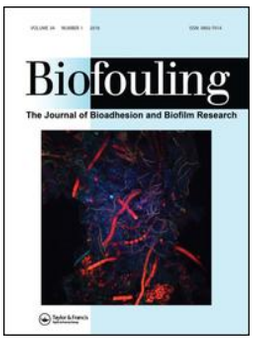

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Ureteral stent-associated infection and sepsis: pathogenesis and prevention: a review

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ABSTRACT

Ureteral stents are commonly used devices in hospital settings. However, their usage is often complicated by associated urinary tract infections as a result of bacterial adhesion onto the indwelling implant surfaces, followed by the formation of layers of biofilm. Once formed, the biofilm is exceedingly difficult to remove, potentially leading to further morbidity and even urosepsis. Urosepsis, where pathogens from the urinary tract enter the bloodstream, has a mortality rate of up to 50% of severely infected patients. Hence, it is important to understand its pathogenesis. In this review, ureteral stent-associated urinary tract infection and urosepsis will be addressed. In particular, the bacterial mechanisms involved, as well as the prevention and treatment of these infections will be discussed.

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Ureteral stents and their complications

The use of indwelling stents to maintain ureteral patency is routine in urologic practice. These medical devices are often used for the management of a wide range of circumstances, including the relief of upper urinary tract obstruction, the prevention of stricture formation, the drainage of urinary tract leaks and for the prevention of post-surgical complications, making them indispensable devices in modern urology practice (Paick et al. 2003). However, the use of these devices is often associated with several complications, particularly when they are left *in situ* for prolonged time periods (Giannarini et al. 2011). These complications include mild morbidity such as dysuria, fever, suprapubic pain, urinary frequency and urinary tract infections (UTI) (Liaw and Knudsen, 2016). In some cases, infection associated with urinary stents can lead to significant morbidity such as acute pyelonephritis, bacteremia, renal failure and even death (Paick et al. 2003). This review focuses on ureteral stent-associated UTIs and urosepsis. The mechanisms of bacteria-mediated urinary tract infections in patients with indwelling stents will be discussed, as well as the development of these infections into urosepsis.

Symptoms of urinary tract infection

The presence of bacteria in the urinary tract without associated morbidity is defined as asymptomatic bacteriuria. This often presents as abnormal cloudiness and/or a change in scent of urine (Macias Nuñez et al. 2008). Symptomatic UTI is the presence of $\geq 10^5$ colony forming units (CFU) per ml within the patient's urine specimen accompanied by symptoms including fever, localized pain within the urinary tract, and hematuria as well as dysuria, flank or suprapubic pain, frequency, urgency, and increased incontinence (Macias Nuñez et al. 2008). Table 1 lists some of the differences in clinical signs presented by asymptomatic bacteriuria and symptomatic UTI patients (Table 1).

Biofilm formation on ureteral stents

The pathogenesis of implant-associated infection involves interactions between the pathogen, the implant surface, and the host (Zimmerli and Trampuz 2011). Bacterial colonization on the ureteral stent plays an essential role in the initiation of pathogenesis of stent-associated infections (Liaw and Knudsen, 2016). In a study by Riedl et al. (1999) the authors found that the incidence of stent colonization and bacteriuria in patients with chronic indwelling stents was 100%. Temporary stents were also highly colonized, with an incidence rate of 69% and bacteriuria detected in 45% of patients (Riedl et al. 1999). There are some data suggesting an association between

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Table 1. Clinical signs presented by asymptomatic *vs* symptomatic UTI patients.

Asymptomatic UTI	Symptomatic UTI
Cloudiness or murkiness in urine	Fever
Foul or strong odor in urine	Urinary tract obstruction
Chronic incontinence	Urinary retention
	Hematuria
	Acute lower tract irritation (frequency, dysuria, urgency, increased incontinence)
	Acute pyelonephritis (fever, flank pain, tenderness)

indwelling ureteral stents and urinary tract infections, including a recent prospectively performed study reporting an 11% incidence of UTIs in stented patients (Altunal et al. 2017).

Successful treatment of ureteral stent-associated UTI is aided by background knowledge of the pathogenesis of infection. When sterile urinary stents are inserted into the human body, components such as polysaccharides, ions, and glycoprotein in urine, blood, or surrounding tissue deposit on the surface of the device within minutes forming a urinary conditioning film (Dave et al. 2011; Nowatzki et al. 2012; Ozgur et al. 2013). The deposition of conditioning film components alters the surface properties of the implants, allowing various planktonic bacteria to adhere to the surface *via* multiple putative mechanisms including electrostatic interactions and bacterial adhesins (Tenke et al 2012; Büttner et al 2015). Conditioning film is a layer of protein and polysaccharide molecules adsorbed to the surface of a foreign body. Diffusion of these components toward the implants is the initial event of conditioning film formation. The protein constituents of conditioning film provide receptor sites for bacterial adhesion (Montealegre et al. 2015). This role of conditioning film as a scaffolding for microorganisms is vital as many pathogens do not otherwise have mechanisms to adhere directly onto the bare surface of a stent.

It is unclear whether these free-floating bacteria enter the urinary bladder upon insertion of the stent or are a result of movement of the device while indwelling (Chatterjee et al. 2014). The initial interaction between bacteria and the device surface is reversible as it is driven by weak hydrophobic and electrostatic forces (Tenke et al. 2012). However, over time, the adherence becomes irreversible due to the binding of bacterial adhesins to their target molecules on the device surface as well as bacterial exopolysaccharide secretion, resulting in the formation of a biofilm (Tenke et al. 2012). Biofilms are highly structured and actively growing communities of microorganisms, proteins and extracellular polymers on an implant surface. Within a biofilm, multiple bacterial layers are also protected by a thick exopolysaccharide layer excreted by the bacteria (Zimmerli and Trampuz 2011; Tenke et al. 2012). The presence of this protective layer results in biofilms being significantly more resistant to antimicrobial drugs or disturbances than their planktonic counterparts. Antimicrobial agents cannot penetrate sufficiently through the exopolysaccharide layer to the underlying bacteria likely due to the strength with which it holds the community together (Hoiby et al. 2011). In addition, the phenotypes and metabolic functions of the embedded bacteria are modified, with organisms growing within a biofilm tending to have a slower rate of growth, allowing them to be more resistant to the effects of many antimicrobial agents which are typically effective against actively growing bacteria (Tenke et al. 2006). These embedded bacteria are also phenotypically different from their planktonic counterparts against which numerous antimicrobial agents have been developed, hence causing the drugs to fail at eradicating organisms within the biofilm (Tenke et al. 2006). Quorum sensing is also prevalent in biofilms; bacteria within the film are able to sense the external environment, communicate with adjacent cells, and transfer genetic information and plasmids to them. As such, bacteria in a well-established biofilm have been shown to survive in antibiotic concentrations up to 1,000-fold higher than the minimal inhibitory concentration for their planktonic counterparts (Tenke et al. 2012). This helps provide a reservoir where viable organisms can continue to cause infection and encrustation, potentially leading to blockage of the stent (Zumstein et al 2017).

