A BETTER UNDERSTANDING OF RISK FACTORS AND BACTERIA IN LOWER UTI IN WOMEN TO PREVENT RECURRENCE

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29-06-2021
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Abstract
The most frequent diagnosed infections worldwide are urinary tract infections (UTIs). This literature study evaluates the most important risk factors and characteristics of common bacteria in recurrent lower UTIs and suggests potential interventions based on these risk factors and bacterial properties. There are several lifestyle risk factors, anatomical risk factors and genetic risk factors for developing a recurrent UTI. Common recurrent UTIs are caused by the Gram-negative bacteria UPEC, *Proteus mirabilis*, *Klebsiella pneumoniae* and *Proteus aeruginosa*. Gram-positive bacteria that cause recurrent UTIs are *Staphylococcus saprophyticus*, *Staphylococcus aureus*, *Staphylococcus epidermidis* and *Enterococcus faecalis*. Possible interventions to prevent recurrent UTIs can target physical factors that influence the urogenital environment, immunological factors important in recurrent UTIs, factors responsible for the disruption of the healthy urinary microbiome and vaginal microbiome and specific characteristics of uropathogens.

Urinary tract infections (UTIs) are the most frequent diagnosed infections worldwide (Öztürk & Murt, 2020). Due to this high prevalence, UTIs have a negative effect on quality of life as well as on health care costs. Furthermore, the professional treatment strategies are inconsistent (Aslam et al., 2020). Antibiotics are currently used as the main treatment for UTIs, which is expensive and an important source of antibiotic resistance selection pressure (Wagenlehner, 2017). One in four of the women that have had a UTI develop a recurrent UTI within 6-12 months (Nielubowicz and Mobley, 2010). The high recurrence rate of UTIs and the increasing antimicrobial resistance, due to the great distribution of antibiotics, increase the health care costs even more (Flores-Mireles et al., 2015).

Several terms are used when discussing UTIs. The main focus of this literature study is on recurrent lower UTIs, which can be complicated or uncomplicated. Lower UTIs are infections in the bladder (cystitis) and the urethra (urethritis) (Aydin et al., 2015). An uncomplicated UTI sporadically occurs in otherwise healthy patients. A complicated UTI occurs in compromised patients, who for example have another illness, are catheterized or have abnormalities in their urinary tract (Nielubowicz and Mobley, 2010). Recurrent UTIs can be defined as a relapse or reinfection. When a UTI is caused by the same bacterial strain within two weeks after treatment, the UTI is defined as a relapse. When the UTI recurs after more than two weeks, it is defined as a reinfection. If the urine culture is measured as sterile after the infection and the infection recurs within two weeks, the UTI is also defined as a reinfection (Aydin et al., 2015).

It is of importance to study the microbial ecosystem with all bacteria involved in the urinary tract, since bacteria do not only affect the host, but also each other (de Vos, 2018). This literature study evaluates the most important risk factors and characteristics of common bacteria in recurrent lower UTIs and suggests potential interventions based on these risk factors and bacterial properties.

Risk factors for developing UTI

There are several risk factors for developing a UTI, increasing the risk for developing a recurrent UTI as well. The risk factors can be categorized in three different groups: lifestyle risk factors, anatomical risk factors and genetic risk factors.

Lifestyle risk factors

History of UTIs

When a UTI has occurred, the risk of developing a recurrent UTI increases, because recurrent UTIs are mainly caused by reinfection by the same uropathogen (Al-Badr & Al-Shaikh, 2013). Therefore, once the uropathogen has colonized the urinary tract, the risk of recurrence increases. A history of UTIs during childhood, before the age of 15 years old (Epp & Larochelle, 2017), is a risk factor for developing a UTI in premenopausal women. A history of premenopausal UTIs is a risk factor for developing a UTI in postmenopausal women (Storme et al., 2019).

