Recent advances in antimicrobial surfaces for urinary catheters
Rita Teixeira-Santos¹,², Luciana C. Gomes¹,² and Filipe J. M. Mergulhão¹,²

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 antimicrobial activity is 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].

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 sepsisemia [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 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, tetracycline, and sparflaxin 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...
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 anti-biofilm performance of coated catheters was kept for 14 days. Altogether these results highlight the potential of silver-based catheters in controlling the CAUTI 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>
<thead>
<tr>
<th>Strategy</th>
<th>Coating</th>
<th>Material</th>
<th>Microorganism</th>
<th>Major conclusions</th>
<th>Ref.</th>
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<tbody>
<tr>
<td>Release of antimicrobial compounds</td>
<td>Chlorhexidine (CHX) varnishes</td>
<td>Siliconized latex</td>
<td><em>P. aeruginosa</em>&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Chlorhexidine-coated catheters almost completely inhibited biofilm formation compared to uncoated samples (<em>p</em> &lt; 0.05) due to the controlled CHX release.</td>
<td>[27]&lt;sup&gt;a&lt;/sup&gt;</td>
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<td></td>
<td>Chlorhexidine-loaded poly(ε-caprolactone) nanospheres (CHX-NS)</td>
<td>n.d.</td>
<td><em>E. coli</em>&lt;sup&gt;2&lt;/sup&gt;, <em>S. aureus</em>&lt;sup&gt;3&lt;/sup&gt;, <em>C. albicans</em>&lt;sup&gt;4&lt;/sup&gt;</td>
<td>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. 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 <em>C. albicans</em> biofilm formation until day 4. Moreover, coated catheters demonstrated biocompatibility properties.</td>
<td>[28]&lt;sup&gt;a&lt;/sup&gt; *&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>Chlorhexidine-loaded poly(ethylene glycol)-block-poly(ε-caprolactone) micelles</td>
<td>n.d.</td>
<td><em>E. coli</em>&lt;sup&gt;2&lt;/sup&gt;, <em>S. aureus</em>&lt;sup&gt;3&lt;/sup&gt;, <em>C. albicans</em>&lt;sup&gt;4&lt;/sup&gt;</td>
<td>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, <em>in vivo</em> biocompatibility tests indicated that there was no dermal toxicity associated with coated catheters.</td>
<td>[30]&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>Chlorhexidine-loaded nanoparticles (CHX-NPs)</td>
<td>n.d.</td>
<td>–</td>
<td>Coated catheters prevented colonization by MRSA, MRSE, ESBL <em>E. coli</em>, and NDM-1 <em>E. coli</em> for 12 consecutive weeks.</td>
<td>[22]&lt;sup&gt;a&lt;/sup&gt; *&lt;sup&gt;b&lt;/sup&gt;</td>
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<td></td>
<td>Rifampicin, triclosan, and sparflaxacin</td>
<td>Silicone</td>
<td>MRSA&lt;sup&gt;3&lt;/sup&gt;, MRSE&lt;sup&gt;3&lt;/sup&gt;, ESBL <em>E. coli</em>&lt;sup&gt;2&lt;/sup&gt;, NDM-1 <em>E. coli</em>&lt;sup&gt;2&lt;/sup&gt;</td>
<td><em>In vivo</em> 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.</td>
<td>[36]&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Silver and other metals</td>
<td>Alternate layers of silver nanoparticle (AgNP) and polydopamine</td>
<td>Silicone</td>
<td><em>E. coli</em>&lt;sup&gt;2&lt;/sup&gt;</td>
<td>AgNPs-coated catheters inhibited biofilm formation in 85.8 ± 1.5%, 82.8 ± 1.8%, and 71.4 ± 1.3% for <em>P. aeruginosa</em>, <em>S. aureus</em>, and <em>E. coli</em>, respectively. 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&lt;sup&gt;6&lt;/sup&gt; and 10&lt;sup&gt;6&lt;/sup&gt; cells/mL in the bladder, respectively.</td>
<td>[32]&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>Category</td>
<td>Material 1</td>
<td>Material 2</td>
<td>Effect</td>
<td>Reference</td>
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<td><strong>Silver-polytetrafluoroethylene (Ag-PTFE) nanocomposite</strong></td>
<td>Silicone</td>
<td>E. coli$^2$</td>
<td>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.</td>
<td>[33]$^{a,b}$</td>
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<tr>
<td><strong>3,4-dihydroxyphenylalanine (DOPA)-based copolymers in combination with silver nitrate particles</strong></td>
<td>Polyurethane</td>
<td>Gram-negative and Gram-positive bacteria</td>
<td>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.</td>
<td>[34]$^a$</td>
<td></td>
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<tr>
<td><strong>Silver-polyethylene glycol (Ag-mPEG-DOPA$_3$)</strong></td>
<td>Polyurethane</td>
<td>E. coli$^2$</td>
<td>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.</td>
<td>[35]$^b$</td>
<td></td>
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<tr>
<td><strong>Silver and zinc</strong></td>
<td>Silicone</td>
<td>E. coli$^2$</td>
<td>All coated catheters (Ag/Ag$_2$O, Zn/Ag$_2$O, and Ag$_2$O) inhibited planktonic growth and delayed biofilm development for 6 days compared to controls.</td>
<td>[37]$^a$</td>
<td></td>
</tr>
<tr>
<td><strong>Silver and zinc</strong></td>
<td>Silicone</td>
<td>E. coli$^2$</td>
<td>pDA films showed significant antimicrobial activity (death fraction = 0.5) and high biocompatibility.</td>
<td>[16]$^a$</td>
<td></td>
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<tr>
<td><strong>Chelated copper ions on polydopamine films (pDA)</strong></td>
<td>Silicone</td>
<td>E. coli$^2$</td>
<td>PCL(P)-POPC(P)-coated catheters significantly reduced planktonic growth compared to uncoated silicone catheters ($p &lt; 0.05$). 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 x 10$^2$ CFU) compared to control (2.4 x 10$^7$ CFU). In addition, this coating demonstrated high biocompatibility with mammalian cells.</td>
<td>[25]$^{a,b}$</td>
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</table>