As the biofilm becomes more developed, its expansion to 'unpopulated' areas of the stents is facilitated by the detachment of bacterial cells from the biofilm followed by subsequent conversion back into the planktonic or free-swimming state. Diffusion of these planktonic bacteria allows for their adherence to subsequent non-colonized areas of the surface, initiating new biofilm formation (Arciola et al. 2012).

Past studies have demonstrated that biofilm formation can occur within 24 h post-stent insertion, with adherent bacteria being present on up to 90% of indwelling stents upon removal from patients (Kehinde et al. 2002). Since bacterial adhesion occurs within a short period of time after stent insertion, the risk for infection may not only be present in chronically stented patients, but also in patients receiving short-term stents of one to two weeks. Lojanapiwat (2006) showed that bacterial colonization is common

even when the indwelling time is as little as two weeks. As demonstrated by Kehinde et al. (2002) patients with indwelling stents for >90 days had significantly more positive urine cultures when compared with those who had stents indwelling for <30 days, indicating that the duration of stent retention affects the rate of bacteriuria and stent colonization. This vulnerability of ureteral stents to bacterial colonization may promote the development of a UTI. The persistence of these bacterial colonies contributes to the overall growth of bacteria in the urine. This in turn allows for the adherence of increasing numbers of uropathogens to the urothelial cells, thus mediating subsequent infection (Kehinde et al. 2002). While asymptomatic bacteriuria is often multifactorial, symptomatic stent-associated UTIs are most often secondary to single or few bacterial strains (Kehinde et al. 2004).

Mechanisms of adhesion

The first step to biofilm formation is bacterial adhesion; interaction between the uropathogen and the host cell allows the organism to avoid being drained out of the body by the flow of urine (Minardi et al. 2013). This is an important step in allowing the bacteria to colonize, internalize, and persist inside the host's urinary tract, and to potentially cause infection (Minardi et al. 2013). This adhesion and colonization process is usually mediated by pathogenic outer membrane structures known as adhesins. The adhesins are able to recognize and bind to specific receptor moieties on the host cell surface, allowing the bacterium to colonize. Examples of such receptor moieties include oligosaccharide residues of glycoprotein or glycolipid receptors, collagen and fibronectin (Minardi et al. 2013).

Bacterial adhesins are also present in many forms, such as surface structures and proteins including pili, fimbriae, lipopolysaccharide and capsular polysaccharide (Chew and Lange 2009). Since both the pathogen and the host cell or stent surface biomaterial are often negatively charged, bacterial cells often experience repulsive forces from host or implant surfaces. This can be overcome through the development of specialized cell surface structures where the adhesin is located at the tip of hair-like filamentous surface appendages known as the fimbriae or pili, which can be found on both Gram-positive and Gram-negative bacteria. An example of a uropathogen that utilizes this type of extended adhesin is *Escherichia coli*. The bacterium possesses several virulence factors allowing it to adhere to both indwelling stent surfaces and to host cells. Type I pili are one such virulence factor present on most *E. coli* strains, particularly uropathogenic strains (Chew and Lange 2009). A well-characterized component of type I pili is the fimbrial protein fimH. FimH binds to mannose-containing molecules such as Tamm-Horsfall protein (THP), which is the most abundant protein in the urine and often found bound to indwelling ureteral stents. Interestingly, THP is normally part of the host urinary mechanism for preventing bacterial adhesion to bladder cells, as it contains mannose moieties and has high affinity for mannose-binding virulence factors of *E. coli* species, preventing them from interacting with mannose on the bladder epithelial cell surface. As a result, the THP: bacterial complex is eliminated in the urine. However, when indwelling medical devices are present, THP acts as a facilitator of bacterial adhesion where stent-bound THP becomes an anchor for bacterial cells to bind to, allowing bacteria to colonize the implant surface (Chew and Lange 2009). Similarly, *Proteus mirabilis* and *Pseudomonas aeruginosa* have also been found to bind THP, although *via* an adhesin that is different from FimH (Chew and Lange 2009).

Several other adhesins discovered in *E. coli* have also been found to potentially play a role in attaching to ureteral stent surfaces. This includes members of the Dr adhesin family, which bind to integrins and type IV collagen (Chew and Lange 2009). Likewise, the Ace adhesin from *Enterococcus faecalis* and adhesins from *S. aureus* and *S. epidermidis* are also capable of binding to collagen as well as to other extracellular matrix components that can attach to indwelling stent surfaces (Chew and Lange 2009).

The problems presented by the vast number of bacterial adhesins that exist are further complicated by the ability of uropathogens to alter the expression of these surface structures. Lipopolysaccharide, exopolysaccharide and capsular polysaccharide assist in the attachment of bacterial cells to indwelling medical devices. This is made possible by the ability of bacteria to become attracted to the hydrophilic polymer coating that is commonly found on ureteral stents to allow for a smoother, more comfortable insertion. Initially, bacteria adhere to the hydrophilic coating *via* weak hydrophobic and electrostatic forces (Tenke et al. 2012). However, irreversible adherence soon follows as bacterial adhesins bind to their target molecules on the device surface along with bacterial exopolysaccharide secretion, resulting in the formation of nascent clusters which eventually mature into multi-layer biofilms (Chew and Lange 2009). An example of such interaction involves the unique

Table 2. Different types of antimicrobial implant coatings used to prevent bacterial adhesion and subsequent urinary tract infections.