Sexual intercourse and contraceptives

The main lifestyle risk factor for both premenopausal and postmenopausal women is frequent sexual intercourse or sexual intercourse with various partners (Storme et al., 2019). Uropathogens from the intestinal tract, such as *Escherichia coli* and *Proteus mirabilis*, can easily access the bladder due to penetration. The risk of getting a UTI increases when having frequent sexual intercourse or when having intercourse with various partners (Franco, 2005). Post-coital prophylaxis could be offered to women suffering from a recurrent UTI due to sexual intercourse as an alternative therapy (Epp & Larochelle, 2017).

Disturbance of urinary and vaginal microbiome

The vaginal microbiome is an important factor in the susceptibility to UTI. The vagina can serve as a reservoir for uropathogens, but several vaginal bacterial species detected in urine cultures are not recognized as uropathogens. These vaginal bacteria may cause injury or immunomodulation by briefly surviving in the urinary tract (Lewis & Gilbert, 2020). Disturbances of the healthy urinary and vaginal microbiome increase the risk of colonization by uropathogens, because the alterations in the urinary and vaginal flora generate a more optimal environment for these uropathogens (Storme et al., 2019). For instance, the loss of lactobacilli in postmenopausal women causes an alteration of the normal vaginal microbiome (Aydin et al., 2015). The differences in vaginal microbiome between premenopausal women and postmenopausal women make it of importance to distinguish between these women when studying UTIs. A healthy vaginal microbiome in premenopausal women consists mainly of lactobacilli and staphylococci which protect the urethra (Franco, 2005) (Meštrović et al., 2020). Lactobacilli maintain an acidic vaginal environment, that inhibits the growth of uropathogens and decreases the risk of developing a UTI. Vaginal *E. coli* colonies are mainly found in women with decreased levels of lactobacilli. These women have a loss of lactic acid producing vaginal lactobacilli, which causes the vaginal pH to increase and decreases the protection of the urinary tract against uropathogens (Storme et al., 2019). The vaginal microbiome of postmenopausal women is more diverse than the vaginal microbiome of premenopausal women, with low levels of lactobacilli and a mixture of Gram-negative anaerobic organisms, Actinobacteria, and other Firmicutes (Meštrović et al., 2020). These women have a higher risk of developing a UTI (Aydin et al., 2015). The loss of lactic acid producing vaginal lactobacilli in postmenopausal women is caused by the decline in estrogen levels (Storme et al., 2019). Estrogen itself is also important for maintenance of the vaginal flora. However, estrogen as a therapy to decrease recurrent UTI in postmenopausal women does not work, because increased amounts of estrogen actually ease the adherence of uropathogens to the uroepithelial cells (Franco, 2005).

The use of antimicrobials and contraceptives such as spermicides, diaphragms and oral contraceptives may also alter the urinary and vaginal flora, thus generating a more optimal environment for uropathogens, which increases the risk of developing a recurrent UTI (Franco, 2005) (Storme et al., 2019). Information about the risks as well as an alternative form of contraception should be offered to women using antimicrobials and these contraceptives (Epp & Larochelle, 2017).

Catheters

The most common infection in health care facilities is UTI due to an indwelling urinary catheter (Nicolle, 2014). The insertion of an indwelling catheter into the bladder increases the susceptibility of a patient to UTIs, as the catheter introduces opportunistic organisms, such as fecal contaminants or skin residents from the patient's microflora, to the urinary tract (Jacobsen et al., 2008). Studies have shown that mechanical stress induced by urinary catheterization results in an inflammatory response of the uroepithelium, due to the histological and immunological changes in the bladder induced by the catheterization (Goble et al., 1989) (Flores-Mireles et al., 2015). The duration of the catheterization is the main risk factor, with an increasing risk of bacterial growth in the urine of 3-7% per day of catheterization (Lo et al., 2014). Additionally, in 15-20% of the hospitalized patients, catheters are overused, increasing the risks for developing urinary infections even more (Taha et al., 2017). Biofilm forming on the catheter acts as a source of bacteria which can potentially cause infections (Nicolle, 2014). The biofilm protects the bacteria to antibiotics (Kline & Lewis, 2016). In such a case, the development of complications and frequent recurrence of UTIs occurs due to catheter-associated urinary tract infections (CAUTIs) (Jacobsen et al., 2008). CAUTIs are in the most cases caused by the gram-negative bacteria *E. coli* and *P. mirabilis*

