Antibiotic-Free Solutions for the Development of Biofilm Prevention Coatings

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1 Introduction

Stents and urinary catheters are commonly used medical devices, whose need is forecasted to grow considering not only the world population increase but also its aging and sedentary lifestyle [1].

Independently of the great development on biomaterials and device design, infection represents still a major cause of failure of these devices, with undeniable humane and economical costs. Different antibiotic-based solutions have appeared in the market to try to address the matter. However, there is growing evidence on the impact of antibiotic-resistant microorganisms on urinary tract medical-devices infections, and respective outcomes [2]. Within this chapter, several antibiotic-free alternatives, dedicated to the urinary tract, will be discussed.

Most device associated-infections are originated by biofilm establishment. Bacterial colonization through irreversible attachment, allows the production of extracellular matrix, forming ultra-organised three-dimensional bacterial structures, with orchestrated phenotypes that provide microorganisms resistance mechanisms to survive both the immune system and conventional antibiotics [3]. From the knowledge of these bacterial constructs, researchers have been exploring different angles of action that enforce the balance towards the infection obliteration and host recovery (Fig. 1).

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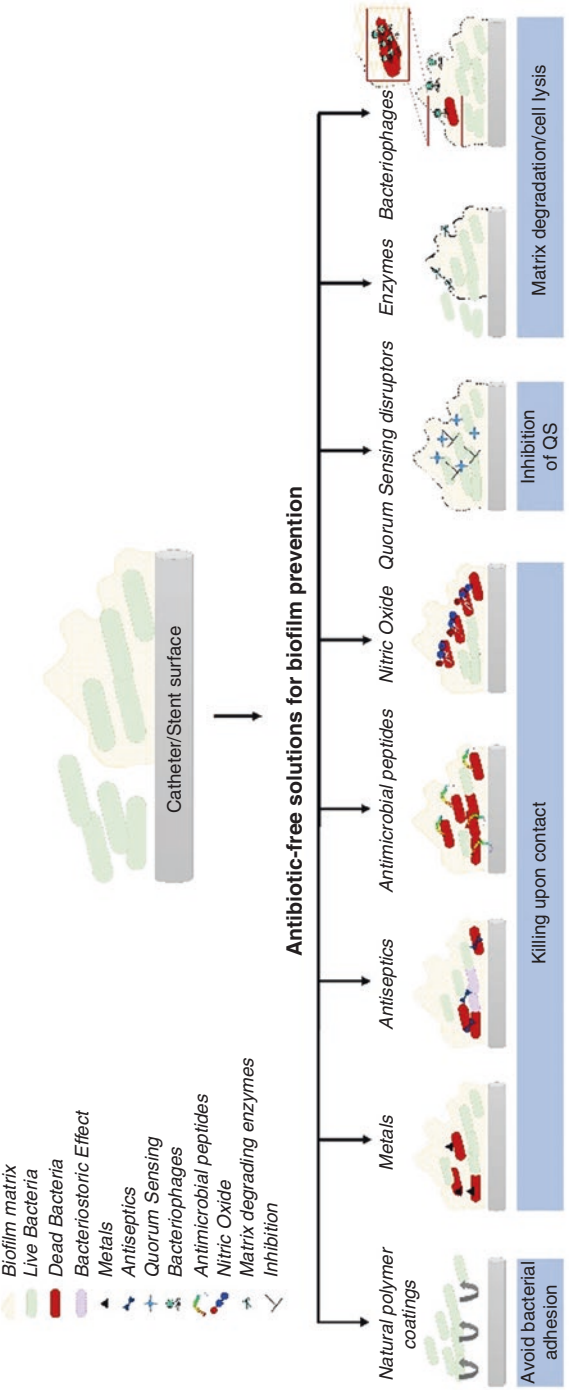

Fig. 1 Antibiotic-free strategies for combating biofilms on urinary stent or catheter surfaces