Type of coating	Description
Antibiotics	Can be eluting or non-eluting Due to bacteria regularly acquiring resistance, combination of different antibiotics made need to be coated
Triclosan	A ubiquitous compound that affects both Gram-positive and Gram- negative bacteria by affecting the stability of their cell walls
Silver	An effective broad-spectrum antimicrobial agent at low concentrations However, the inflexible nature of silver-coated implants cause abdominal pain in patients
Hydrogel	A hydrophilic, cross-linked polymer capable of absorbing large volumes of liquid forming a thin layer of water on coated device, preventing conditioning film formation
Polyvinylpyrrolidone	A hydrophilic, water-soluble polymer with excellent lubricant properties which result in a soft, smooth and non-adhesive implant surface
Heparin	A highly sulfated glycosaminoglycan, often used as an anticoagulant with the highest negative charge density amongst all known biological molecules Has shown great clinical performance in vascular catheters
Hyaluronic acid	An inhibitor of nucleation, growth, and aggregation of salts Coating is associated with increased hydration, decreased adsorption of proteins, and decreased bacterial adhesion
Gendine	A novel antiseptic that contains gentian violet and chlorhexidine Shown to be more effective than silver hydrogel-coatings in terms of bacterial adhesion
Chitosan	A non-toxic biopolymer obtained *via* chitin deacetylation, with broad-spectrum activity against bacteria Hypothesized to result in leaky cell membranes
Low-energy surface acoustic waves	• Transmitted directly to indwelling devices via a portable actuator generating piezoelectric vibrations between frequencies of 100–200 kHz • Disrupts formation of biofilms
Salicylic acid-releasing polyurethane acrylate polymers	• Salicylic acid known to have various effects on bacteria • Polymer coating hydrolyzes and releases salicylic acid, which has been shown to inhibit biofilm formation, possibly via inhibition of bacterial quorum sensing
Antimicrobial peptides conjugated to co-polymer brushes	• Antimicrobial peptides believed to disrupt bacterial cell wall and cell membrane, as well as many other bacterial processes • Bacteria less likely to develop resistance due to the peptides' multiple targeting system

surface characteristics of *P. aeruginosa* which allow the bacterium to bind to both hydrophilic and hydrophobic surfaces. When A-band lipopolysaccharide is expressed, the bacterium possesses a hydrophobic surface. This is in contrast to when B-band lipopolysaccharide is expressed, which gives the pathogen a hydrophilic surface. By expressing either the A-band or the B-band lipopolysaccharides, the bacterium is able to switch between binding to hydrophilic or hydrophobic surfaces, allowing it to adhere *via* interaction with urine components which bind to indwelling ureteral stents (Chew and Lange 2009).

A similar mechanism for the flexibility in bacterial surface characteristics can be found in *E. faecalis*, where subpopulations of the bacterium are capable of expressing different surface charges. This allows for adhesion of the bacterium to a broad range of surface materials. Past studies have found such heterogeneous strains to bind better to hydrophilic surfaces than strains that do not possess this capability (Chew and Lange 2009). Once adhered, bacteria can grow and develop biofilms on indwelling implant surfaces. These biofilms can play an important role in urinary tract infections and develop into the more critical condition of urosepsis (Wagenlehner et al. 2013).

Prevention and treatment of stent-associated urinary tract infections

Prevention of stent-associated UTIs is largely predicated on the attempt to avoid or decrease the colonization of these temporary implants. A practical strategy for prevention employed by urologists is the frequent replacement of chronic ureteral stents or, in the case of patients with short-term stents, the removal of these implants as soon as clinically appropriate.

Conventional treatment of urinary tract infections (UTIs) has been the use of antibiotics (Gupta et al. 2017). However, due to the resistance of bacteria in biofilm to antibiotics, bacteria can adhere, colonize, and survive on indwelling medical devices even when these antimicrobial drugs are in use (Tenke et al. 2006). Hence, other types of treatment or preventive measures need to be considered. Modification of biomaterial surface has been a proposed solution during recent years, with some surface changes and coatings showing promising results (Gao et al. 2011). Table 2 lists some of the antimicrobial implant coatings that have been developed to prevent bacterial adhesion and subsequent urinary tract infection. Full details regarding each coating are described by Lo et al. (2014) in a relatively recent review article. Other

options include the development of easier methods for diagnosis and quantification of biofilm infection, as well as the development of more specific antimicrobial agents and surface materials to help fight against biofilm formation (Tenke et al. 2006). In cases where a resultant infection is left untreated or proceeds to spread due to antibiotic resistance, urosepsis may result.

Urosepsis

Sepsis is defined as a combination of pathologic systemic infection and the body's physiological changes in response to the infection. The response in sepsis is disordered, which can lead to widespread tissue injury and organ dysfunction (Heidenreich and Thissen 2014). It is often deadly, killing up to 50% of severely affected patients (Heidenreich and Thissen 2014). When sepsis is caused by a urinary tract infection where pathogens from the urinary tract reach the bloodstream, it is defined as urosepsis (Wagenlehner et al. 2013).

Stent-associated urosepsis is thought to result from several mechanisms. The ability of indwelling stents to promote the vesicoureteral reflux of urine from the bladder into the renal collecting system assists in the process of retrograde ascension of bacteria, resulting in the spread of an initially localized infection (Dyer et al. 2002). The colonization of ureteral stents by bacteria also facilitates the retrograde ascent of bacteria from the bladder to the kidney *via* the ureter (Dyer et al. 2002). Additionally, indwelling stents have been demonstrated to decrease ureteral peristalsis (Venkatesh et al. 2005), thus further assisting bacterial ascent. Bacteria at the renal collecting system are able to subsequently enter the renal parenchymal tissue *via* the papillary collecting ducts in the renal calyces. This process is likely promoted by the increased intrapelvic pressure resulting from ureteral stent-mediated reflux (Shao et al. 2009). Once bacteria have entered the renal parenchyma, they are then capable of gaining access to the renal circulatory system, leading to bacteremia. This spread of infection from the urine to the blood is the initiation of urosepsis.

