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Review Article

Urinary Tract Infections: Current and New Preventative Options

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Introduction

Urinary Tract Infection (UTI) is one of the most prevalent conditions worldwide. Typically, bacteria invade by ascending from the peri-anal region. Though bacteria within the bladder can be asymptomatic and self-resolve, it can also cause symptoms including irritation, urgency, frequency and dysuria [1]. The National Institute of Clinical Excellence (NICE) defines UTIs as the presence of bacteria in the urine with a combination of clinical features indicating an infection of the urinary tract. The top 4 uropathogens are *Escherichia coli*, *Staphylococcus saprophyticus*, *Klebsiellapneumonia* and *Proteus mirabilis* [2,3].

Positive culture for UTI was classically described by Kass [4] as greater than 10^5 bacteria on culture. More recently, 10^3 bacteria with symptoms have been shown to be significant to patients, with levels of bacteria less than 10^5 shown to contribute towards refractory overactive bladder [5].

Infections can often also be under-diagnosed due to laboratories often targeting only "known pathogenic bacteria" as opposed to all bacteria. Furthermore reports of "mixed growth of doubtful significance" have often been disregarded. Recent evidence however shows that asymptomatic bacteria in the urine as well as mixed growth on culture can be contributors to lower urinary tract symptoms, in particular in regards to incontinence, storage symptoms and markers of inflammation [6].

In the UK, UTIs affect a disproportionally larger number of women than men [7], with 40-50% of women experiencing at least one episode of UTI in their lifetime [8]. For both the USA and the UK, UTI is the most common reason for women to present to ambulatory care [7,8] with the incidence of UTIs increasing with age [9], though younger women are more likely to seek out medical help. In premenopausal patients, UTIs are commonly associated with sexual activity, with the usage of diaphragm with spermicide being a known trigger factor [10]. For postmenopausal women, the risk factors were found to be incontinence (both urge, stress and mixed), vaginal atrophy, the presence of a cystocele and a high post-void residual volume [9,11].

Recurrent UTIs have been previously defined in literature as "three or more episodes of UTI during a twelve month period" or "two or more within 6 months" [12] and have been found to occur in up to 20-30% of women who have previously had a UTI [12].

Over 95% of all recurrent UTIs are accounted for by persistent infections of the same organisms, indicating the presence of a potential focus of infection that may be sessile and intracellular between clinically overt infections; an area which is difficult for antibiotics to access [13]. The rest are caused by re-infections by a new organism, signifying a possible underlying host susceptibility to infection.

Whilst the mainstream treatments for recurrent UTIs are to initially provide relief of symptoms with antibiotics, the prevention of recurrence is more problematic. Often prevention relies upon long-term antibiotic prophylaxis in various regimes depending of local sensitivities [14]. However, multi-resistant bacteria are emerging in many regions of the world, giving urgency to the need to discover prophylaxis that avoids antibiotics and reinforces the natural mechanism of pathogen defense.

This review will examine the current and new options available in the prevention of recurrent UTIs.

Investigations

Initial management for women with recurrent UTIs are to diagnose and treat the acute infection, ensuring urine microscopy, culture and sensitivities are requested to confirm the presence of bacteria and allowing for pathogen specific antibiotic prescribing.

Further investigations may include excretory urography, cystoscopy and imaging to exclude underlying structural or functional abnormalities. However, multiple studies have found the yield

in finding an underlying pathology in patients with recurrent UTIs when using the above investigations was low [15-19]. In particular, one study reported no significant pathology on all cystoscopies performed in patients with recurrent UTIs [17] whilst another reported positive cystoscopic findings in only 8% of women with recurrent UTIs, with the majority being over 50 years old and advised omitting cystoscopies in women with no risk factors and normal radiological imaging [15].

Instead, studies recommend a more targeted approach, utilising urodynamic studies, cystoscopy and imaging in only patients with specific risk factors, including frank or unexplained haematuria, obstructive symptoms, renal calculi, underlying bladder dysfunction or evidence for enterovescial fistula [15,16].

Current treatment

Conservative measures

Lifestyle modifications are often recommended to patients in the outpatient setting with recurrent UTIs. However their efficacy can be variable.