2 Natural Polymer Coatings

Apart from the different synthetic polymers with non-fouling properties described in previous chapters, naturally-occurring polysaccharides are presently being explored to design environmentally friendly and non-toxic materials. Several examples can be found in the literature, ranging from hyaluronic acid, heparin to ulvan or dextran [4–10], with potential for urinary applications. Gadenne et al., explored ulvans, with different molecular weight and sulfate ratio, for bacterial adhesion inhibition. Ulvans inhibited 36–88% of *Staphylococcus aureus* adhesion comparing to control [7]. Ruggieri et al., showed that latex catheters coated with a complex of heparin with tridodecylmethylammonium chloride were capable of reducing 53–84% *Escherichia coli* adherence comparing to controls: untreated latex, teflon coated latex (Bardex) and vinyl catheter [10]. Tenke et al., performed a 20 patients pilot assay and claimed that heparin-coated ureteral stents remained unaffected by encrustations and biofilm after 6 weeks [11]. Later, Lange et al., showed that heparin-coated Radiance © ureteral stents (Cook® Medical) failed in the prevention of *E. coli*, *Klebsiella pneumoniae*, *Enterococcus faecalis*, *S. aureus* and *Pseudomonas aeruginosa* adhesion and biofilm formation, while triclosan-eluting stents had an evident inhibitory effect on bacterial adherence for 7 days [8]. So further studies are needed to conclude about heparin coatings potential. A copolymer of polyurethane with dermatan sulfate (DS) was developed as new non-adhesive material, showing a significant *E. coli* adhesion decrease (29–57%) with increasing DS content [12].

Carboxymethyl chitosan was explored as an antimicrobial coating onto medical-grade silicone. Higher anti-biofilm efficiency was found against *E. coli* than *P. mirabilis* under flow-conditions. This effect can be explained by *P. mirabilis* high motility, which favors biofilms establishment downstream of an infected site [13]. Bracic et al., evaluated the anti-biofilm properties of colloidal polysaccharide complexes [chitosan, carboxymethyl chitosan, and hyaluronic acid in combination with a lysine-based surfactant (HA-MKM)] grafted on silicone sheets and tubes. All coatings showed antibacterial and antifungal properties, being HA-MKM the only solution capable of suppressing biofilm growth by ~ 50–75% during 18 h [14].

Recently, the anti-adhesive potential of cyanobacteria-based polymer coating (CyanoCoating) was reported against *Proteus mirabilis*, *E. coli*, *P. aeruginosa*, *K. pneumoniae*, Methicillin-resistant *Staphylococcus aureus* (MRSA) and *Candida albicans*. CyanoCoating hydrophilicity, negative charge and smooth surface may explain its broad anti-adhesive efficiency against all the uropathogens tested (68–95%), even in the presence of artificial urine (58–100%) [4]. Also, this anti-adhesive coating prevented big crystals deposition, reducing encrustation. CyanoCoating could also withstand ethylene oxide sterilization [5].

Biosurfactants represent an alternative strategy to promote anti-adhesiveness to the surfaces, which is thoroughly explained at Chap. 20.

3 Metal Alternatives

Metal alternatives such as silver (Ag), gold nanoparticles, copper oxide (CuO) or zinc (Zn), have been explored for urinary medical devices. The use of Ag or Ag alloys has been broadly exploited, having a wide expression in the market.

Gold nanoparticles antimicrobial effect is associated to bacterial membrane potential disruption, ATP levels reduction and tRNA inhibition [15]. Gold nanoparticles have been tested against important uropathogens, including *S. aureus*, *K. pneumonia*, *P. aeruginosa*, and *E. faecalis*, suppressing their bacterial growth at 24 h. However, the antimicrobial effectiveness diminished when used at longer-term, raising concerns about possible gold-resistance emergence [16].

Copper (Cu) promotes bacterial DNA degradation, enzymes inactivation and cell wall disruption [17–19]. Agarwala et al., tested CuO against *E. coli*, *P. mirabilis*, *E. faecalis*, *Pseudomonas* sp., MRSA and *S. epidermidis*, showing promising anti-biofilm activity even at sub-Minimum Inhibitory Concentrations (MIC) [20]. Rtimi et al., incorporated Cu alone or in combination with Ag onto polyurethane catheter surfaces using a new magnetron sputtering coating technique [21]. Cu–Ag hybrid coating catheters accelerated *E. coli* K12 inactivation ($\leq$ 5 min) compared to Cu or Ag coating catheters (30 min) [21].

