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Biofilm formation on ureteral stents – incidence, clinical impact and prevention

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Summary

Ureteral stents are a simple, minimally invasive method of maintaining ureteral drainage to assure renal function, treat pain caused by ureteral obstruction and avoid external or visible devices. Ureteral stenting is, however, associated with a clear side-effect profile, including irritation on voiding, pain and haematuria. Complications such as stent dysfunction and clinically significant urinary tract infections are also regularly observed. Although this has not yet been thoroughly researched, it appears that biofilm formation on ureteral stents plays a key role in the associated morbidity. In this review, we summarise the current evidence and identify areas that should be further studied to reduce the morbidity associated with ureteral stenting.

Key words: *ureteral stent; mineralised biofilm; encrustation, morbidity; prevention; treatment; review*

Introduction

Internal drainage of the upper urinary tract by ureteral stents is used for different purposes in urology [1]. They are a simple and effective method of maintaining ureteral drainage to assure renal function, treat pain caused by ureteral obstruction, and avoid external or visible devices.

However, ureteral stenting has a well-defined side effect profile. Most patients suffer pain, as well as irritation on voiding, and haematuria often while the stent is *in situ* [2, 3]. Complications such as stent dysfunction and clinically significant urinary tract infections (UTIs) are regularly observed. The procedure therefore also constitutes a relevant economic burden [4]. In view of the prevalence of ureteral stenting and the associated symptoms, Joshi et al. made an important step forward by developing and validating a specially designed questionnaire, the Ureteral Stent Symptoms Questionnaire (USSQ), which analyses the various domains of health affected by stents [5].

Despite this, the possibilities of preventing and treating stent-associated morbidity are still limited. Alpha-blockers [6], antimuscarinics [7] and good patient education [8] can reduce symptoms caused by ureteral stents, whereas the influence of the intravesical stent position is still controversial [9, 10]. So far, none of the materials or designs tested has reduced symptoms significantly [11]. Further studies in this field and novel concepts to reduce stent-associated morbidity are urgently required.

The role of biofilm formation on ureteral stents and its prevention have been discussed as a possible approach. Biofilms are defined as an accumulation of microorganisms and extracellular biopolymers that form a structured community on a surface [12]. Ureteral stents offer an ideal surface substrate for such microbial colonisation and biofilm formation [13, 14]. Biofilms have been suspected to be the main reason for stent obstruction, stent dysfunction and clinically relevant infections leading to premature or emergency stent changes, antibiotic treatment and hospitalisation. Moreover, it has been proposed that biofilms lead to irritation and inflammation of the urothelium, which may aggravate the symptoms described.

In this review, we give an overview of the topic and describe the current evidence. We provide information on the incidence and development of biofilms, including the process and timeframes of biofilm formation, and the distribution and composition of biofilms. We also review methods for biofilm assessment, such as bacterial involvement, mineralogical composition and quantification of biofilms. We discuss the clinical impact of biofilms on stent-associated symptoms, infections, encrustation and obstruction. Moreover, we report on the most recent concepts for preventing and treating biofilms, including antimicrobials and different materials and coatings.

Methods

We performed this systematic review in accordance with Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement [15]. The protocol for the review is available on PROSPERO, the international prospective register of systematic reviews (CRD42016037872, http://www.crd.york.ac.uk/PROSPERO). MEDLINE and SCOPUS were independently searched by two authors (VZ and PB), screening for eligibility was performed in accordance with the Cochrane

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Handbook for Systematic Reviews of Interventions, followed by crosschecking and clarification of any differences by a third author (DA). The following search terms including the relevant MeSH terms were used: ((ureteral catheter OR ureteral stent OR DJ stent OR double J stenting) AND ((lower urinary tract symptoms OR LUTS) OR morbidity OR incidence OR (prophylaxis or prevention) OR treatment OR (dysuria OR symptoms OR pain) OR (complications OR problems) OR biofilm OR infection OR (stent material OR stent design) OR questionnaire OR encrustation)) AND (etiology OR pathogenesis OR causality OR causes). Results were limited to English language, abstract and full-text availability. In addition, references of relevant articles were screened for additional important papers.