Sepsis is a systematic response to an initially localized infection. Recent data reveal that >1.3 million cases are diagnosed in the USA alone (Rubens et al. 2018). Approximately a quarter of all adult sepsis cases are considered to be urosepsis, with a majority resulting from complicated urinary tract infections (Gómez-Núñez et al. 2011; Wagenlehner et al. 2013). In addition, ~17% of all urosepsis cases develop after urological interventions, such as the use of indwelling ureteral stents (Gosciniak et al. 2014).

Clinical symptoms of urosepsis include hypotension, hypoxemia, and oliguria (Christoph et al. 2005). Combinations of these symptoms may lead to multi-organ failure and death (Gómez-Núñez et al. 2011). Patients who are elderly, diabetic or otherwise immunosuppressed such as those receiving cancer chemotherapy or corticosteroids, or are diagnosed with acquired immunodeficiency syndrome are more prone to the development of urosepsis (Heidenreich and Thissen 2014). Local factors such as urinary tract obstruction, presence of urinary tract calculi, congenital uropathies, endoscopic maneuvers, and neurogenic bladder disorders also increase the likelihood of being diagnosed with urosepsis (Wagenlehner et al. 2013).

Symptoms of urosepsis

Symptoms of urosepsis may include fever and chills, flank or abdominal pain, tachycardia and tachypnea. In more severe cases, hypothermia and confusion can also be observed (Heidenreich and Thissen 2014). If left untreated, further complications may involve hypotension, circulatory failure, oliguria or kidney failure (Heidenreich and Thissen 2014). In sepsis, the body deals with systemic infection by triggering an inflammatory cascade which may rapidly become overwhelming, causing endothelial injury (Heidenreich and Thissen 2014). Once the endothelium is damaged, capillary leakages result, potentially leading to venous pooling and peripheral vasodilation (Heidenreich and Thissen 2014). This in turn leads to the depletion of intravascular volume, tissue hypoxia and ultimately organ failure (Heidenreich and Thissen 2014). Up to 30% of severe sepsis patients develop septic shock, a critical condition with 30–40% mortality rates. This can occur particularly in refractory septic shock, where the patient fails to respond to fluid and pharmacological interventions (Heidenreich and Thissen 2014).

Common types of uropathogens

Device associated infections in urology are complicated by the fact that the majority of uropathogens are able to form complex biofilm communities including both Gram-positive and Gram-negative bacteria, as well as yeast (Lee et al. 2016; Eroshenko et al. 2017). The most commonly isolated strains associated with uropathogenic biofilms are *Escherichia coli*, *Enterococcus faecalis*, and *Pseudomonas aeruginosa*. *E. faecalis* along with *Proteus mirabilis*, *Staphylococcus aureus* and *Candida tropicalis* are considered to be the strongest biofilm formers among uropathogens (Hola et al. 2010). *P.*

Table 3. The Molecular Biology and Symptomatology of Urosepsis

Stage	Molecules	Response	Symptoms
Bacterial Colonization & Biofilm Formation	Adhesins: Type I Pili, fimH, Dr family, Ace • LPS (B-band and A-band switching)	–	Urethritis Cystitis • Pyelonephritis
Host's Immune Reaction to Bacteremia: *Pro-inflammatory response*	PAMPs: LPS, peptidoglycan, lipotechoic acids PRRs: TLRs, CD14, CD18, selectin Chemokines, thromboxane, prostaglandins, leukotriene, NO, MyD88, IL-1, IL-6, TNF-alpha, IL-17	Cell necrosis	
Coagulation Cascade	Thrombin, fibrin	Excess thrombin production Impaired fibrinolysis	impaired blood flow to vital organs leading to tissue and cell hypoxemia organ failure ultimately leading to fatality
Immunosuppression	Anti-inflammatory cytokines	TH2 anti-inflammatory response counter-regulatory anti-inflammatory response syndrome	Absence of normal immune response leading to nosocomial infections and eventually fatality

mirabilis biofilms are further complicated by its expression of urease, an enzyme capable of hydrolyzing urea up to 10× faster than the rate of other bacterial species. This process generates ammonia, which rapidly increases the alkalinity of urine, creating an environment that promotes formation of hydroxyapatite and struvite crystals, thus resulting in the encrustation of the device surface (Fusco et al. 2017). Aside from promoting further bacterial adhesion and biofilm formation, these encrustations also block the stent lumen often resulting in complete device failure (Nowatzki et al. 2012; Tenke et al. 2012). Stent-associated UTIs may progress to urosepsis. Indeed, in most cases of urosepsis, the microorganisms isolated from the patient's blood are the same as those isolated from their urine (Wagenlehner et al. 2013). Thus, the predominant pathogens identified from uroseptic patients include *E. coli*, which is the cause of 50% of urosepsis infections (Wagenlehner et al. 2013). Other commonly isolated species include *Proteus* spp. and *Enterobacter*/*Klebsiella* spp., each of which comprise 15% of the infections as well as *P. aeruginosa* and *Serratia* spp. which are of particular concern due to their resistance to multiple antibiotics (Heidenreich and Thissen 2014). Gram-positive cocci, mainly staphylococci and streptococci, are also key pathogens involved in urosepsis (Gómez-Núñez et al. 2011). Patients with impaired host defenses can also be susceptible to infection caused by less virulent strains of bacteria, such as enterococci and coagulase-negative staphylococci (Wagenlehner et al. 2013).

Pathogenesis of urosepsis: the pro-inflammatory response

Although an underlying infectious agent is required for sepsis, it is believed that the host is the main culprit in creating the disease, where the severity of sepsis is dependent on the host response. The development of sepsis is a complex process involving multiple protein families and pathways (Table 3). Urosepsis takes place when pathogen-associated molecular patterns (PAMPs) residing on the bacterial cell, such as endotoxins, lipopolysaccharides of Gram-negative bacteria or peptidoglycan, teichon- or lipoteichon acids of Gram-positive bacteria, are recognized by the host's innate immune system *via* interaction with pattern recognition receptors (PRRs) found on the cell membranes of host innate and adaptive immune cells (Schaeffer et al. 2010). These PRRs come in many forms, such as Toll-like receptors (TLRs), CD14, CD18, and selectin, which are typically present on the surface of neutrophils, macrophages, endothelial cells, and urothelial cells. As a result, intracellular messengers, such as nuclear factor-κB and protein-kinase C, are activated, inducing the transcription of important pro-inflammatory cytokines, which include tumor necrosis factor (TNF)-α, interferon gamma (IFNγ), interleukin (IL)-1, IL-6, IL-8 and platelet activating factor (PAF) (Farias et al. 2015). These factors act cooperatively or antagonistically on target organs, incorporating other mediators such as chemokines, thromboxane, prostaglandins, leukotriene, and endogenous vasodilators such as nitric oxide (NO) (Wagenlehner et al. 2013). All these substances lead to the local and systemic effects in the target organism (Wagenlehner et al. 2013).