Zinc antimicrobial activity has been associated with hydrogen peroxide production [22]. Zn has been combined with CuO to mitigate bacterial colonization [17]. Shalom et al., showed that Zn-doped CuO nanoparticles coated catheters reduced *E. coli*, *S. aureus*, and *P. mirabilis* biofilm formation (> 90%) under flow conditions for 24 h [23]. Moreover, these coated catheters prevented biofilm formation over 7 days in a catheter-associated urinary tract infection (CAUTI) rabbit model [23].

Despite, the promising antimicrobial effects, well-designed toxicity and irritation studies are still needed.

4 Chlorhexidine

Chlorhexidine (CHX) is a well-known antiseptic agent used for skin, dentistry, and in medical devices [24]. CHX is broad-spectrum bacteriostatic at low and bactericidal at high concentrations [24]. Recently, CHX has also been tested as a coating on urinary catheters [25–27]. Shapur et al., explored a CHX-releasing ethylcellulose varnish as antimicrobial coating, showing a 94% reduction of *P. aeruginosa* biofilm formation on catheters coated with 1% CHX [26]. Later, Segev et al., proved the anti-biofilm effectiveness of 1% CHX ethylcellulose-varnish coated urinary catheters using a dog model [25]. Zelichenko et al., evaluated growth inhibition on ureteral stent segments coated with 1% and 2% CHX, showing that 2% CHX-varnish prevented $\geq$ 99.9% biofilm formation of *E. faecalis*, *P. aeruginosa* and *E. coli* up to 2 weeks [28]. Gefter et al., compared anti-biofilm properties and dissolution kinetic of two sustained-release CHX-varnishes (ethylcellulose or Eudragit® RL) under the static or flow-conditions [27]. In both situations, ethylcellulose

coatings had longer sustained release of CHX (for at least 2 weeks), which resulted in an inhibition of ≥ 90% *P. aeruginosa* biofilm formation at 24 h [27]. Wood et al., developed a CHX hematophosphate nanoparticles (NP) ethylene-vinyl acetate-based coating [29]. The NP-coated surfaces inhibited MRSA and *P. aeruginosa* growth (measured at 24 h), and allowed for CHX sustained release over 56 days [29]. Phuengkham et al., spray-coated CHX-loaded polycaprolactone nanospheres onto silicone surface, reducing *S. aureus* (3 logs), *S. epidermidis* (2 logs) and *E. coli* (3 logs) biofilm formation over 7 days [30]. Then, Srisang et al., using the same coating reported 4 logs of reduction after 4 days, and 2 logs after 12 days of *E. coli*, *S. aureus*, and *C. albicans* tested in artificial urine [31]. Gaonkar et al., compared *in vitro* three different impregnated silicone catheters on urinary tract model: CHX–triclosan, CHX–Ag–sulfadiazine–triclosan, and nitrofurazone-coated catheters. CHX–triclosan catheter suppressed *P. mirabilis* growth for 20–30 days, compared to 4–10 days observed on the CHX–Ag–sulfadiazine–triclosan or nitrofurazone-coated catheters [32].

Despite, the extended protection period and promising antimicrobial effects, well-designed toxicity and safety studies are desirable to validate these coatings safety to patients.