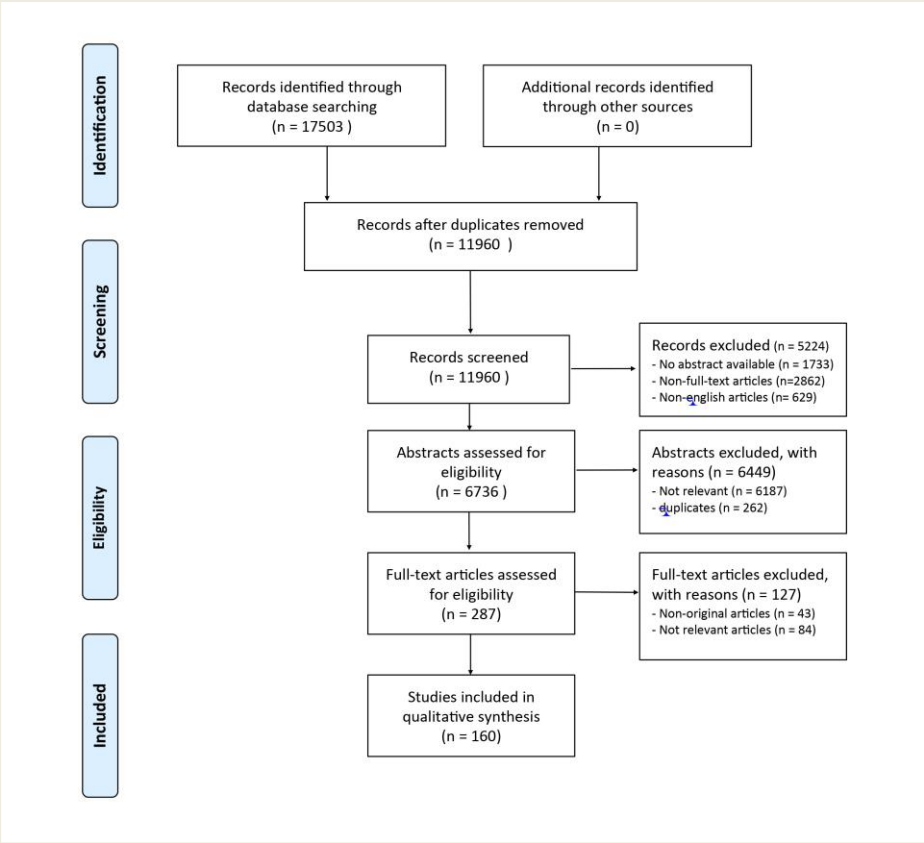

Figure 1: PRISMA flow diagram. Modified from: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. For more information, visit www.prisma-statement.org.

Results

We identified 17 503 records through database searching, with 160 articles finally included in this systematic review. The PRISMA flow diagram is shown in figure 1.

Development and incidence of biofilms on ureteral stents

Process of biofilm formation

In general, the development of a biofilm is regarded as a multistep process, where the first step involves the formation of a conditioning film made up of extracellular molecules [16, 17]. After insertion, the stent material comes into contact with body fluids such as urine and blood, and with uroepithelial tissue. As a result of the complex and variable composition of human urine, information on the composition of the conditioning film on stents is still limited. Elwood and co-workers examined the *in vitro* formation of conditioning films on stents after incubation in urine and found adsorbed cytokeratins in particular. These are glycosylated cell-surface proteins abundantly present on the surface of uroepithelial cells. Additionally, blood proteins, such as haemoglobin and fibrinogen, and inflammatory proteins appear to be involved in conditioning film formation, possibly owing to injuries and inflammation often associated with the surgical insertion of ureteral stents [18].

Even though uromodulin (Tamm-Horsfall protein), one of the most abundant urinary antimicrobial proteins, has been found in stent biofilms in most patients, it appeared not to be among the relevant proteins for conditioning film formation in the first 72 hours after insertion and seems to play only a marginal role in further biofilm development and encrustation [19]. In contrast, it has previously been shown to be a key factor in the development of conditioning films [16, 20].

It is assumed that, in a second step, these conditioning film proteins facilitate the adsorption of various molecules from the surrounding fluids and tissues, such as collagen, fibrinogen and albumin [17], which then alter the surface of the ureteral stent and may allow attachment of microorganisms [21]. However, a recent study indicates that the presence of a conditioning film might not increase bacterial adhesion and colonisation of stents by uropathogens [18]. The mechanisms of attachment of microorganisms to ureteral stent surfaces therefore still remain unclear. It has been shown that urinary pH, ionic strength, and electrostatic and hydrophobic interactions play an important role [12, 22–24]. The investigation of proteins present in encrustations and biofilms showed that five different proteins are present in high numbers: alpha-1 antitrypsin, immunoglobulin kappa (Ig

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kappa), immunoglobulin heavy chain G1 (IgH G1), and histones H2b, and H3a.