(Jacobsen et al., 2008) and the gram-positive bacteria *Enterococcus faecalis* (Tien et al., 2017). Less common CAUTIs are caused by the gram-negative bacteria *Pseudomonas aeruginosa* (Ferreiro et al., 2017) and the Gram-positive bacteria *Staphylococcus aureus* (Megged, 2013). Strategies to limit CAUTIs are surveillance of catheter use, only catheterizing patients when necessary and frequent control of potential complications. The catheter itself requires technical changes to prevent bacterial access and biofilm formation to the urinary tract (Nicolle, 2014).

Vitamin D deficiency

Vitamin D is important in the innate immunity, as it increases neutrophilic motility and phagocyte function. Neutrophils are important in the defense against uropathogens in UTIs. Furthermore, vitamin D potentially stimulates antimicrobial peptides that protect against bacterial infection (Nseir et al., 2013). In response to UTI, epithelial cells of the urinary tract produce cathelicidin, which protects the urinary tract from adherence of bacteria. Cathelicidin has a defined vitamin D-dependent mechanism (Shalaby et al., 2018). Vitamin D decreases cytokine release and inflammation and therefore reduces the severity of infection (Döven and Erdoğan, 2021). Women with a vitamin D deficiency have a decreased protection against uropathogens, which makes them prone to UTIs. The deficiency of vitamin D also contributes to an increased inflammation in patients with recurrent UTIs, causing severe damage such as renal scarring (Döven and Erdoğan, 2021). Women of reproductive age with low vitamin D levels are more at risk of developing a UTI, due to differences in their urinary tract, which makes them more prone to bacterial infection overall (Ali et al., 2020). Since vitamin D has an inflammation limiting effect and enhances the neutrophils in the host response, vitamin D supplementation could be used as a combination therapy with antibiotics to treat UTIs (Shalaby et al., 2018). The use of this combination treatment potentially limits the amount of antibiotics needed to treat UTIs, therefore reducing bacterial resistance.

Anatomical risk factors

Urethra-anus distance

The main anatomical risk factors for developing a UTI is a distance shorter than 4.5 cm between the urethra and the anus (Hooton et al., 1999). The intestinal tract is the main source of organisms infecting the urinary tract (Nielubowicz and Mobley, 2010) (Epp & Larochelle, 2017). A shorter distance between the urethra and the anus increases the risk of infection from the intestinal tract, increasing the risk of recurrent UTIs as well. One theory suggests that the higher prevalence in women compared to men is due to the shorter female urethra, facilitating an easier migration of gut microorganisms into the urinary tract (Meštrović et al., 2020).

Urinary frequency, urinary flow & obstructions

A healthy urinary tract is maintained by the forward flow of urine (Hickling et al., 2015). Urine flow and bladder contraction prevent obstruction of urine and colonization of uropathogens (Najar et al., 2009). Urine eliminated out of the lower urinary tract plays a crucial role in cleansing the urinary tract, removing microbes that might have entered (Hickling et al., 2015). Urinary retention and obstructions hindering the flow of urine promote the development of a recurrent UTI, since they prolong the time for bacteria to adhere to the urothelium and invade the urinary tract (Hickling et al., 2015). The obstructions mainly form due to pregnancy, pelvic malignancy and kidney stones (Iyasere et al., 2012). Drainage using catheterization and surgical removement of the obstruction, complemented by antibiotic treatment, should cure the infections of these patients (Heyns, 2012), but can also induce recurrent infections.