**Contact-killing**

<table>
<thead>
<tr>
<th>Category</th>
<th>Material 1</th>
<th>Material 2</th>
<th>Effect</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Other compounds</strong></td>
<td>Silicone</td>
<td>Gram-negative and Gram-positive bacteria</td>
<td>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.</td>
<td>[39]$^{a,b}$</td>
</tr>
<tr>
<td>Tetraetherlipid-Silver-Norfloxacin-Polylactid (TANP)</td>
<td>Polyurethane</td>
<td>C. albicans$^4$</td>
<td>Immobilized L-AMB reduced fungal attachment by 10$^5$-fold reduction and displayed low toxicity.</td>
<td>[23]$^{a,b}$</td>
</tr>
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(continued on next page)
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).

No biofilm was formed on coated surfaces.

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.

DLC-coated films significantly reduced the culturability of \( P. \) \textit{aeruginosa} \( (9.2 \times 10^2, p < 0.001) \) and \( E. \) \textit{coli} \( (9.2 \times 10^3, p = 0.036) \) compared to the control. In addition, biofilms formed on the uncoated silicone films were larger than those on the DLC-coated films.

NLC-chitosan impaired the bacterial viability of biofilms at all stages \( (p < 0.05) \) and suppressed bacterial growth in 48 h-biofilms.

Copolymers showed lower bacterial adherence with a reduction greater than 90% compared to control.

P388-coated catheters reduced up to 0.83 Log the \( E. \) \textit{coli} biofilm. In dynamic conditions, \( E. \) \textit{coli} was undetected on P388-coated silicone films.

Compared to the commercially silver-coated latex and silicone catheter surfaces, TFP–PDMS showed a lower amount of adhered bacteria over 14 days.

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...
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

<table>
<thead>
<tr>
<th>Hydrogel</th>
<th>Coating Material</th>
<th>Adhered Bacteria</th>
<th>Adhered Biofilm Coverage</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>N-halamine-impregnated hydrogel</td>
<td>Silicone</td>
<td>E. coli&lt;sup&gt;2&lt;/sup&gt;</td>
<td>99.7% after 3 days</td>
<td>[50]&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>E. coli&lt;sup&gt;2&lt;/sup&gt;</td>
<td>S. aureus&lt;sup&gt;3&lt;/sup&gt;</td>
<td>96.5% after 14 days</td>
<td>[50]&lt;sup&gt;a&lt;/sup&gt;</td>
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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.

### Polymer brushes

<table>
<thead>
<tr>
<th>Polymer brushes</th>
<th>Coating Material</th>
<th>Adhered Bacteria</th>
<th>Adhered Biofilm Coverage</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poly[N-(2-hydroxypropyl) methacrylamide] (poly(HPMA)) brush</td>
<td>Glass</td>
<td>E. coli&lt;sup&gt;2&lt;/sup&gt;</td>
<td>90% after 3 days</td>
<td>[21]&lt;sup&gt;a&lt;/sup&gt;</td>
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</table>

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.