TLRs are amongst the most thoroughly studied PRRs. They are transmembrane receptors found on monocytes and macrophages. A total of 10 TLRs have been discovered thus far, which are named from TLR1 to TLR10, where each TLR specifically binds to a different type of molecule (Schaeffer et al. 2010). For instance, TLR2 binds specifically to lipoteichoic acid (LTA) of Gram-positive cocci while TLR4 binds

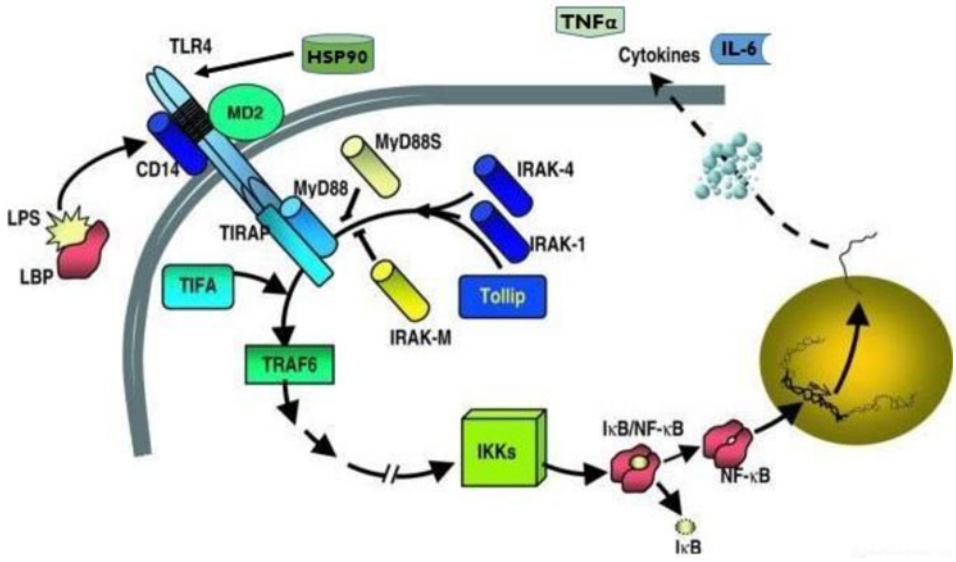

Figure 1. Binding of TLR4 to LPS triggers a cascade of events. Illustrated is a hypothesized pathway leading to the release of cytokines and effector molecules by the cell. Adapted from Villar et al. (2004).

to lipopolysaccharides (LPS) on the outer membrane of Gram-negative bacteria and to heat shock protein 90 (HSP90) (Schaeffer et al. 2010). Binding of TLR4 to LPS activates the adaptor molecule myeloid-differentiation factor-88 (MyD88), which in turn activates a cascade of intracellular signaling reactions, involving signaling molecules such as the MyD88-adapter like or TIR-associated protein (Mal/TIRAP) (Schaeffer et al. 2010). Figure 1 shows the activation pathway of the cascade of events triggered by TLR4 binding to LPS. Eventually, the initial host–microbial interaction leads to a widespread activation of the innate immune response. Pro-inflammatory cytokines, such as IL-1, IL-6, and TNF-alpha are released by mononuclear cells.

The release of pro-inflammatory mediators can eventually activate a second level of inflammatory cascades, which includes cytokines, lipid mediators, and reactive oxygen species. Cell adhesion molecules can also become upregulated, resulting in the initiation of inflammatory cell migration into tissues (Minasyan 2017). Host cells can undergo necrosis, which in turn can lead to the release of alarmins, molecules similar to PAMPs that further stimulate PRR. An example of an alarmin is HMGB1 (Wagenlehner et al. 2013). Together, alarmins and PAMPs are referred to as damage-associated molecular patterns (DAMPs) (Wagenlehner et al. 2013). Eventually, a transition from an innate response to an adaptive response occurs with the help of IL-17, which provides cross-talk between lymphocytes and phagocytes (Wagenlehner et al. 2013).

As sepsis persists, a TH2 anti-inflammatory response can take place, which is characterized by immunosuppression, a state which promotes cell healing and recovery, but also predisposes patients to nosocomial infections, which account for the mortality in the longer course of sepsis seen in hospitalized patients (Farias et al. 2015). Patients with a suppressed immune system may experience a shift to production of anti-inflammatory cytokines, an absence of normal immune responses to PAMPS, and the death of immune cells. This immunosuppressed state is responsible for the mortality in more severe cases of sepsis. Macrophages and neutrophils can become dysfunctional without undergoing apoptosis, while dendritic cells and lymphocytes can undergo excessive apoptosis. This is known as the counter-regulatory anti-inflammatory response syndrome (CARS) or as a transient immune paralysis (Wagenlehner et al. 2013).

Pathogenesis of urosepsis: the coagulation cascade

While a pro-inflammatory response is generated, excessive production of pro-inflammatory cytokines also increases the permeability of endothelial cells. This causes a blood shift into the interstitial space, triggering a coagulation cascade. This is characterized by excess production of thrombin and impaired fibrinolysis. The net result is an enhanced production of and reduced removal of fibrin, which leads to fibrin clots being deposited in small blood vessels (Minasyan 2017). As a result of the homeostatic imbalance toward coagulation, there is an impaired blood flow to vital organs, leading to tissue and cell

hypoxemia, and circulatory and multiple organ failure, ultimately leading to fatality (Wagenlehner et al. 2013; Heidenreich and Thissen 2014).