Bacteria attach to foreign body surfaces via various species-specific strategies that define the biofilm-building potential of an organism. For example, bacterial cell-surface appendages, such as type 3 fimbriae, are regarded as important virulence factors as they play a large role in surface attachment and biofilm formation by *Klebsiella pneumoniae* [25, 26] and *Escherichia coli* [27]. Other adhesion strategies include adhesion to secreted bacterial extracellular polymeric substances that may also contribute to conditioning-film formation [28]. Regarding the formation of mineralised biofilms on ureteral stents, urease-secreting strains, such as *Pseudomonas aeruginosa* and *Proteus mirabilis* in particular, have been extensively investigated. They secrete urease, which increases the urine pH resulting in the precipitation of struvite and hydroxyapatite crystals, adhesion factors, transporters, transcription factors, enzymes and two component systems. Of note, co-infection with two bacteria leads to synergistic induction of urease activity [29–33]. Molecular research and mutagenesis analysis are ongoing and promise a better understanding of the mechanisms of biofilm formation by bacteria [25, 32, 34–40] and fungi [41–45].

Many authors have emphasised the importance of flow dynamics in the stented ureter and the implications of vesicoureteral reflux, and several *in vitro* models have been developed to further investigate the process of biofilm formation [17, 23, 46–52]. However, many of the *in vitro* bacterial adhesion assays have been derived mostly from classic microbiological approaches, and often do not reflect important *in vivo* factors such as stasis vs flow, rich medium vs physiological or pathological urine environment, or the involvement of multiple species which may be synergistic or inhibitory.

In the last stage of stent biofilm development, complex biofilm structures are formed, where groups of bacteria are divided by spaces filled with surrounding fluid, and open water channels allow the transport of oxygen and nutrients to assure further cellular growth. Depending on the microorganisms involved, ureteral stent biofilms are composed 10 to 25% of cells and 75 to 90% of exopolysaccharide matrix [16], mostly with a rough, often mineralised, surface (figures 2, 3).