Genetic risk factors

Maternal history of UTI

Maternal history of UTIs is proven to increase the risk of developing recurrent UTIs (Stapleton et al., 2008). This suggests an involvement of genetic factors in the increased risk of developing a recurrent UTI.

Blood group

The blood group type of a women has influence on their susceptibility to develop recurrent UTIs. For example, a study showed that 34.8% of women with recurrent UTIs were non-secretors of ABO histo-blood group antigens (May et al., 1989). The uroepithelial cells in women that are non-secretors contain unique globoseries glycolipid receptors. These receptors combined with the absence of the antigens promote the adherence to the uroepithelial cells of uropathogens, such as uropathogenic *E. coli* (UPEC) (Franco, 2005). It is suggested this promotion is caused by the diglucosyldiacylglycerol that normally blocks the host binding

sites in secretors, which is not present in non-secretors (Diederich et al., 2014). The promotion of adherence of uropathogens by the glycolipid receptors contributes to the increased risk of developing a UTI, therefore increasing the risk of developing a recurrent UTIs. More research is needed on the non-secretion of ABO histo-blood group antigens and the increased susceptibility to develop a recurrent UTI, to potentially inhibit the promotion of adherence of the uropathogens.

TLR4 and CXCR1 mutations

Toll-like receptor 4 (TLR4) and CXC chemokine receptor type 1 (CXCR1) play an important role in the immunological response of the host to uropathogens. The host response against uropathogens consists of two steps. The first step is the release of chemokines by uroepithelial cells after the adherence of uropathogens to these cells. The released chemokines recruit neutrophils to the infection site. The second step consists of bacterial killing by the neutrophils (Wullt et al., 2003). During infection, the adhering uropathogens to the uroepithelial cells are recognized by the TLR4 on the bladder cells, due to the lipopolysaccharide (LPS) on the surface of the uropathogens (Song & Abraham, 2008). Recognition by TLR4 of type 1 and P type pili on UPEC strains results in an IL-6 and IL-8 cytokine response (Karam et al., 2019). CXCR1, the receptor for IL-8, is an important part of the second step, as it is responsible for the migration and activation of neutrophils (Nielubowicz and Mobley, 2010). In mice with a TLR4 deletion, the recognition of uropathogens adhering to the uroepithelial cells is impaired. This impairment results in an asymptomatic carrier state in these TLR4 deleted mice (Fischer et al., 2006), with the increased risk of recurrence of infection or death due to the infections (Nielubowicz and Mobley, 2010). It is suggested that CXCR1 is important in the protection against more severe infections. In CXCR1 deleted mice infected with uropathogens, an increased presence of uropathogens was found (Nielubowicz and Mobley, 2010). The neutrophils in CXCR1 deleted mice were stuck under the uroepithelium, inhibiting the elimination of the uropathogens by the neutrophils and increasing the susceptibility to infection (Godaly et al., 2000). This increased susceptibility contributes to the increased risk of developing recurrent UTIs. Further research is needed on the effects of TLR4 and CXCR1 mutations in humans, to potentially use these immunological factors in a treatment for recurrent UTIs.

Common bacteria in UTI

Since it is thought Gram-negative bacteria are the cause of 80-95% of UTIs, research on UTIs has mainly focused on Gram-negative bacteria (Zandbergen et al., 2021). However, it has been found that Gram-positive bacteria are also a common cause of UTIs (Kline & Lewis, 2016). Similar to Gram-negative bacteria, it is most likely the genital tract is the source of Gram-negative bacteria in the urinary tract (Zandbergen et al., 2021). It is of importance to study the microbial ecosystem with all bacteria involved in the urinary tract, since bacteria do not only affect the host, but also each other. The microbial ecosystems are important for ecological stability, which is the maintenance of species together in an environment (de Vos et al., 2018). In this literature study the emphasis lies on bacteria affecting the host.