Treatment and inhibition of urosepsis

Urosepsis is often treated using broad-spectrum antibiotics (Heidenreich and Thissen 2014). Once urine and blood cultures have been speciated, the antimicrobial coverage can be adjusted and an antibiotic is chosen to directly treat the specific uropathogens involved (Gosciniak et al. 2014; Heidenreich and Thissen 2014). Supportive and adjunctive treatment can also be administered, which includes oxygen, fluid and dialysis therapy, steroids and catecholamines (Gosciniak et al. 2014). Human recombinant activated protein C can also be administered as its anticoagulant properties aid in improving sepsis-induced coagulopathy (Heidenreich and Thissen 2014). Interdisciplinary management, early therapy, infection control, frequent monitoring, balancing fluid and electrolyte levels, and adjustment of irregular coagulation remain crucial challenges for the treatment of urosepsis (Heidenreich and Thissen 2014).

Due to the high mortality rates of urosepsis, a growing number of treatment options have been proposed to alleviate the pathogenicity of this condition. One possible therapy includes the use of TLR4 inhibitors; radioprotective 105 (RP105) and a splice variant of MyD88 (sMyD88) are examples of such inhibitors. By inhibiting the initial interaction between the TLR and its receptors, or by inhibiting a step in the cascade of events leading to necrosis, the degree of injury experienced by patients undergoing sepsis can potentially be diminished.

The alarmin, HMGB1, has also been identified as a potential therapeutic target. It has been shown that when mice responding to injected LPS are administered an antibody against HMGB1, they can be protected from LPS-induced shock even if the antibody was given up to two hours post-injection with LPS (Wang et al. 1999).

Another potential therapeutic target is the macrophage migration inhibitory factor (MIF) (Minasyan 2017). Bozza et al. (2004) demonstrated that disruption of the MIF gene leads to the development of mice which are resistant to LPS-induced shock. An antibody against MIF has also been shown to be fully protective against LPS-induced shock. In addition, since MIF is involved in shock pathways induced by both Gram-negative and Gram-positive bacteria, blocking MIF activity may be an effective strategy against a broad spectrum of PAMP-induced sepsis (Renner et al. 2005).

Indeed, many molecules involved in the urosepsis activation pathways have been deemed as potential therapeutic targets for the inhibition of the development of urosepsis. However, additional studies must be conducted before an appropriate inhibitor is identified and can be safely administered to uroseptic patients.

Inhibition of stent-associated urosepsis

Research efforts aimed at achieving the inhibition of infection in patients with ureteral stents have focused on modifications to the stents themselves. Multiple types of stents and stent coatings have been developed to combat infection (Lo et al. 2014). Several of these devices have proven problematic or insufficiently effective *in vivo*. Initial prototypes included antimicrobial eluting ureteral stents which were promising but ultimately unsuccessful due to uncontrolled drug release and concerns for the development of resistant bacteria. More recent stents have demonstrated controlled elution of antibiotics incorporated into the device coatings. Ongoing work now focuses on incorporating combinations of antibiotics into stent coatings in order to combat possible bacterial resistance.

Other methods of decreasing bacterial adherence that have shown promise include the development of hydrophilic catheters whose properties would include ease of implantation and decreased urethral and ureteral irritation. Continued development of such non-adhesive implants with potential incorporation of antimicrobials may prove advantageous in addressing the issues of infection as well as stent discomfort.

A challenge to the development of novel materials or coatings that resist bacterial adhesion and biofilm formation still remains the deposition of the conditioning film, which is known to facilitate irreversible attachment of bacteria to the stent surface. Given the significant variability in the chemical and physical characteristics of conditioning film components along with the arsenal of adhesion mechanisms that bacteria can choose from to interact with these components, the deposition of urinary components on the device surface needs to be prevented. An alternative approach to overcoming the challenges the conditioning film poses without preventing its formation is to move the active antimicrobial agent away from the surface preventing its inactivation by deposited urinary components. Yu et al. (2015, 2017) developed a novel coating that makes use of polymer brushes to move antimicrobial peptides away from the device

surface, preventing any depositing conditioning film components from covering it and rendering it ineffective. Although this coating has shown significant efficacy at preventing bacterial biofilm formation in an *in vivo* model of catheter-associated urinary tract infection, its use on medical devices is somewhat limited due to the cost of peptide synthesis. Despite this, however, this concept did successfully overcome the limitations that the conditioning film has placed on previously attempted coatings and materials developed to prevent bacterial biofilm formation and resultant indwelling device-associated infections.

An enhanced understanding of the mechanisms underlying biofilm formation and the dependence of bacterial adhesion on implant properties such as surface roughness has led to several advances in biomaterial surface engineering (Ramasamy and Lee 2016). Recent efforts have employed nanotechnological advances to address biofouling of medical devices including ureteral stents. Due to their small size and corresponding ability to potentially penetrate biofilm layers on an implant, there has been significant interest in the use and manipulation of nanoparticles with the goal of preventing biofilm-mediated infection (Ramasamy and Lee 2016). These strategies to date have employed the technique of nanoparticle coating of device surfaces (Taylor and Webster 2011). It is hoped that these efforts will lead to the development of biomaterials with strong and enduring antimicrobial properties while being safe for patients (Ramasamy and Lee 2016).

Conclusions

Indwelling ureteral stents have been associated with the development of UTIs. This is thought to be secondary to the formation of microbial biofilm on the stent surface. Bacteria in biofilm are able to avoid antimicrobial activity *via* a number of mechanisms and phenotypic changes. Further investigations of these mechanisms will aid in identifying therapeutic targets in the treatment of urinary tract infections and urosepsis. While several strategies have been employed for ureteral stent coatings, there has been little historical success. Newer efforts are now focused on the use of nanotechnology, particularly the use of nanoparticle impregnation of medical devices, in an attempt to devise implants with antimicrobial properties while having minimal toxicity for patients. This field holds promise for the development of improved ureteral stents. Current management of ureteral stents includes practical strategies for decreasing stent-associated infection and urosepsis such as frequent replacement and early removal. Treatment of these infections continues to depend largely on the use of antibiotics. The choice of culture specific, effective antibiosis must be carefully considered with respect to both the rising public health costs of urosepsis and the seriousness of this infection.

Disclosure statement

No potential conflict of interest was reported by the authors.