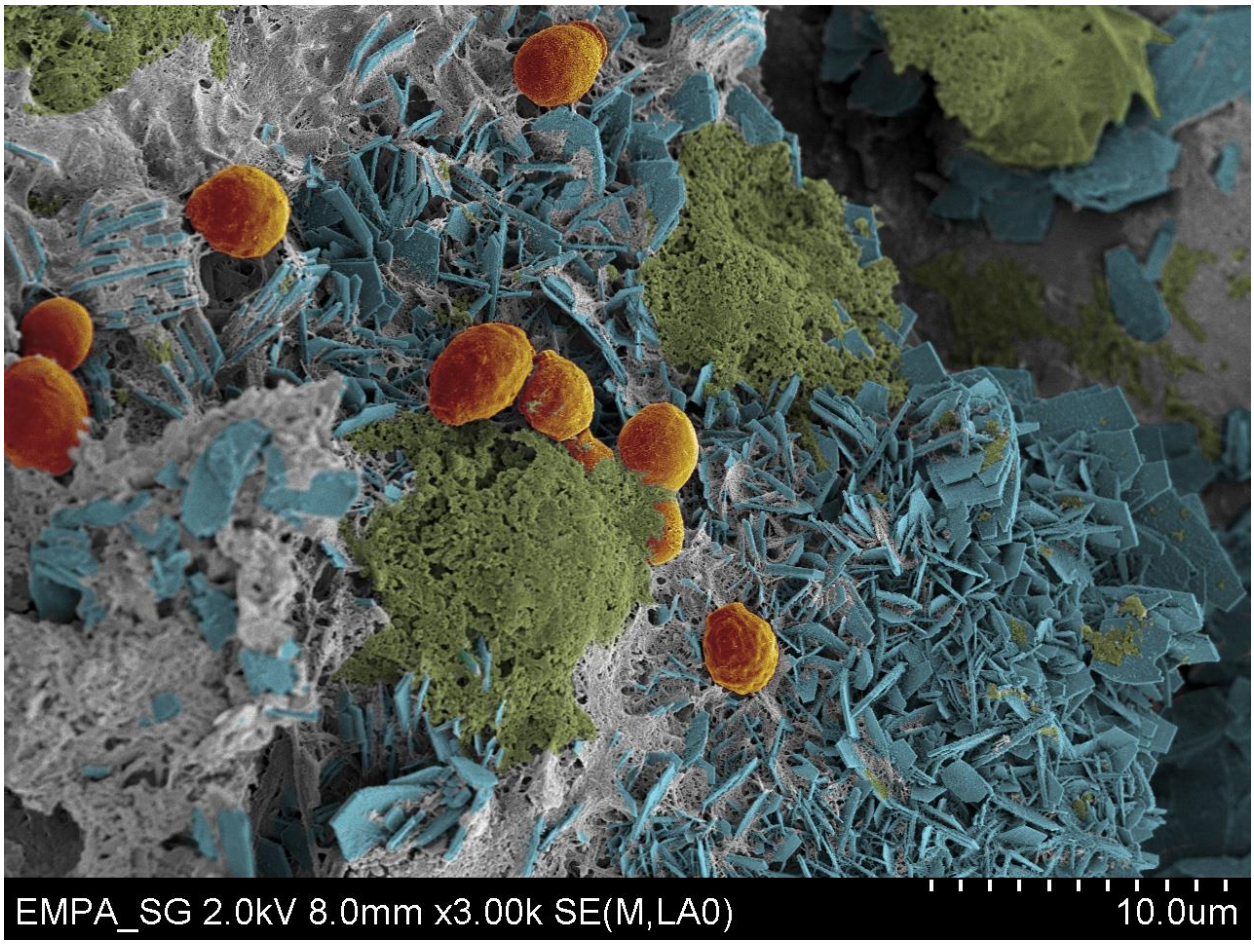

Figure 2: Colourised scanning electron micrograph of a stent biofilm showing microbes (highlighted in orange), hexagonal carbonate hydroxyapatite crystals (blue) and amorphous crystal-like structures (green). For imaging, stent sections were fixed with glutaraldehyde and formaldehyde in phosphate-buffered saline, followed by Au/Pd sputtering after chemical dehydration.

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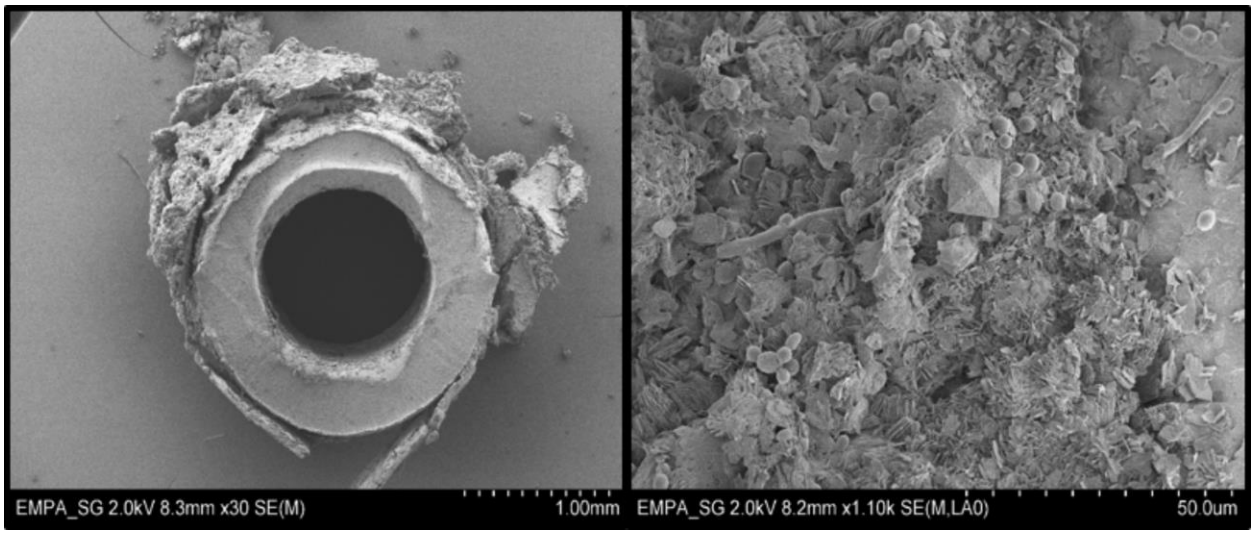

Figure 3: Example of a cross-section of a ureteral stent (left image) and a scanning electron micrograph of the stent biofilm (right image).

