



The Impact of Recurrent Urinary Tract Infections on Sexual Function

6

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6.1 Definition of Urinary Tract Infection

A urinary tract infection (UTI) is the presence of significant bacteria and pus in the urine, along with increased bladder sensation, urgency, frequency, dysuria, urgency urinary incontinence and/or pain (Naber et al. 2001). In hospital medicine, UTI is significant, as it can be a precursor to infection of the upper urinary tracts (pyelonephritis). With an anatomically normal urinary tract, the progression from UTI to pyelonephritis is 2% (Christiaens et al. 2002).

6.2 Symptoms

For most women, it is not the risk of ascending infection that is troublesome, but the symptoms of the UTI. Many women will describe the symptoms experienced as ‘cystitis’. The most common symptoms are frequency of urine and dysuria, but others encountered are suprapubic pain, haematuria, urethritis or vaginitis and feeling generally unwell (Bent et al. 2002; Stamm et al. 1982). As the risk of ascending infection is low, the main aim of diagnosis and treatment is amelioration of these symptoms.

Symptoms of UTI

Passing urine frequently

Pain on passing urine

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Symptoms of UTI
Pain in the lower abdomen
Irritation of the urethra or vagina
Feeling unwell
Smelly urine

6.3 Diagnosis

UTI can be difficult to diagnose but it is generally accepted that a positive urine culture is indicative of UTI. Urine is cultured in a laboratory and the predominant organisms identified. Significant growth is defined as identification of a single organism $\geq 10^5$ colony forming units (CFU) in a specimen of urine obtained from the middle of the stream of urine (Naber et al. 2001). Bacteria grown at culture usually originate from the gut or vagina (Foxman 2010).

These diagnostic criteria are historical and are based on increasing risk of ascending infection rather than impact of symptoms on the patient. Because of this, some clinicians feel that these criteria may not be a sensitive enough tool for diagnosing troublesome UTI. It has been shown that if a more sensitive test to look for bacterial DNA in the urine (polymerase chain reaction; PCR), 80% of women with symptoms of UTI and a negative culture will be positive for a uropathogen (Heytens et al. 2017). We may need to rethink how UTI is diagnosed in women.

Culturing urine can take a number of days, so in order to guide rapid treatment a bedside test widely utilised is the urine dipstick. The presence of nitrites in the urine (produced by bacteria) has a positive predictive value of 96% but a sensitivity of 35–57% (Masajtis-Zagajewska and Nowicki 2017). When the presence of white blood cells (leukocytes) and nitrites are used, the positive predictive value is 66.7% and the negative predictive value is 77.4% (Najeeb et al. 2015). These figures demonstrate the imperfect nature of urine dipstick in diagnosing UTI in women. The dipstick is also not reliable in women over the age of 65 and those with catheters in situ. In these cases, a urine culture should be sent.

Symptoms correlate well with diagnosis and it has been shown that when frequency and dysuria are reported, there is a 90% risk of there being a UTI diagnosed (Bent et al. 2002). Therefore the National Institute for Clinical Excellence (NICE) advises treatment for presumed UTI when the patient reports symptoms along with a urine dipstick positive for nitrites (the result of reduction of nitrates by bacteria) (Excellence NifHaC 2018). Pyuria on microscopy or dipstick is widely used as a surrogate marker for UTI, but its presence or absence may not correlate with infection (Kupelian et al. 2013). NICE recommends that if the dipstick is positive for leukocytes and blood then UTI is likely, but if only leukocytes then other diagnoses are equally as likely (Excellence NifHaC 2018). They advised that urine dipstick should not be used to diagnose UTI in patients who have a catheter in situ. The presence of a catheter can cause an increase in leukocytes in the urine in the absence of infection, so increasing false-positive diagnoses.

The finding of blood on urine dipstick or microscopic haematuria can be indicative of serious underlying pathology such as urolithiasis (stone formation), malignancy or renal disease and appropriate investigations should be undertaken (Linder et al. 2018).