References

Altunal N, Willke A, Hamzaoğlu O. 2017. Ureteral stent infections: a prospective study. Braz J Infect Dis. 21: 361–364. doi:10.1016/j.bjid.2016.12.004

Arciola CR, Campoccia D, Speziale P, Montanaro L, Costerton JW. 2012. Biofilm formation in *Staphylococcus* implant infections. A review of molecular mechanisms and implications for biofilm-resistant materials. Biomaterials. 33:5967–5982. doi:10.1016/j.biomaterials.2012.05.031

Bozza FA, Gomes RN, Japiassú AM, Soares M, Castro-Faria-Neto HC, Bozza PT, Bozza MT. 2004. Macrophage migration inhibitory factor levels correlate with fatal outcome in sepsis. Shock. 22:309–313. doi:10.1097/01.shk.0000140305.01641.c8

Büttner H, Mack D, Rohde H. 2015. Structural basis of *Staphylococcus epidermidis* biofilm formation: mechanisms and molecular interactions. Front Cell Infect Microbiol. 5:14.

Chatterjee S, Maiti P, Dey R, Kundu A, Dey R. 2014. Biofilms on indwelling urologic devices: microbes and antimicrobial management prospect. Ann Med Health Sci Res. 4:100–104.

Chew BH, Lange D. 2009. Ureteral stent symptoms and associated infections: a biomaterials perspective. Nat Rev Urol. 6:440–448. doi:10.1038/nrurol.2009.124

Christoph F, Weikert S, Muller M, Miller K, Schrader M. 2005. How septic is urosepsis? Clinical course of infected hydronephrosis and therapeutic strategies. World J Urol. 23:243–247. doi:10.1007/s00345-005-0002-x

Dave RN, Joshi HM, Venugopalan VP. 2011. Novel biocatalytic polymer-based antimicrobial coatings as potential ureteral biomaterial: preparation and *in vitro* performance evaluation. Antimicrob Agents Chemother. 55:845–853. doi:10.1128/AAC.00477-10

Dyer RB, Chen MY, Zagoria RJ, Regan JD, Hood CG, Kavanagh PV. 2002. Complications of ureteral stent placement. Radiographics. 22:1005–1022. doi:10.1148/radiographics.22.5.g02se081005

Eroshenko D, Polyudova T, Korobov V. 2017. N-acetylcysteine inhibits growth, adhesion and biofilm formation of Gram-positive skin pathogens. Microb Pathog. 105: 145–152. doi:10.1016/j.micpath.2017.02.030

Farias J, Kamel M, Eltahawy E. 2015. Evaluation and treatment urosepsis. Curr Bladder Dysfun Rep. 10:193–197. doi:10.1007/s11884-015-0301-z

Fusco A, Coretti L, Savio V, Buommino E, Lembo F, Donnarumma G. 2017. Biofilm formation and

immunomodulatory activity of *Proteus mirabilis* clinically isolated strains. Int J Mol Sci. 15:18.

Gao G, Lange D, Hilpert K, Kindrachuk J, Zou Y, Cheng JT, Kazemzadeh-Narbat M, Yu K, Wang R, Straus SK, et al. 2011. The biocompatibility and biofilm resistance of implant coatings based on hydrophilic polymer brushes conjugated with antimicrobial peptides. Biomaterials. 32:3899–3909. doi:10.1016/j.biomaterials.2011.02.013

Giannarini G, Keeley Jr FX, Valent F, Manassero F, Mogorovich A, Autorino R, Selli C. 2011. Predictors of morbidity in patients with indwelling ureteric stents: results of a prospective study using the validated Ureteric Stent Symptoms Questionnaire. BJU Int. 107:648–654. doi:10.1111/j.1464-410X.2010.09482.x

Gómez-Núñez JG, Alvarez UM, Fernandez F, Gutierrez-Aceves J, Lopez-Marin LM, Loske AM. 2011. Infected urinary stones, endotoxins and urosepsis. INTECH Open Access Publisher.

Gosciniak M, Kawecki D, Miklaszewska M, Truszewski Z, Lazowski T, Wielgos M, Radziszewski P. 2014. Fatal urosepsis: a 41 year-old pregnant woman¡ªCase Report. Open J Urol. 4:5.

Gupta K, Grigoryan L, Trautner B. 2017. Urinary tract infection. Ann Intern Med. 167:ITC49–ITC64. doi:10.7326/AITC201710030

Heidenreich A, Thissen A. 2014. Urosepsis. In: Merseburger AS, Kuczyk MA, Moul JW, editors. Urology at a glance. Heidelberg (Germany): Springer; p. 47–52.

Hoiby N, Ciofu O, Johansen HK, Song ZJ, Moser C, Jensen PO, Molin S, Givskov M, Tolker-Nielsen T, Bjarnsholt T. 2011. The clinical impact of bacterial biofilms. Int J Oral Sci. 3:55–65. doi:10.4248/IJOS11026

Hola V, Ruzicka F, Horka M. 2010. Microbial diversity in biofilm infections of the urinary tract with the use of sonication techniques. FEMS Immunol Med Microbiol. 59:525–528. doi:10.1111/j.1574-695X.2010.00703.x

Kehinde EO, Rotimi VO, Al-Awadi KA, Abdul-Halim H, Boland F, Al-Hunayan A, Pazhoor A. 2002. Factors predisposing to urinary tract infection after J ureteral stent insertion. J Urol. 167:1334–1337. doi:10.1016/S0022-5347(05)65294-9

Kehinde EO, Rotimi VO, Al-Hunayan A, Abdul-Halim H, Boland F, Al-Awadi KA. 2004. Bacteriology of urinary tract infection associated with indwelling J ureteral stents. J Endourol. 18:891–896. doi:10.1089/end.2004.18.891

Lee KJ, Lee MA, Hwang W, Park H, Lee KH. 2016. Deacylated lipopolysaccharides inhibit biofilm formation by Gram-negative bacteria. Biofouling. 32:711–723. doi:10.1080/08927014.2016.1193595

Liaw A, Knudsen B. 2016. Urinary tract infections associated with ureteral stents: a review. Arch Esp Urol. 69:479–484.