Gram-negative

Escherichia coli

UPEC contain pili and different adhesins to recognize specific receptors on the epithelium of the bladder (Wright & Hultgren, 2006). Type 1 pili, which is the most common pili of UPEC, is essential for colonization, invasion and persistence of UPEC in the bladder. Adhesin FimH on the pili binds the surface of umbrella cells on the bladder and induces a reaction via an uroplakin mechanism and an $\alpha 3 \beta 1$ integrin mechanism. This results in invasion of the umbrella cells due to a rearrangement of actin (Hannan et al., 2012) (Eto et al., 2007). Inside the umbrella cells of the bladder, UPEC is able to evade the defense mechanism of the host. The defense mechanism of the host against adherence of UPEC to the uroepithelium depends on TLR4 expression by the uroepithelial cells (Bien et al., 2012). UPEC can also contain P pili with the adhesin PapG (Flores-Mireles et al., 2015). PapG can interact with TLR4 and reduce the expression of the immunoglobulin A-receptor. This blocks the transport of immunoglobulin A through the lamina propria and uroepithelial cells, thus evading the host defense mechanism (Rice et al., 2005) (Ashkar et al., 2008). Due to the various strategies of UPEC to evade host defenses, UPEC can cause recurrent UTIs. Another property of UPEC is that it can escape into the cytoplasm of the umbrella cells, where it can form transient biofilm-like intracellular bacterial communities (IBCs) (Anderson et al., 2003) (Hannan et al., 2010). Bacteria can infect surrounding cells after they have matured in the IBCs. Simultaneously the IBC

cycle repeats, creating a source of UPEC that the immunological response of the host cannot reach, thus facilitating recurrent infections of UPEC (Anderson et al., 2003) (Hannan et al., 2010) (Kostakioti et al., 2013). On the other hand, UPEC can also create quiescent intracellular reservoirs (QIRs) with non-replicative bacteria in the transitional cells underlying the umbrella cells in the bladder. The viability of these QIRs remains for several months (Hannan et al., 2012). When the uroepithelial layer is renewed, the underlying transitional cells differentiate into new umbrella cells (Flores-Mireles et al., 2015). This can trigger the QIRs in the transitional cell layer to release bacteria back into the lumen of the bladder, causing a recurrent UTI (Blango et al., 2014). Another immune-evasive property of UPEC is based on the pathogenic strategies of UPEC, like adherence, motility, immune evasion, toxin production and acquisition of metals. Iron is a critical nutrient for UPEC, which is acquired using the siderophore enterobactin. UPEC can escape the neutrophil-mediated host response by glycosylating the enterobactin to salmochelin, so the protein lipocalin-2 expressed on the neutrophils cannot recognize UPEC any longer (Nielubowicz and Mobley, 2010). Unrecognized, UPEC can freely cause recurrent UTIs.

Proteus mirabilis

P. mirabilis can colonize the bladder and form biofilms. The biofilms are formed due to the production of mannose-resistant Proteus-like pili (Nielubowicz and Mobley, 2010). The biofilms mainly form in catheters (Jacobsen et al., 2008). To colonize the bladder *P. mirabilis* uses *P. mirabilis*-like fimbriae (PMFs) and attaches to uroepithelial cells using non-agglutinating fimbriae (NAFs) in vitro (Armbruster & Mobley, 2012). Infection of the bladder caused by *P. mirabilis* is caused by the autotransporter trimeric autoagglutinin autotransporter of Proteus (TaaP) in vitro, where AipA binds to collagen I (Alumuri et al., 2010). Further research needs to be done to PMFs, NAFs, TaaP and their mechanisms to better understand their functions in vivo. Recurrent UTIs are also caused by *P. mirabilis* due to its ability to synthesize urease, which hydrolyzes urea to ammonia with the byproduct carbonate. The carbonate forms kidney stones, which can provide a new source of infection, causing recurrent UTIs by *P. mirabilis* (Nielubowicz and Mobley, 2010).