5 Triclosan

Triclosan was the first compound to be approved for clinical use in ureteral stents, having potent broad-spectrum antimicrobial and anti-inflammatory activity. Cadieux et al., first tested triclosan impregnated ureteral stents on a *P. mirabilis* rabbit urinary tract infection model: 69% triclosan-stents showed no CFU counts and the remaining 31% had fewer CFU than controls. Also, triclosan group presented bladders with significantly less inflammation, although no significant difference in encrustation was observed among the groups [33]. However, in a long-term application (3 months) no clinical benefit was observed in terms of urine and stent cultures or overall subject symptoms in triclosan-eluting stents patients. Nevertheless, their use did result in decreased antibiotic usage and fewer symptomatic infections [34]. Later, a prospective randomized trial, reported that triclosan-eluting stent cannot reduce infection rates alone compared with antibiotic use [35]. This stent can, however, reduce several stent-related symptoms, and may have a role in combination with standard antibiotherapy.

6 Antimicrobial Peptides

Antimicrobial peptides (AMPs) may constitute an alternative to fight antibiotic resistance [36–39]. AMPs are part of the innate immune system of many organisms, having broad-spectrum, high anti-biofilm activity, and even immunomodulatory

potential [40–43]. Due to an unspecific mode of action, targeting the bacterial membrane or affecting multiple targets within bacteria, AMPs are much less likely to induce resistance [44]. Monteiro et al., immobilized the AMP Chain201D on model self-assembled monolayers [45]. Chain201D has broad antimicrobial activity against relevant uropathogens (bacteria and yeast), being highly stable in a wide range of temperatures, pH and salt concentrations [45]. Increased amounts of grafted AMP led to higher numbers of adhered/dead bacteria, revealing a concentration-dependent behavior. Chain201D surfaces could bind and contact kill 89% of *E. coli* and 99% of *S. aureus* adherent bacteria, suggesting a good candidacy for urinary applications [45].

Minardi et al., compared the efficacy of the AMP Tachyplesin III-coated ureteral stent alone or combined with piperacillin–tazobactam (TZP) intraperitoneal injection in the prevention of *P. aeruginosa* biofilm in a rat model. Tachyplesin III combined with TZP showed efficacies higher (3 logs of reduction) than each single therapy [46].

Lim et al., conjugated an engineered arginine–tryptophan rich AMP (CWR11) onto polymethylsiloxane (PDMS) surfaces and catheters through different chemistries [47, 48]. The CWR11-PDMS slides displayed excellent bactericidal effect against *E. coli*, *S. aureus* and *P. aeruginosa*, preventing ~ 92% *P. aeruginosa* biofilm formation after 24 h. The CWR11-silicone Foley catheter antimicrobial properties were retained for at least 21 days, with negligible cytotoxicity [47].

Li et al., grafted two broad-spectrum and salt-tolerant arginine/lysine/tryptophan-rich AMP (RK1 and RK2), onto PDMS surfaces via an allyl glycidyl ether (AGE) polymer brush interlayer. AMP-PDMS killed over 80% of *E. coli*, *S. aureus*, and *C. albicans* in either media, PBS or urine, and impaired biofilm formation for up to 3 days [49].

Mishra et al., developed a Lasioglossin III AMP chemically modified with a cysteine residue (CysLasio-III) to selectively immobilize covalently onto commercial silicone catheter [50]. CysLasio-III-catheter showed significant anti-biofilm properties, reducing 40% and 60% of *E. coli* and *E. faecalis* biofilm, respectively [50].

Lo et al., used polymer brushes to graft different AMPs (E6, Tet20, Kai13, and Tet26) to surfaces. *In vitro* tests revealed E6 was the most effective against *P. aeruginosa,* decreasing ~ 94.1% of bacterial adhesion [51]. Later, Yu et al., similarly grafted E6 on polyurethane tubing, reporting a > 4 logs reduction in *P. aeruginosa* adhesion to the tube and 3 logs in the bladder in a CAUTI mouse model [52].

Pinese et al., developed a silylated analogue of the AMP Palm–Arg–Arg–NH_2 [1], to directly graft onto a plasma-activated PDMS catheter [53]. The authors suggested a dual anti-adhesive/bactericidal effect of the coating, since a decrease of ~ 75% *E. coli*, *P. aeruginosa* and *S. aureus* adhesion was observed and 92% of bacteria were killed on peptide-grafted catheters within 1 h. This AMP-catheter was superior to a commercial Ag-based silicone catheter (Covidien) against *S. aureus,* with earlier and persisting activity over 2 weeks [53].