Lo J, Lange D, Chew BH. 2014. Ureteral stents and Foley catheters-associated urinary tract infections: the role of coatings and materials in infection prevention. Antibiotics. 3:87. doi:10.3390/antibiotics3010087

Lojanapiwat B. 2006. Colonization of internal ureteral stent and bacteriuria. World J Urol. 24:681–683. doi:10.1007/s00345-006-0135-6

Macias Nuñez JF, Cameron JS, Oreopoulos DG. 2008. The aging kidney in health and disease. New York: Springer; p. 1.

Minardi D, Conti A, Santoni M, Cantoro D, Cirioni O, Ghiselli R, Silvestri C, Guerrieri M, Giacometti A, Muzzonigro G. 2013. Urinary catheters and biofilm formation. RPBM. 3:196–203. doi:10.2174/22103090113036660010

Minasyan H. 2017. Sepsis and septic shock: pathogenesis and treatment perspectives. J Crit Care. 40:229–242. doi:10.1016/j.jcrc.2017.04.015

Montealegre MC, La Rosa SL, Roh JH, Harvey BR, Murray BE. 2015. The *Enterococcus faecalis* EbpA pilus protein: attenuation of expression, biofilm formation, and adherence to fibrinogen start with the rare initiation codon ATT. MBio. 6:e00467–e00415.

Nowatzki PJ, Koepsel RR, Stoodley P, Min K, Harper A, Murata H, Donfack J, Hortelano ER, Ehrlich GD, Russel AJ. 2012. Salicylic acid-releasing polyurethane acrylate polymers as anti-biofilm urological catheter coatings. Acta Biomater. 8:1869–1880. doi:10.1016/j.actbio.2012.01.032

Ozgur BC, Ekici M, Yuceturk CN, Bayrak O. 2013. Bacterial colonization of double J stents and bacteriuria frequency. Kaohsiung J Med Sci. 29:658–661. doi:10.1016/j.kjms.2013.01.017

Paick SH, Park HK, Oh SJ, Kim HH. 2003. Characteristics of bacterial colonization and urinary tract infection after indwelling of double-J ureteral stent. Urology. 62:214–217. doi:10.1016/S0090-4295(03)00325-X

Ramasamy M, Lee J. 2016. Recent nanotechnology approaches for prevention and treatment of biofilm-associated infections on medical devices. BioMed Res Int. 2016:1851242.

Renner P, Roger T, Calandra T. 2005. Macrophage migration inhibitory factor: gene polymorphisms and susceptibility to inflammatory diseases. Clin Infect Dis. S513–S519.

Riedl CR, Plas E, Hubner WA, Zimmerl H, Ulrich W, Pfluger H. 1999. Bacterial colonization of ureteral stents. Eur Urol. 36:53–59. doi:10.1159/000019927

Rubens M, Saxena A, Ramamoorthy V, Das S, Khera R, Hong J, Armaignac D, Veledar E, Nasir K, Gidel L. 2018. Increasing sepsis rates in the United States: results from National Inpatient Sample, 2005 to 2014. J Intensive Care Med. [Epub ahead of print].

Schaeffer AJ, Naber KG, Heyns CF, Matsumoto T, Shoskes DA, Bjerklund Johansen TE. 2010. Urology, urogenital infections. European Association of Urology.

Shao Y, Shen ZJ, Zhuo J, Liu HT, Yu SQ, Xia SJ. 2009. The influence of ureteral stent on renal pelvic pressure *in vivo*. Urol Res. 37:221–225. doi:10.1007/s00240-009-0199-z

Taylor E, Webster TJ. 2011. Reducing infections through nanotechnology and nanoparticles. Int J Nanomedicine. 6:1463–1473.

Tenke P, Kovacs B, Jackel M, Nag E. 2006. The role of biofilm infection in urology. World J Urol. 24:13–20. doi:10.1007/s00345-005-0050-2

Tenke P, Koves B, Nagy K, Hultgren SJ, Mendling W, Wullt B, Grabe M, Wagenlehner FM, Cek M, Pickard R, et al. 2012. Update on biofilm infections in the urinary tract. World J Urol. 30:51–57. doi:10.1007/s00345-011-0689-9

Venkatesh R, Landman J, Minor SD, Lee DI, Rehman J, Vanlangendonck R, Ragab M, Morrissey K, Sundaram CP, Clayman RV. 2005. Impact of a double-pigtail stent on ureteral peristalsis in the porcine model: initial studies using a novel implantable magnetic sensor. J Endourol. 19:170–176. doi:10.1089/end.2005.19.170

Villar J, Maca-Meyer N, Pérez-Méndez L, Flores C. 2004. Bench-to-bedside review: understanding genetic predisposition to sepsis. Critical Care. 8:180–189. doi:10.1186/cc2863

Wagenlehner FM, Lichtenstern C, Rolfes C, Mayer C, Uhle F, Weidner W, Weigan MA. 2013. Diagnosis and management for urosepsis. Int J Urol. 20:963–970.

Wang H, Bloom O, Zhang M, Vishnubhakat JM, Ombrellino M, Che J, Frazier A, Yang H, Ivanova S, Borovikova L, et al. 1999. HMG-1 as a late mediator of endotoxin lethality in mice. Science. 285:248–251. doi:10.1126/science.285.5425.248

Yu K, Lo JCY, Mei Y, Haney EF, Siren E, Kalathottukaren MT, Hancock REW, Lange D, Kizhakkedathu JN. 2015. Towards infection resistant surfaces: polymer brush chemistry and peptide structure modulate the potency of antimicrobial peptides. ACS Appl Mater Interfaces. 7:28591–28605. doi:10.1021/acsami.5b10074

Yu K, Lo J, Mei Y, Yang X, Brooks DE, Hancock REW, Lange D, Kizhakkedathu JN. 2017. Anti-adhesive antimicrobial peptide coating prevents catheter associated infection in a mouse urinary infection model. Biomaterials. 116:69–81. doi:10.1016/j.biomaterials.2016.11.047

Zimmerli W, Trampuz A. 2011. Implant-associated infection. In: Biofilm infections. New York: Springer; p. 69–90.

Zumstein V, Betschart P, Albrich WC, Buhmann MT, Ren Q, Schmid HP, Abt D. 2017. Biofilm formation on ureteral stents - Incidence, clinical impact, and prevention. Swiss Med Wkly. 147:w14408.