Klebsiella pneumoniae

K. pneumoniae is an important uropathogen in UTIs and CAUTIs (Rosen et al., 2008). *K. pneumoniae* and UPEC are the most common cause of extended spectrum β lactamase (ESBL) infections (Bitsori & Galanakis, 2019). Extended-spectrum β-lactamases (ESBLs) are a group of rapidly evolving enzymes, which provide antibiotic resistance. This makes treatment against bacteria that produce ESBLs, like UPEC and *K. pneumoniae* difficult (Rawat & Nair, 2010). The ability to rapidly develop antibiotic resistance due to the ESBLs make that *K. pneumoniae* causes recurrent UTIs. UPEC is more common than *K. pneumoniae*. The presence of *K. pneumoniae* in the bladder is generally lower than the presence of UPEC in the bladder, due to weaker adherence to the uroepithelium of *K. pneumonia*. Also, just like UPEC, *K. pneumoniae* is able to form IBCs. However, the level of formation of the IBcs is lower in *K. pneumoniae* (Stahlhut et al., 2009) (Rosen et al., 2008). *K. pneumoniae* can colonize the bladder and form biofilms using pili type 1 (Gerlach et al., 1989) and pili type 3 (Murphy et al., 2013). Heptyl mannose inhibits the adhesin FimH on *K. pneumoniae*, which is different than the methyl mannose-mediated inhibition of UPEC FimH.

Pseudomonas aeruginosa

7-10% of the UTIs acquired in hospital settings are caused by *P. aeruginosa* (Ferreiro et al., 2017). *P. aeruginosa* has the ability to quickly develop antibiotic resistance during the treatment of a UTI (Lister et al., 2009), which makes it difficult to treat *P. aeruginosa*. The quick development of resistance against antibiotics is due to the overproduction of the enzyme AmpC and the overexpression of multidrug efflux pumps in *P. aeruginosa*. The AmpC enzyme hydrolyzes antibiotics (Jacoby, 2009) and the multidrug efflux pumps allow the uropathogen to actively extrude the antibiotics out of the uropathogen (Blanco et al., 2016). The decreased expression of outer membrane porin OprD also plays an important role in the development of resistance in *P. aeruginosa* (Lister et al., 2009). OprD facilitates the antibiotic uptake, thus the decrease in expression of OprD on *P. aeruginosa* contributes to the antibiotic resistance of this uropathogen (Ochs, 1999). The ability to rapidly develop antibiotic resistance increases the risk of recurrence of *P. aeruginosa*.

Gram-positive

Staphylococcus saprophyticus

S. saprophyticus is the most common Gram-positive bacteria to cause UTI (Kline & Lewis, 2016). *S. saprophyticus* adheres to the bladder by binding the tight junctions between the uroepithelial cells (McTaggart et al., 1990). All *S. saprophyticus* strains contain the glycoprotein Aas. Aas plays an important role in colonization and adhesion of *S. saprophyticus* to the urinary tract (Meyer et al., 1996). The lipase Ssp is important for persistence of *S. saprophyticus* and is found on the majority of *S. saprophyticus* strains (Kline et al., 2010). These factors provide *S. saprophyticus* with abilities to cause recurrent UTIs. Similar to *P. mirabilis*, *S. saprophyticus* can also synthesize urease. Urease is important for colonization and inflammation of the bladder and the formation of kidney stones (Kline & Lewis, 2016). Unique for *S. saprophyticus* is the ability to tolerate high D-serine concentrations in the urine, by upregulating Ssp when D-serine is present. D-serine is toxic to many bacteria, but the upregulation of Ssp increases persistence, providing a protection for *S. saprophyticus* (Sakinç et al., 2009) (Korte-Berwanger et al., 2013). Furthermore, *S. saprophyticus* can express a capsule, which provides resistance to neutrophils and also prevents uroepithelial adhesion (Park et al., 2010). These abilities increase the survival rate of S. saprophyticus, increasing the likelihood of this uropathogen to recur.