Chua et al., compared an AMP CP11-6A-coated silicone catheter to an Ag-hydrogel-coated and an uncoated catheter using *E. coli* inoculated human urine. Within 3 days, both uncoated and Ag-coated catheters were heavily colonized, while CP11-6A-coated catheter showed negligible biofilm colonization and no detectable "bacteriuria" [54].

Although progress has been made, and many AMP-based coatings have impressive antimicrobial activity, further studies are needed to establish clinical significance.

7 Nitric Oxide

Nitric oxide (NO) has been used as an antimicrobial, showing great potential for biomedical applications [55], although poorly explored for urinary devices [56–58]. NO covalently binds DNA, proteins and lipids, thus inhibiting or killing pathogens [59]. NO-donating polymers may provide localized treatment with minor toxicity. Nevertheless, further studies are needed to understand the NO effects in the bladder, since it is known that NO plays an important role in other biological conditions (e.g. vasodilatation, neurotransmission) [56]. Regev-Shoshani et al., showed that gaseous NO-impregnated catheters have a sustained NO release over 14 days with stable storage. The NO release was faster in urine than in water, suggesting pH influence in the release, which might have implications at patient level [56]. Colletta et al., developed *S*-nitroso-*N*-acetyl-D-penicillamine impregnated Foley catheters with outstanding anti-biofilm effect, reducing *S. epidermidis* (3.7 logs) and *P. mirabilis* (6 logs) biofilm formation after 14 days [60]. Later, Ketchum et al., applied tertiary *S*-nitrosothiol and *S*-nitroso-*tert*-dodecyl mercaptan (SNTDM) as NO donors onto catheter tubings. NO-tubings reduced *S. aureus* colonization (4 logs) on SNTDM-impregnated catheters at 1 week, maintaining high anti-biofilm efficacy (3 logs of reduction) even after 3 weeks [61].

8 Quorum-Sensing Disrupters

Quorum-sensing (QS) corresponds to a cell–cell communication process, based on signaling molecules secreted by adhered bacteria to determine if a sufficient number of microorganisms is present that can initiate the expression of a particular biofilm-associated phenotype [62]. Quorum quenching, can severely hinder biofilm formation, diminishing bacteria antimicrobial resistance [63].

Ureteral stents coated with QS-inhibitor RNAIII-inhibiting peptide (RIP) reduced *S. aureus* adhesion (2 logs) to stents implanted in rat bladders. No bacteria were

detected either on the stent or urine when the peptide treatment was combined with teicoplanin (which achieved only 3 logs reduction in single teicoplanin therapy) [64].

A combination of alpha-amylase and acylase was tested as a layer-by-layer coating on silicone urinary catheters [65, 66]. Alpha-amylase interferes with assembly of the extracellular matrix and acylase degrades small quorum signaling molecules. When tested *in vitro*, this coating reduced *P. aeruginosa* (> 40%), *S. aureus* (> 30%) and mixed-species biofilms (> 50%), although planktonic growth was not inhibited. *In vivo* (rabbit model) biofilm formation on the catheter's balloon section was decreased by 90%, although this was not seen in the lumen of the catheter. Furthermore, the quorum quenching action of single acylase, reduced significantly *P. aeruginosa* biofilm formation on a catheter under static and dynamic conditions [66].

Recently, furanone, a QS-inhibitor, was also tested as a coating for urinary catheters (latex, silicone and polyurethane), preventing *Candida* sp. biofilm formation in more than 80% [63].

9 Extracellular Matrix Degrading Enzymes

Exopolysaccharides are a crucial component of biofilm architecture, providing protection against drugs and host immunity [67]. Therefore, enzymes capable of degrading one of biofilm matrix components (proteins, extracellular DNA, polysaccharides), would impact on biofilm establishment [68].

