inactivate a broad range of microorganisms for several days. The anti-adhesive coatings follow in terms of efficacy to inhibit microbial attachment and biocompatibility. However, in both strategies, coatings act by delaying microbial attachment rather than preventing it, indicating that future advances should aim at designing antimicrobial coatings that combine antifouling and killing mechanisms, and its long-term activity to inhibit biofilm formation should be conveniently tested against major uropathogens.

Funding

This work was financially supported by: LA/P/0045/2020 (ALiCE), UIDB/00511/2020 and UIDP/00511/2020 (LEPABE), funded by national funds through FCT/MCTES (PIDDAC); project PTDC/CTM-COM/4844/2020; project 2SMART (NORTE-01-0145-FEDER-000054), supported by Norte Portugal Regional Operational Programme (NORTE 2020), under the PORTUGAL 2020 Partnership Agreement, through the European Regional Development Fund (ERDF). The research was also supported by the SurfSAFE project funded by European Union's Horizon 2020 research and innovation programme under grant agreement No 952471. R.T.-S. acknowledges the receipt of a junior researcher fellowship from the Project PTDC/BII-BIO/29589/2017 - POCI-01-0145-FEDER-029589 - funded by FEDER funds through COMPETE2020 - Programa Operacional Competitividade e Internacionalização (POCI) and by national funds (PIDDAC) through FCT/MCTES. L.C.G. thanks the Portuguese Foundation for Science and Technology (FCT) for the financial support of her work contract through the Scientific Employment Stimulus -Individual Call - [CEECIND/01700/2017].

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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