Other staphylococci

S. aureus is an uncommon bacteria involved in CAUTI and in UTI during pregnancy (Muder et al., 2006) (Kline & Lewis, 2016). *S. aureus* can synthesize urease, in a similar way as *S. saprophyticus* and *P. mirabilis* (Kline & Lewis, 2016). Member of the human skin microorganism *Staphylococcus epidermidis* is a more prevalent uropathogen, involved in CAUTI, mainly acquired in hospital settings (Kline & Lewis, 2016). *S. aureus* and *S. epidermidis* express the staphylococcal pro-inflammatory cytolytic toxin phenol soluble modulin (PSM), involved in recruitment, activation and lysis of neutrophils, making PSMs crucial in immune evasion (Kline & Lewis, 2016). Furthermore, polysaccharide intercellular adhesin (PIA) is expressed by both *S. aureus* and *S. epidermidis*. PIA contributes to the formation of biofilms, as well as the inhibition of phagocytosis (Otto, 2012). Developing a vaccine with a component of PIA could be a potential specific therapy against UTI caused by *S. aureus* and *S. epidermidis* (Nguyen et al., 2020).

Other less common staphylococci that cause UTIs, found in urinary cultures are *Staphylococcus haemolyticus, Streptococcus agalactiae* and *Staphylococcus hominis.*

Enterococcus faecalis

The Gram-positive bacteria that mainly causes CAUTI is *E. faecalis* (Kafil & Mobarez, 2015). *E. faecalis* facilitates adhesion with the collagen adhesin Ace, enterococcal surface protein (Esp), enterococcal polysaccharide antigen (Epa), and endocarditis- and biofilm-associated (Ebp) pili (Arias & Murray, 2012). The Ebp pili play an important role in persistence of the infection and in CAUTIs (Nielsen et al., 2012). Persistence of *E. faecalis* is promoted by attachment and biofilm production on urinary catheters (Guiton et al., 2010). The biofilm produces a favorable environment for survival of *E. faecalis*, protecting the bacteria against the host defense and antibiotics (Kafil & Mobarez, 2015), making recurrence possible for this uropathogen. However, *E. faecalis* itself cannot attach to the catheter in vivo. *E. faecalis* uses fibrinogen as a food source to grow and form biofilm on the catheter (Flores-Mireles et al., 2015). The fibrinogen, which is emitted in the bladder due to the inflammatory response to the catheter, attaches to the catheter. Subsequently, *E. faecalis* adheres to the fibrinogen using the Ebp pilus adhesin EbpA (Flores-Mireles et al., 2014).

Possible interventions

This literature study has evaluated the risk factors and bacteria involved in recurrent UTI. Due to the high health care costs and the negative effect on the quality of life caused by to UTI, developing new treatment strategies is of much importance.

Interventions on physical factors that influence the urogenital environment

Of all lifestyle risk factors discussed, sexual intercourse is one of the main risk factors for developing UTI. An alternative therapy to decrease the prevalence of recurrent UTIs induced by sexual intercourse could be post-coital prophylaxis. With this method, women are given the opportunity to control their antibiotic intake themselves. However, as this is still an antibiotic treatment, post-coital prophylaxis is not an optimal solution to prevent recurrent UTI. Nevertheless, it would still limit the amount of antibiotics given, as it is a preventive measure with a low dose. The use of contraception

such as spermicides, diaphragms and oral contraceptives is also a big risk factor for developing UTI. As there are many alternative contraceptives nowadays, women should be noted of the risks of these contraceptives and other options should be offered to women. One of the biggest risk factors associated with UTI are CAUTIs. Catheterization induces CAUTI in almost 100% of the cases and approximately one fifth of the catheters in hospitalized patients are overused. Therefore, it is important to limit the use of catheters. There should be strict surveillance and monitoring of possible complications on each patient receiving a catheter. To decrease the prevalence of CAUTI and to prevent bacterial access and biofilm formation to the urinary tract, technical changes to the catheter itself should be developed.