Timeframes of biofilm development and encrustation

Discussions about the optimum indwelling time for ureteral stents are still ongoing. One reason for this might be that only sparse data on the temporal development of stent biofilms are available. The initial steps of biofilm formation – conditioning film formation – occur immediately after stent insertion, whereas clinically significant encrustation seems to require longer indwelling times. It has been shown that after short-term antibiotic prophylaxis of 2 to 3 days, bacterial colonisation of the stent is detectable 2 weeks after implantation, and that stent colonisation precedes urine colonisation, with detection of planktonic bacteria [53, 54]. Kawahara et al. [55] described an encrustation rate of 27% at less than 6 weeks, 57% at 6 to 12 weeks, and 76% at more than 12 weeks. They did not, however, quantify the biofilm mass in detail. Rahman et al. [56] reported on colonisation rates of 24% before 4 weeks, 33% after 4 to 6 weeks, and 71% after 6 weeks. Riedl et al. [14] reported 100% ureteral stent colonisation in permanently stented patients (mean stent indwelling time 39.5 days) and 69% in the temporarily stented (mean 11 days). In a retrospective study of severely impacted ureteral stents requiring advanced removal procedures, 43% of the stents had become encrusted within 4 months and 76% within 6 months [57]. In patients with risk factors, such as diabetes mellitus, chronic renal failure and diabetic nephropathy, shorter stent indwelling times have thus been recommended because of a significantly higher risk of colonisation and bacteriuria [58].

Distribution and composition of biofilms

In spatial distribution, the biofilm mass seems to decrease towards the distal tip of the stent [59], and inner deposits seem to be very rare, even in "obstructed" stents [60]. Calcium oxalate appears to be the predominant type of encrustation, followed by struvite, in the mineralised biofilms [61], and it has been shown that the mineral composition on ureteral stents significantly correlates with stone analysis in patients with urinary stones [59, 62].
Enterococcus faecalis and *E. coli* seem to be the most commonly involved microbial colonizers on ureteral stents [63]. Bacteria expressing urease, such as *Proteus* spp., *Providencia* or *Pseudomonas*, are also involved and can induce rapid growth of biofilms. Urease activity causes alkalisation of the urine, leading to undersaturation of magnesium and calcium with resulting precipitation on the stent [61]. Other bacteria that have been associated with stent biofilm formation are *Staphylococcus* and *Edwardsiella* spp. [64–66]. However, the type of microbes identified on ureteral stents strongly depends on the method of detection, and information enabling comparisons is lacking at present. Aydin et al. [66] recently suggested that pathogens identified in urine cultures are the same as those colonising the stent. In contrast, other authors have reported that urine culture has a low sensitivity (40%) for stent colonisation [67]. In the study by Riedl et al. [14], pathogens colonising the stent were correctly identified by means of urine cultures in only 21% of patients.

Assessment of biofilms

As previously described, the stent biofilm composition and the process of biofilm development are complex, and include organic and inorganic components. Different approaches are therefore used to assess biofilms on ureteral stents.

Assessment of bacteria involved

Although several methods have been described, the most appropriate examination procedure still needs to be defined. The European Society of Clinical Microbiology and Infectious Diseases (ESCMID) Guidelines 2015 propose assessment by use of microscopy, and with culture or culture-independent techniques, preferably after sonication to investigate microbial diversity [68]. However, these recommendations do not guarantee complete release of biofilm from stents. Bonkat et al. [69] showed advantages over sonication with a roll-plate technique in the diagnosis of microbial ureteral stent colonisation. They also reported that urine culture is less sensitive than both sonication and the roll-plate technique.
Recently, Choe et al. [64] showed that different techniques must be applied simultaneously to increase the detection of bacterial species in a urinary catheter biofilm. They compared four different 16S ribosomal RNA analysis techniques: capillary electrophoresis, terminal restriction fragment length polymorphism, denaturing gradient gel electrophoresis and pyrosequencing. All showed different bacteria. Wilks et al. [70] described the combination of an advanced light microscopy

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technique, episcopic differential interference contrast microscopy with epifluorescence, as a real-time imaging method to track all stages of biofilm development.