Once UTI is diagnosed, we must consider further investigations. If anatomical abnormality of the urinary tract is suspected, imaging in the form of ultrasound or enhanced CT can be useful. Cystoscopy with or without biopsy can be used to identify inter-vesical lesions and inflammation.

When to send a urine culture?
Women over 65 years
Pregnant women
Persistent symptoms not improving with antibiotics
Recurrent UTI
Catheterised women
If there are risk factors for complicated UTI (e.g. renal failure, abnormal anatomy)
Visible or non-visible haematuria

6.4 Definition of Recurrent Urinary Tract Infection (rUTI)

Recurrent UTIs (rUTI)s are symptomatic infections following the complete resolution of a previous infection (Hooton 2001). Once a woman has had a UTI, she has a 25% chance of suffering a recurrence of infection in the next 3–6 months (Foxman 1990). This is more common in women over the age of 55 years, with 53% of these women reporting a recurrence in the following 12 months (compared to 36% in those aged 18–55) (Ikäheimo et al. 1996). RUTI are defined as >2 infections over a 6-month period or 3 infections over 12 months with complete resolution for at least 2 weeks (Foxman 1990).

Some women may suffer from symptoms more suggestive of one persistent infection rather than multiple recurrent UTIs, which may benefit from similar management strategies to rUTI.

6.5 Uropathogens

UTIs are caused by a wide range of organisms which are termed ‘uropathogens’ when causing infection in the urinary tract. They can be gram-negative or gram-positive bacteria or even fungi.

Escherichia Coli is the most commonly identified uropathogen in complicated (65%) and uncomplicated (75%) UTIs. The other uropathogens implicated are *Klebsiella pneumoniae*, *Staphylococcus saprophyticus* and *Enterococcus faecalis*. *Of interest, candida is the causative organism in 7% of complicated UTIs but only 1% of uncomplicated infections* (Flores-Mireles et al. 2015).

E. coli is demonstrated in up to 80% of cases in Europe (Carlsen et al. 2019; Kornfält Isberg et al. 2019; Alós 2005). *E. coli* is the most prevalent bacteria in the human gastrointestinal tract (Sahoo et al. 2012) and when this is transferred to the urinary tract, the bacteria can become pathological causing the symptoms of UTI. Women have a much shorter urethra compared to men, thus allowing the retrograde passage of uropathogens more easily which explains why men do not tend to suffer from UTIs as much. Women who suffer from rUTI are more likely to have rectal *E. coli* diagnosed than those without (Stamey and Sexton 1975). It is felt that any activity, which facilitates the passage of bacteria between the anus and the urinary tract, may cause or exacerbate UTIs. Sexual intercourse is an obvious factor to cause this, and it has been shown that it is a risk factor for rUTI (Scholes et al. 2000). Whilst *E. coli* is the most commonly implicated bacteria, there are many others that can cause problematic infection of the urinary tract, many of these also from the gram-negative *Enterobacteriaceae* family (Kodner and Thomas Gupton 2010).

When thinking about UTI in the context of sex, an important organism to mention is *Ureaplasma urealyticum*. It belongs to the *Mycoplasmataceae* family of bacteria, which lack a cell wall and live inside the host cells. *Ureaplasma* has been shown to be present in 33% of women attending with lower urinary tract symptoms (Latthe et al. 2008). It is a sexually transmitted infection and can also cause pelvic inflammatory disease and subsequent infertility.

6.6 Pathogenesis of rUTI

UTIs can be classified as uncomplicated or complicated. Complicated UTIs are those associated with factors that compromise the urinary tract or immune system. These can include abnormal anatomy of the urinary tract (including calculi), immunosuppression, renal failure or indwelling catheters (Flores-Mireles et al. 2015).

Uncomplicated UTIs are those occurring in women without these risk factors who are otherwise healthy. In this group of women, the transfer of uropathogens from the rectum to the urethra is a key action in the causation of repeated infections. However, it has been shown that following an initial UTI and antibiotic treatment, 77% of subsequent infections are with the identical strain of *E. coli* (Ejrnæs 2011). This implies an alternative mechanism where the primary infection is not completely cleared. This is supported by data showing that antibacterial perineal washing does not reduce the risk of rUTI (Cass and Ireland 1985). There is most likely two mechanisms by which women suffer rUTI; repeat infection from gut commensals and chronic cystitis flares.