Women who use spermicide-coated diaphragms/condoms often are more at risk of UTIs than those who do not, meaning alternative contraception choice, or even abstinence is a possible treatment option [10,20-23]. Further to that, education is vital in order to ensure patients understand the characteristics and triggers of their re-infections from sexual activities [13].

Mictuation post coitus is thought to rinse the bladder of pathogens, thus decreasing UTI rates [10], in addition, women with recurrent UTIs who urinate before and after sexual intercourse were less likely to get UTIs, though this was not statistically significant [20]. The theory is that the bladder may have a low volume after intercourse and so is inefficient in getting rid of any bacteria due to a poor flow rate.

Cranberry products have often been recommended in the prevention of UTIs. These can include juices, capsules and tablets. A 2012 Cochrane review of 24 randomized control trials found a relative risk reduction of 0.86 (95% CI 0.71 to 1.04) when comparing cranberry products (which includes juice and tablets) to placebo, water or no treatment, showing that cranberry products are much less effective than originally thought from the 2008 Cochrane review of 10 studies which found a relative risk reduction of 0.65 (95% CI 0.46 to 0.90) [24,25].

The conclusion however is weakened by the large number of dropouts/withdrawals (estimated between 20-55%) within the studies as well as their being no clear indication of optimum administration method or standardisation of dosage used in each study.

Within the trials themselves, smaller studies reported a significant outcome benefit in using cranberry products for patients with symptomatic UTIs, however no significance was found in the larger studies [24-26].

Whilst cranberry products are listed on national guidelines including the UKs National Institute of Clinical Excellence guidance, the guidelines advise to avoid cranberry products in patients on warfarin. This is because cranberry is a CYP enzyme inhibitor, which theoretically can prevent the metabolism of warfarin when taken in high doses [27].

Antibiotic therapy

Prophylactic antibiotic therapy is currently used as a treatment for recurrent UTIs, with pathogen sensitivities, local resistance patterns, allergies and cost and effects determining the antibiotic of choice [28]. A 2004 Cochrane review [12] of 19 randomised control trials demonstrated that when compared to placebo, continuous antibiotic prophylaxis for 6-12 months reduced UTI recurrence rates, with a relative risk of microbiological recurrence from between 0.15 (95% CI 0.08 to 0.28) to 0.31 (95% CI 0.19 to 0.52).

However antibiotic prophylaxis inevitably led to higher rates of adverse effects. There was a relative risk of 1.58 (95% CI 0.47-5.28) for severe side effects, which required the cessation of treatment, included severe nausea and skin rashes when compared to placebo. Other side effects included vaginal and oral candidiasis, as well as gastrointestinal symptom, displayed a relative risk of 1.78 (95% CI 1.06-3.00) favouring placebo.

One method however to minimize side effects is to prescribe patient controlled short courses of antibiotics, in particular targeting risk factors such as post-coitus. The Cochrane review on low dose antibiotic prophylaxis noted no significant difference in recurrence risks between using continuous daily or patient controlled post-coital ciprofloxacin [12].

By utilizing a short-targeted course, antibiotic usage is reduced in patients by one third, with corresponding fewer reports of side effects [29,30]. 100mg of trimethoprim has been recommended as an option for post-coital therapy [10] and patients are recommended to take the antibiotic within 2 hours of coitus [28].

The current 2010 International Clinical Practice Guidelines [3] recommends the following antibiotics for uncomplicated cystitis if the local resistance rate is below 20% for that antibiotic:

1. Nitrofurantoin 100 mg twice a day – 5 day course. This has been found to be equivable to a 3 day course of Trimethoprim-sulfamethoxazole as detailed below
2. Trimethoprim-sulfamethoxazole 960 mg (160/800 mg) twice a day – 3 day course.
3. Trimethoprum 100 mg twice a day – 3 day course. This is considered equitable to a 3 day course of Trimethoprim-sulfamethoxazole as detailed above
4. Fosfomycin trometamol 3 g – single dose. When compared to short short-course regimes, this has inferior efficacy.
5. Pivmecillinam 400 mg – 3-7 day course. In North America, this treatment is not licensed or available
6. Fluoroquinolones – 3 day course. This is recommended only when alternative options cannot be used due to the promotion of resistance development in uropathogens and other organisms (including Methicillin-resistant Staphylococcus aureus)
7. β-lactams – 3-7 day course. Compared to Fluoroquinolones, β-lactams are considered to have inferior cure rates and are not recommended unless other agents are inappropriate.