Mineral composition

Both X-ray diffraction [59, 61] and optical coherence tomography [71] are feasible and effective methods [62] to determine the specific mineralogy of encrustations. Furthermore, Bithelis et al. [61] reported that Fourier-transform infrared spectroscopy was superior to classical scanning electron microscopy.

Quantification of biofilms

Little has been published on quantitative biofilm analysis of ureteral stents. As mentioned above, the overall spatial distribution of the stent biofilms is somewhat inhomogeneous. Bithelis et al. [61] analysed the mean mass of encrustation per stent, finding 71 mg on average in stone-forming patients compared with 1 mg in patients with no history of stone formation. Sighinolfi et al. [59] assessed the weight of encrustations separately at different positions along the ureteral stent. The median weight of encrustation was 6 mg/cm at the proximal end and 3 mg/cm at the distal end of the stent. However, no well-defined methods to assess total biofilm mass on ureteral stents or to reliably quantify bacterial load have been published.

Clinical impact of biofilms

Impact on stent-associated symptoms

Ureteral stents have a well-defined side effect profile. Amongst other complaints, irritation on voiding and stent-related pain affecting daily activities have been reported in 78 and 80% of patients [2], and 42% of patients suffer from haematuria [3]. Only two studies have assessed the influence of biofilms on stent-associated symptoms. Bonkat et al. showed a significant association between biofilms on ureteral stents and the incidence of lower urinary tract symptoms [72]. Moreover, a longer stent indwelling time and positive urine cultures have been reported to be significantly associated with patient discomfort [73]. Nevertheless, a negative impact of biofilms on stent-associated symptoms seems to be plausible, even though the correlation of biofilms and stent comfort has not yet been investigated sufficiently. In particular, studies using the USSQ [5], a validated questionnaire assessing the whole spectrum of stent-associated morbidity, are not available to date.

Impact on urinary tract infections and bacteriuria

Stent colonisation has been reported to precede urine colonisation [54]. However, stent colonisation does not always entail symptomatic UTI, particularly given that the bacteria may live the biofilm lifestyle instead of detaching and living as planktonic swarmers [66, 74]. As urine cultures have a low sensitivity (40%) for stent colonisation, a negative culture does not rule out a colonised stent [67]. On the day of stent removal, only 13% of patients with colonised stents showed bacteria ($>10^5$ colony-forming units/ml) in culture of urine obtained prior to stent removal (mean indwelling time of stent 33.9 ± 22.4 days) [66]. However, these are controversial findings, as other authors found sensitivities of 21 to 93% [75, 76]. Moreover, bacteria from stented patients, even when cultured from urine, are more resistant to antibiotics than those cultured from urine before stent insertion. This is probably associated with the expression of biofilm-specific genes [67]. Thus, even in the case of sterile urine cultures, secondary endoscopic procedures after stent removal are likely to put the patients at an increased risk of infectious complications.

UTIs associated with indwelling ureteral stents are most frequently caused by *E. coli*, *Enterococcus* spp., *Staphylococcus* spp., *Pseudomonas* spp. and *Candida* spp. [67, 74]. Comorbidities such as chronic renal failure, diabetes and pregnancy have been shown to increase the risk of lower UTIs associated with ureteral stents [77]. A study assessing complications after renal transplantation concluded that early removal of the stent 2 weeks after renal transplantation decreases morbidity and UTI rates [78].

Impact on stent encrustation and obstruction

Markedly encrusted ureteral stents can pose a serious challenge to the urologist when the stent has to be removed or changed. In serious cases, a multimodal approach using extracorporeal shock wave lithotripsy, ureteroscopy or even more invasive techniques may be necessary [57]. As the grade of encrustation is related to the indwelling time [55], "forgotten stents" in particular often give rise to problems [79].

Obstruction of the stent can lead to upper urinary tract retention resulting in flank pain, deterioration of renal function, obstructive pyelonephritis and even sepsis, and therefore often requires surgical intervention. However, even completely obstructed stents often pass unnoticed as the urine is still often able to pass along the dysfunctional stent [79, 80].