6.7 Prevalence

UTI is a common condition that one in three women will experience by the age of 24 and half of all women will suffer at least one UTI during their lifetime (Foxman 2003). UTI is generally managed in primary care and is the most commonly

diagnosed infection in this setting (Car 2006). UTI therefore accounts for a significant proportion of antibiotics prescribed by general practitioners (Foxman 2003).

The incidence of UTI in women increases with age, with the exception of a spike in younger women aged 14–24 years (Schmiemann et al. 2010). This coincides with a peak in sexual activity, particularly between the ages of 18 and 39 (Medina and Castillo-Pino 2019).

6.8 Risk Factors for UTI

Looking at all causes of UTIs, it is clear that iatrogenic causes are common. Hospital-acquired urinary tract infections are a leading cause of health-care infections in geriatrics, psychiatry and obstetrics and gynaecology. These are primarily caused by the use of indwelling urinary catheters (Gardner et al. 2014) and are therefore classified as complicated UTIs.

Obstruction or abnormal anatomy of the urinary tract can cause urinary stasis or ureteric reflux, allowing establishment of UTI and suboptimal clearance of infection. Likewise, voiding dysfunction with a significant residual volume (>100 ml) is associated with UTI. Urinary tract stones may serve as a focus for the formation of infection (Tandogdu and Wagenlehner 2016).

Women with diabetes demonstrate an impairment in innate and acquired immune function which can make them more susceptible to any infection including UTIs (Tanaka 2008). Equally, women with renal failure and those on immunosuppressive medication are less able to mount a defence to bacteria in the urinary tract.

It is thought that some behavioural or hygiene practices may be associated with an increased risk of rUTI, some of which may be supported by evidence and/or anecdote. It is clear that increasing water intake can reduce UTI (Popkin et al. 2010); however, there is no evidence to suggest that this can help rUTI (Scholes et al. 2000). Women who regularly use spermicidal agents or those on the combined oral contraceptive pill are at an increased risk of rUTI (Scholes et al. 2000). It is known that voiding less than three times a day is associated with higher risk of UTI (Nielsen and Walter 1994) and frequent voiding can be protective (Su et al. 2009). Toileting habits such as the use of feminine/baby wipes can be associated with UTI (Crann et al. 2018).

A recent study showed some evidence for several modifiable behavioural patterns which influence frequency of rUTI. They reported that wiping back to front, not voiding within 15 min of intercourse, not drinking water after intercourse and using soap to wash genitals were all associated with an increased risk of UTI (Al Demour and Ababneh 2018).

Recurrent UTI can be triggered by intercourse and increased frequency of intercourse increases risk of UTI, as does having a new sexual partner in the preceding 12 months (Scholes et al. 2000). We know that a majority of uropathogens originate in the gastrointestinal tract. Vaginal penetrative intercourse can exacerbate transfer of these bacteria from the gastrointestinal tract to the urethra.

Over recent years, trends in sexual behaviour have been changing. Although the number of occasions of sexual activity in the last month has decreased between 1990 and 2010 (6.1 to 4.8), the number of women who had anal intercourse in the preceding year had more than doubled, from 6.5 to 15% in the same time period (Mercer et al. 2013). It is likely that anal intercourse increases the risk of bacterial transfer, particularly if vaginal penetration occurs subsequently.

6.9 Impact on Quality of Life

There are a paucity of data on the impact of rUTI on quality of life, but that available would suggest it is associated with mental stress (Wagenlehner et al. 2018; Ennis et al. 2018; Ellis and Verma 2000), and that patients would like their physicians to have a better understanding of their symptoms and the impact they have on their lives (Moskowitz and Lee 2018).