Alpha-chymotrypsin (α-CT), a serine endopeptidase that cleaves peptide bonds [69, 70], was grafted on polyethylene surfaces, significantly reducing adherent cells, affecting the biofilm thickness, roughness and coverage. Additionally, the biovolume of the polysaccharide matrix decreased [70].

Also, recombinant human DNase (rhDNase), has efficiently inhibited *S. aureus* biofilm formation at 1–4 μg/L [71].

Cellobiose dehydrogenase (CDH), an oxidative enzyme that produces hydrogen peroxide, was grafted CDH onto PDMS catheters by ultrasonic waves, reducing *S. aureus* growth (60%), biomass deposition (30%), and biofilm production (70%) when compared to control catheters [72]. Thallinger *et al.*, tested CDH-grafted urinary catheter in artificial urine, over 16 days, observing a 60% reduction of the viable *S. aureus*, and a 70% biofilm formation decrease, comparing to control [73].

Glycoside hydrolases (Ghs) selectively target and hydrolyze the glycosidic bonds of exopolysaccharide components of the biofilm matrix [74, 75]. Asker et al., used Ghs that specifically targets Psl, a neutral exopolysaccharide, grafted to silica glass, PDMS, or polystyrene surfaces. PslGh-grafted surfaces reduced adhered *P. aeruginosa* in 3 logs up to 8 days, suggesting this strategy keeps bacteria in a planktonic state more susceptible to antimicrobials [76].

More studies might further validate this strategy, alone or in combination with other antimicrobials [75].

10 Bacteriophages

Bacteriophage (phage) therapy is proposed as a safe and effective strategy to address biofilms and multidrug-resistant pathogens, without impairing the resident microbiota [77, 78]. Lytic phages infect and kill specific bacteria, so their spectrum can be tuned creating a phage cocktail [77–80]. Phages are self-replicating at infection sites, producing new phage progeny that can migrate to a new focus of infection. Additionally, phages encode enzymes that degrade biofilm matrix [77, 78, 80]. Phages-impregnated catheters have been used against common uropathogens [78, 80–83].

Curtin et al., reported a significant reduction of coagulase-negative *S. epidermidis* biofilm formation (2.34 logs) over 24 h on hydrogel Foley catheter impregnated with phage 45,682. Later, Carson et al., showed that T4 or coli–proteus phages impregnated hydrogel-coated Foley catheters were able to reduce 90% of *P. mirabilis* or *E. coli* biofilm formation over 24 h, respectively [78].

Lehman et al., showed hydrogel catheters pretreated with anti-Pseudomonas and anti-Proteus phage cocktails have anti-biofilm activity against single- (1.5 logs *P. aeruginosa* and 2.5 logs *P. mirabilis*) and dual-species (4 logs and 2 logs, respectively) biofilms, over 48 h [77]. Previously, the same group reported that anti-Pseudomonas phage cocktail catheters is more effective than single phage-loaded catheters [82].

Milo et al., showed that the dual-layered polymeric coating, based on PVA hydrogel impregnated with phage, capped by a pH-sensitive polymer (EUDRAGIT S 100), was able to prevent *P. mirabilis*-associated encrustation of the catheter lumen through the pH-triggered release of phage [80].

Liao et al., compared the efficacy of 4 silicone catheter segments pretreated with sterile media, *E. coli* HU2117, anti-pseudomonal phage (ΦE2005-A) and *E. coli* HU2117 plus phage ΦE2005-A, on prevention *P. aeruginosa* biofilm formation for 72 h. A synergistic effect between pre-established biofilm of *E. coli* HU2117 and phage ΦE2005-A was observed, reducing efficiently (4 logs after 24 h and 3 logs after 72 h) *P. aeruginosa* adherence to catheters [83].

11 Conclusions

The urinary tract device-associated infections prevalence and the rise of multidrug-resistant microorganisms have prompt researchers towards the development of antibiotic-free solutions. A broad number of alternatives have been proposed, however, given the wide variability of results for different strategies, there remains a tremendous need to validate their clinical significance, particularly assuring patient safety. Additionally, most of these strategies might be advantageous while in combination with current therapies, so further studies are needed.

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