Prevention and treatment

Antimicrobials

Several studies have emphasised the efficacy of fluoroquinolones in preventing biofilm formation. However, the use of antibiotics at the time of stent insertion can only postpone but not prevent biofilm formation [14], and eradication of already preformed biofilms cannot be achieved by antibiotics [81–83]. To reinforce the antibacterial activity of fluoroquinolones, various combinations have shown promising effects. Pentacyclic triterpenes [84], N-acetylcysteine [85] or rifampin [81] may enhance the antibiotic activity of fluoroquinolones, even against preformed mature biofilms [85]. However, none of these combinations have found their way into clinical practice, and bacterial diversity and antibiotic resistance present an increasing problem in clinical practice.

Besides antibiotics, cis-2-decenoic acid, an unsaturated fatty acid, showed promising results in the prevention of biofilm formation on catheter biofilms [86]. Along with the ability to inhibit biofilm formation by *P. aeruginosa*, cis-2-decenoic acid is capable of inducing the dispersion of established biofilms formed by multiple types of microorganisms.

Although some of the experimental approaches described above showed promising results against specific microbes, clinical implementation is difficult due to the variety of bacteria involved in the process of biofilm formation.

Stent materials

Important properties of an ideal stent are easy insertion, resistance to compression and migration, biodurability and

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biocompatibility [87]. Although numerous types of stent have attempted to meet these requirements, the ideal stent has yet to be created.

While soft materials – synthetic polymeric compounds such as silicone or polyurethane – might be associated with a lower incidence of irritation [87, 88], metal stents seem to perform better in patients with ureteral compression due to extrinsic malignant obstruction. However, the problem of encrustation and bacterial adhesion remains the same [89].

New promising designs, such as novel, gel-based ureteral stents [90] or the use of an electrical microcurrent to prevent biofilm formation [91, 92] are still at the developmental stage, and clinical data have not yet been published. At the moment, none of the materials on the market can prevent or reduce biofilm formation on ureteral stents to a clinically relevant extent. An overview of different stent materials and their performance is given in table 1.

Table 1: Ureteral stent materials and their performance in preventing biofilm formation.

Stent material	Specification	Performance	Clinical stage / availability
Polyurethane stents	– "Soft" ureteral double-pigtail catheter (Sof-Flex®) – "Firm" ureteral double-pigtail catheter (classic polyurethane stent)	– No differences in encrustation and bacterial adhesion of the stents *in vivo* [88] – Less stent related dysuria and pain in patients with "soft" stent type [88]	Both stent types are commercially available
Metal stents	– Self-expandable ureteral stent (Wallstent®, cobalt-based alloy) – Thermo-expandable ureteral stent (Memokath®, nickel-titanium alloy) – "Coil" design ureteral double-pigtail catheter (Resonance®, nickel-cobalt-chromium-molybdenum alloy)	– No advantages regarding encrustation *in vivo* – Fewer urinary tract infections reported *in vivo* – Good performance in malignant ureteric obstruction (especially Memokath®) – Poor performance in benign ureteral obstruction [89]	All three stents are commercially available
Gel-based stents	– Gel-based stent (pAguaMedicina®, highly hydrated, partially hydrolysed polyacrylonitrile polymer)	– Significant reduction (43–71%) of bacterial adhesion and biofilm formation *in vitro*, not yet tested *in vivo* [90]	Commercially available for paediatric use.

Table 2: Coating techniques and their influence on biofilm formation.

Coating technique	Performance	Clinical stage / availability
Heparin coating	– Significant reduction of encrustation *in vivo* – No effect on bacterial adhesion *in vivo* [93–95]	Commercially available product (Radiance®)
Hydrogel-based coatings	– Significant reduction of encrustation *in vitro* – No effect on bacterial adhesion *in vitro* [97]	Commercially available product (HydroPlus® coating)
Diamond-like carbon coatings	– Decrease of encrustation and biofilm formation *in vitro* and *in vivo* [98]	Commercially available product (VisioSafe DIAMOND®)
Triclosan-eluting stents	– No significant reduction of encrustation or biofilm formation *in vitro* and *in vivo* – Significant reduction of stent-related flank pain, abdominal pain and urethral pain [99]	Formerly commercially available (Triumph®); Withdrawn from market because of concerns about the development of bacterial resistance
Oxalate degrading enzyme coatings	– Significant reduction of encrustation, no results on bacterial adhesion *in vitro* and *in vivo* (animal study) [103]	Not yet commercially available
Nanoscale-body coating	– Antibacterial effects resulting in effective prevention of *Pseudomonas aeruginosa* biofilm formation *in vitro* [104]	Not yet commercially available