The GESPRIT study aimed to assess the personal and economic burden of rUTI in Europe. An online questionnaire was sent to women complaining of rUTI and completed by 1275 women who currently had an acute infection and 666 women who had suffered one in the previous 4 weeks. Eighty percent of women reported having received antibiotics to treat their infection and the majority found behavioural changes ineffective. On average, there were 3 days of sick leave taken for UTI symptoms with 3.74 days of limited activity reported in each year (Wagenlehner et al. 2018).

The unpredictable, acute presentation of UTI can cause distress and anxiety in the patient, and treating the acute infection with antibiotics is often not sufficient to prevent this (Schmiemann et al. 2010). Reducing the occurrence of UTI may help reduce the emotional burden.

In an observational study of 575 patients affected by rUTI, 61% exhibited some degree of depression at baseline as assessed by the *Hospital Anxiety and Depression Scale* (HADS). Following treatment with lyophilized bacterial lysate, the number of UTIs decreased by 59% with a corresponding decrease in the HADS by 32.1% (Renard et al. 2014). This shows an association between a decreasing frequency of UTI and improvements in anxiety and depression.

6.10 Treatment of UTI

The first-line of treatment for uncomplicated UTI is antibiotics. A 3-day course is usually recommended as there is better compliance, lower cost and fewer adverse reactions compared to longer courses (Warren et al. 1999). As UTI is the most prevalent infection encountered in primary care (Car 2006), it results in a high number of antibiotic prescriptions which drives resistance (Malcolm et al. 2018). In women with rUTI, urine culture results should guide antimicrobial therapy.

Ureaplasma will not be grown on typical culture so therefore PCR should be undertaken to identify the bacteria's genetic code. If this is found to be positive, a

14-day course of doxycycline is advised along with sexual contact tracing and testing.

When a woman is suffering from rUTI, behavioural modifications should be the first-line once an acute infection has been treated appropriately (Excellence NIfHaC 2018). These involve modifications to sexual activity and contraceptive use. If a woman is using diaphragms or spermicides, alternatives should be offered. As there is a lack of robust evidence on other behavioural practices (e.g. direction of wiping, pre or post-coital voiding), there is disagreement over what advice should be given to patients (Aydin et al. 2015).

Continuous prophylaxis with nightly antibiotic can reduce the frequency of UTI by 95% when compared to placebo (Nicolle and Ronald 1987). However, constant antibiotic use may drive resistance rates and be less acceptable to patients.

Post-coital prophylaxis is when the patient takes a single dose of antibiotics following sexual intercourse. This has been shown to be as effective as continuous prophylaxis and is more acceptable to patients (Hooton 2001).

Other non-antibiotic treatments include cranberry juice or tablets and D-mannose supplements. The evidence for these therapies is mixed but as they have minimal side effects, may be trialled in motivated patients.

Methenamine salts dissolve in urine to form ammonia and formaldehyde, which acts as a bactericide, sterilising the urine. A Cochrane review has shown that methenamine hippurate is effective in preventing UTI in the short term (Lee et al. 2012).

Exogenous oestrogen may be a useful treatment in postmenopausal women suffering from rUTIs. Oestrogen plays an important role in maintaining the health of the vagina and lower urinary tract. Data from a limited number of studies show that vaginal oestrogens can decrease the number of UTIs in postmenopausal women (Perrotta et al. 2008).

A promising new treatment has recently become available in Europe with the aim of modulating the immune system in women with rUTI. Uromune is a sublingual vaccine, which works by stimulating a host response against *E. coli*, *Klebsiella*, *Proteus* and *Enterococcus faecalis*. Data are lacking but a UK study showed a 78% reduction in UTIs when women are treated with the vaccine (Yang and Foley 2018).

Probiotics (e.g. *Lactobacilli*) have been used to help prevent rUTIs. The rationale for their use is that they help maintain a barrier in the lower urinary tract to prevent ascending infection from the vagina and urethra by reducing adherence of the pathogens, growth and colonisation and modulating the host defences. A Cochrane review found that there was no evidence to suggest that their use clinically decreases rate of UTI; however, they did acknowledge that the evidence available was poor (Schwenger et al. 2015).