### Polyzwitterions

<table>
<thead>
<tr>
<th>Polyzwitterions</th>
<th>Coating Material</th>
<th>Adhered Bacteria</th>
<th>Adhered Biofilm Coverage</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chelated copper ions on polydopamine films conjugated with sulfobetaine acrylamide (pDA-SBAA)</td>
<td>Silicone</td>
<td>E. coli&lt;sup&gt;2&lt;/sup&gt;</td>
<td>60% after 24 h</td>
<td>[16]&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>E. coli&lt;sup&gt;2&lt;/sup&gt;</td>
<td>S. epidermidis&lt;sup&gt;3&lt;/sup&gt;</td>
<td>35% less for polymer brush compared to control.</td>
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</table>

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.

### Other compounds

<table>
<thead>
<tr>
<th>Other compounds</th>
<th>Coating Material</th>
<th>Adhered Bacteria</th>
<th>Adhered Biofilm Coverage</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calixarene polymer</td>
<td>Silicone</td>
<td>E. coli&lt;sup&gt;2&lt;/sup&gt;</td>
<td></td>
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<tr>
<td>Natural polymer released by a marine Cyanobacterium - CyanoCoating</td>
<td>Gold substrate</td>
<td>E. coli&lt;sup&gt;2&lt;/sup&gt;</td>
<td></td>
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<tr>
<td>E. coli&lt;sup&gt;2&lt;/sup&gt;</td>
<td>K. pneumoniae&lt;sup&gt;6&lt;/sup&gt;</td>
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<td></td>
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<tr>
<td>P. mirabilis&lt;sup&gt;5&lt;/sup&gt;</td>
<td>MRSA&lt;sup&gt;3&lt;/sup&gt;</td>
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<tr>
<td>C. albicans&lt;sup&gt;4&lt;/sup&gt;</td>
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Coated substrates reduced biofilm development and crystal formation by P. mirabilis. Samples did not leach toxic compounds over the tested period. CyanCoating exhibited a high anti-adhesive efficacy towards the tested uropathogens (68–95%). In addition, CyanCoating decreased biofilm formation by E. coli, P. mirabilis and C. albicans (30–60%) under conditions representative of the urinary tract.

### Disruption of biofilm architecture

<table>
<thead>
<tr>
<th>Disruption of biofilm architecture</th>
<th>Coating Material</th>
<th>Adhered Bacteria</th>
<th>Adhered Biofilm Coverage</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quorum sensing inhibitors</td>
<td>Latex</td>
<td>C. kruse&lt;sup&gt;8&lt;/sup&gt;</td>
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<tr>
<td>C. glabrata&lt;sup&gt;4&lt;/sup&gt;</td>
<td>C. tropicalis&lt;sup&gt;8&lt;/sup&gt;</td>
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<tr>
<td>Coated catheters completely inhibited biofilm growth of non-Candida albicans species.</td>
<td>Polyurethane</td>
<td>S. aureus&lt;sup&gt;3&lt;/sup&gt;</td>
<td>95% compared to the control.</td>
<td>[54]&lt;sup&gt;a&lt;/sup&gt;</td>
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105-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].

<table>
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<th>Table 1. (continued)</th>
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<tr>
<td>Chrysophanol (CP)-functionalized silver nanoparticles</td>
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<td><strong>E. coli</strong></td>
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<tr>
<td>Coated surfaces</td>
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<tr>
<td>Reduced by 76, 77 and 99% for</td>
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<td>P. aeruginosa and E. coli cells to 12</td>
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<tr>
<td>and 6%, respectively, after 3, 6, and 12 h of exposure under flow conditions</td>
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<tr>
<td>In vivo studies demonstrated that implanted coated catheters showed very few cells and did not cause side effects in human bladder fibroblast cells</td>
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</table>
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 chlorhexidine [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.

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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.

References
Papers of particular interest, published within the period of review, have been highlighted as:
* of special interest
** of outstanding interest

In this study, the authors show the potential of poly(ethylene glycol) polymers to reduce bacteria adhesion, biofilm formation, and encrustation on UC surfaces under conditions representative of the urinary tract environment.


This is the first study to show the in vivo and in vitro potential of biocompatible hydrophilic polymers to inhibit bacterial colonization on UC surfaces for long periods.


30. In this study, chlorhexidine-loaded micelles are capable of significantly delaying bacteria and fungi biofilms on UC surfaces under hydrodynamic conditions prevailing in the urinary tract.


The authors carry out a proof of concept and demonstrate that silver coatings confer to silicone catheters the ability to resist bacterial colonization and encrustation by the release of Ag particles.
56. This is the first study to demonstrate the in vitro and in vivo effectiveness of chrysophanol (a quorum sensing inhibitor) to prevent biofilm formation on UC surfaces for 7 days without inducing human toxicity.