Utilizing immunological factors to decrease the risk of developing recurrent UTIs

Interventions based on utilizing factors of the immune-system could potentially be used to limit recurrent UTIs. For instance, the finding that vitamin D enhances neutrophilic function and prevents severe inflammation suggests that combination therapy of vitamin D supplementation with antibiotics could contribute to decreasing bacterial resistance, as it would limit the amount of antibiotics needed to treat the UTI. Genetic immunological risk factors also play a role. However, no interventions are proposed at this level yet. More research on genetical risk factors involving the immune system such as non-secretion of ABO histo-blood group antigens and the effects of TLR4 and CXCR1 mutations in humans would be needed for developing a therapeutic strategy based on these factors against recurrent UTI.

Limiting bacterial resistance to prevent recurrent UTIs

Bacteria are the main culprit of urinary tract infections. According to research the acidic vaginal environment is protective against urinary tract infections. Disturbances of the vaginal microbiome alter the acidity of the vaginal environment and increase the risk of colonization by uropathogens, because a more optimal environment for uropathogens is generated by these alterations. Antibiotics inhibit the growth of uropathogens to limit infections. Uropathogens that are resistant to antibiotics cannot be treated and can continuously infect the host, thus cause recurrent UTIs. Antibiotic resistance is a worldwide problem nowadays and novel therapies should be developed to decrease the prescription of antibiotics. When decreasing the amount of antibiotics prescribed, the risk of bacterial resistance is lower.

Interventions to terminate disruption of the healthy urinary and vaginal microbiome

Another intervention could be based on the disturbance of the vaginal microbiome. Large companies induce the idea that antimicrobials are needed to keep the vagina clean, while these antimicrobials actually harm the healthy vaginal milieu, that is supposed to be inhabited by particular bacterial communities. Eradicating such communities may therefore even increase the risk for UTI. Antimicrobials that affect the vaginal microbiome should be handled with caution and should not be offered unlimited. An intervention regarding these antimicrobials and acidic detergents would be to strictly regulate the availability of antimicrobials that affect the vaginal microbiome. Also, women should be better informed about the consequences of using antimicrobials.

Targeting specific characteristics of uropathogens as a therapy against recurrent UTIs

A more specific intervention to reduce the prevalence of UTIs would be to target characteristics of the uropathogens itself. For instance, targeting PIAs, expressed by both *S. aureus* and *S. epidermidis*. A vaccine with a component of PIA directed against *S. aureus* and *S. epidermidis*, would create a specific therapy against UTIs that are caused by these uropathogens. Another potential specific intervention could be the inhibition of the glycosylation of enterobactin to salmochelin in UPEC, which could contribute to eliminating UPEC, since the hosts' neutrophils recognize enterobactin but not salmochelin. Inhibition of the glycosylation could thus potentially enhance the host response against UTI. Also, IBCs and QIRs play an important role in the recurrence of uropathogens. The formation of IBCs and QIRs are a specific property of several uropathogens. Therapy against the formation of IBCs and QIRs could potentially decrease the recurrence of the uropathogens, as they can form a source of new infections. However, more research needs to be done on specific points to target the IBCs and QIRs formed by uropathogens.

In conclusion, this literature study has evaluated potential interventions based on the risk factors and characteristics of common bacteria in recurrent UTIs.
Possible interventions to prevent recurrent UTIs can target physical factors that influence the urogenital environment, immunological factors important in recurrent UTIs, factors responsible for the disruption of the healthy urinary microbiome and vaginal microbiome and specific characteristics of uropathogens, and may contribute to decreasing the prevalence of recurrent UTIs.

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