A more invasive treatment that has been used since the 1960s involves instillation of agents into the bladder. This can be hyaluronic acid compounds, which aim to replenish the layer protecting the inside of the bladder, or more recently antibiotics. These treatments often involve prolonged courses and a requirement for the patient to be able to self-catheterise to administer the instillation or attend a clinic regularly for treatment. There are mixed results reported but generally it is accepted as an end-stage treatment.

6.11 Sexual Function

It is clear that there is a close relationship between sexual intercourse and recurrent urinary tract infections with increasing frequency of intercourse, worsening rUTI. There is little evidence to explore the effect that suffering from rUTI will have on sexual function although it is known that other lower urinary tract symptoms can have a negative effect on this (Constantine et al. 2017).

As sexual relationships and behaviour are a key-component of maintaining a good quality of life (Mercer et al. 2013), any factors that influence this may not only have an adverse effect on sexual function but on quality of life.

As sexual intercourse is a major factor in triggering UTI, especially in younger women, avoidance strategies may be taken. These can develop into fear of intercourse and subsequently vaginismus. Patients may find these problems difficult to discuss with their partner, causing emotional stress on both the patient and her partner and have a negative impact on the relationship.

Advice on sexual hygiene may help reduce the incidence of UTI by minimising transfer of bacteria. This can include washing genitals prior to intercourse, avoiding anal intercourse particularly with subsequent vaginal penetration. Voiding following sex will empty the bladder and urethra of urine and potential uropathogens (although not supported by evidence, this advice is widely given). However, although potentially helpful, these behavioural and hygiene factors may generate anxiety around sexual intercourse. Partners may not be understanding of the measures required which can cause tension in a relationship. This could also result in the patient holding the partners' hygiene habits responsible for their UTI, which will have a significant impact on the relationship.

The effects of treatment on sexual function are an important factor to consider. Prolonged courses of antibiotics may cause changes in the vaginal flora leading to candida infections. This can make intercourse uncomfortable and again avoidance strategies employed.

If more invasive treatments such as instillations are utilised, there may be stigma surrounding self-catheterisation, which could go on to, affect the woman's feelings towards sexual intercourse.

In general, there is a lack of evidence regarding the effect of rUTI on sexual function in women. It seems evident however that there is a considerable link between not only the cause of UTIs but also the treatments and sex.

When caring for these women in primary and secondary care, we should be mindful of the fact that sexual function may be a sensitive topic for the patient and may even be her reason for seeking help. In routine practice, we advise the behavioural and sexual changes listed below, but we must remember that very few of these are supported by high quality evidence and that we may be having a detrimental impact on the patient's quality of life.

<i>Behavioural changes advised</i>
Wipe perineum front to back
Do not use perfumed wipes or soaps/“feminine hygiene” products
Take showers not baths if possible
Avoid tights/tight trousers
Avoid bladder irritants, e.g. caffeine
Avoid constipation
Void regularly
Drink adequate volumes of water
If diabetic, control your blood sugar
Do not douche
If postmenopause, use vaginal oestrogen if not contraindicated
<i>Sexual changes advised</i>
Void after sex
Avoid anal intercourse (especially if followed by vaginal penetration)
Wash hands before sex
Drink water after sex
Wash genitals before and after sex
Use lubrication
If using sex toys ensure these are cleaned appropriately, regularly and stored properly

6.12 Conclusion

Recurrent urinary tract infections are a significant burden to the population of sexually active women and a cause of sexual avoidance or dysfunction for others. They can have debilitating effects on quality of life. It is known that sexual practices can exacerbate frequency of infections and thus reduce quality of life. Patients suffering from rUTI may avoid intercourse to prevent UTI. Even if intercourse is not avoided, hygiene measures to reduce risk of bacterial transmission may present a limitation for the sexual behaviour of some patients causing a detrimental effect on sexual function.

Clinicians should be aware of the close association between rUTI and sexual function. Efforts should be made to take an accurate history including sexual behavioural and hygiene practices and the temporal relationship of UTI to intercourse. Behavioural and hygiene advice should be given but we should be mindful that little of this is supported by evidence and that it may have a detrimental effect on the sexual function of these women.

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