Coatings

A further approach to preventing biofilm formation is the principle of coating ureteral stents. Although heparin-coated stents significantly reduced ureteral stent encrustation, no positive effect against bacterial adhesion was seen [89, 93, 94]. In the past, hydrogel-based coatings raised expectations that they would effectively inhibit hydroxyapatite encrustation and bacterial biofilm colonisation, and reduce general stent-related morbidity [95, 96]. However, in 2007, John et al. dampened these expectations when they showed that bacterial adhesions were similar using stents with and without hydrogel-based coatings [97]. Laube et al. examined the effect of diamond-like carbon coatings *in vivo* and reported a decrease in encrustation and biofilm formation [98]. In principle, stents can also be coated with various active compounds such as antimicrobials or enzymes. After initial encouraging results, a recently published study showed that triclosan-eluting stents had no significant impact on biofilm formation, encrustation or infection development in short-term stented patients [99]. Some combinations of antimicrobials effectively inhibit biofilm-forming properties of UTI-specific bacteria [100–102]. However, the (co-)induction of antibiotic resistance and the wide range of biofilm-forming bacteria limited the effect of such coatings and their implementation in clinical practice. Nevertheless, initial results indicate that an enzyme-based approach might be an alternative to conventional antibiotic coatings. Watterson et al. [103] found less encrustation on oxalate degrading enzyme-coated silicone, and the most recent findings showed that the use of nanoscale bodies might be promising. Francesko et al. [104] described nanoscale structures in bacteria-responsive surface coatings on medical indwelling devices acting via antibacterial and self-defensive properties. An overview of coating techniques and their influence on biofilm formation is shown in table 2.

As with stent materials, one of the problems in the development of more effective stent coatings seems to be the absence of standardised testing with well-elaborated *in vitro* models. High manufacturing costs are another limitation for the implementation of promising materials and coatings in clinical practice.

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Other methods of biofilm prevention

Correction of metabolic alterations in urine such as hyperoxaluria, hypocitruria or reduced volume can have a positive effect on encrustation and biofilm formation. Bithelis et al. [61] showed that these factors, which are often responsible for stone formation, might also enhance the risk of biofilm forming on ureteral stents.

Discussion

Ureteral stents are a simple, minimally invasive method to ensure urinary transport through the upper urinary tract. They also offer an ideal surface for biofilm formation.

The process of biofilm formation on ureteral stents is complex and includes the early formation of a conditioning film and subsequent accumulation of organic and inorganic molecules, as well as adhesion and colonisation by a variety of uropathogens. Finally, an extracellular polymeric matrix can become the main component of the biofilm, and a structure is formed that ensures nutrition and protection of the microorganisms involved, which show reduced growth rate together with increased resistance to antibiotic therapy.

Great efforts have been made to understand the processes and timeframes of biofilm formation and its composition and distribution. Further research is, however, imperative, as a better understanding of biofilm formation would provide novel approaches for its prevention and treatment.

A lack of well-defined and validated examination methods, especially for the identification and quantification of the bacteria involved, is an important limitation at present.

Existing evidence clearly suggests that stents more resistant to biofilm formation might significantly reduce the incidence of stent encrustation, obstruction and dysfunction, as well as associated UTI. This would probably improve quality of life and also reduce the economic burden of ureteral stenting. It is surprising that the influence of biofilms and encrustation on patient symptoms has hardly been investigated. This should be subject of future clinical trials, where the use of the validated Ureteral Stent Symptom Questionnaire (USSQ) is strongly recommended to assess the whole spectrum of stent-associated morbidity and facilitate better comparisons of findings.

So far, the possibilities for preventing and treating biofilms on ureteral stents are limited. The main reasons for the absence of stents more resistant to biofilm formation are the complexity of biofilm formation with several different bacterial species involved, as well as the formation of host urinary conditioning films that additionally compromise efforts to develop effective coatings and surfaces. To overcome this, more elaborated *in vitro* biofilm models simulating *in vivo* conditions as closely as possible are required so that promising novel stent materials and coatings can be more effectively tested.

Conclusion

Even though many aspects are still unclear, biofilms on ureteral stents appear to be a key factor in the associated morbidity. Thus, further research in this field seems to be worthwhile to reduce the morbidity associated with ureteral stenting.

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Authors' contribution
VZ and PB contributed equally to this work.

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