To note, the above guidelines suggest not using Amoxicillin or Ampicillin due to the high prevalence of bacterial resistance worldwide and poor efficacy.

When considering low dose prophylactic, Nitrofurantoin 50mg daily has been shown to be effective as a low dose prophylactic antibiotic against UTIs, with a 12 month course being more effective than a 6 month course at preventing recurrence [1,31,32]. However nitrofurantoin has been linked to severe side effects, in particular pulmonary reactions and hepatotoxicity. Patients will need to be advised that the chance of pulmonary or hepatic damage is approximately 1 in 750 for each, therefore it would be prudent to advise patients prior to treatment to report any new pulmonary symptoms including dyspnoea and coughs, as well as have regular biochemical liver function tests, though the optimum frequency of screening is unknown [33].

Whilst nitrofurantoin resistance rates have remained static [3,34] and the drug remains effective against the most common pathogen *E Coli*, other pathogens are often resistant to it [13].

However for the other antibiotic agents commonly used against uropathogens, resistance rates are rising. Trimethoprim is a commonly used antibiotic against uropathogens. Furthermore, evidence recommends 50mg daily as a possible low dose prophylactic antibiotic against recurrent UTIs. However, *E coli* trimethoprim resistance in Europe is currently estimated at between 20-46% and rising [35-37]. Trimethoprim-Sulfamethoxazole, was an effective therapy against UTIs, hosting a cure rate of 79% in treating acute cystitis [38], with adverse effects of nausea, diarrhoea headache and dizziness reported in between 1-31% of patients [38,39]. However resistance rates are rising, with as much as 60% resistance reported in developing countries [40,41], though in Europe and America the resistance rate is much lower at around 15% [42-44].

Similarly, previous empirical antibiotics for UTIs including ampicillin, amoxicillin and sulfonamides now exhibit resistance rates of 15-20% in Europe and the USA [13,44,45] with some data suggesting resistance rates of amoxicillin is as high as 50% and ampicillin 73% [37,46].

It is predicted that over time, these resistance figures will continue worsening [47], thus the current resistance trends gives rise to the urgency in finding newer therapies, especially ones which circumnavigate the need to rely on antibiotic therapies and boost up instead the natural body defense mechanisms.

Oestrogen therapy

After menopause, the levels of oestrogen within a women's body decrease. The lack of oestrogen stimulation is thought to decrease the proliferation of *lactobacillus* within the vaginal epithelium, thus preventing the synthesis of lactic acid and the formation of the usual low pH environment within the vagina that prevents colonisation by uropathogens and increasing the risk of UTIs within post-menopausal women [13].

Oestrogen replacement has therefore been investigated as a possible preventative therapy for recurrent UTIs in women. A 2008 Cochrane review found that vaginal oestrogen therapy was effective at inducing a decrease in UTIs, providing a relative risk of developing UTI when compared to placebo between 0.25 (95% CI 0.13 to 0.50) and 0.64 (95% CI 0.47 to 0.86) [48]. Vaginal oestrogens can be applied either via an estradiol-releasing ring for 36 weeks, (changing the ring every 12 weeks), or directly via a nightly 0.5mg estriol vaginal cream for 2 weeks, followed by applying the cream twice a week for 8 months [28].

Oral oestrogen therapies however were found not to be effective at reducing the risk of UTIs within women when compared to placebo [49,50].

The side effects (breast tenderness, vaginal bleeding or spotting, non-physiological discharge, vaginal irritation, burning and itching) of using vaginal oestrogen therapy were more marked in oestrogen creams than vaginal rings. [48,51,52] Current UK guidelines recommend local oestrogen therapy only in post-menopausal women who are not on oral oestrogen replacement and do not recommend oral oestrogen therapy in the prevention of UTIs.

Methenamine hippurate

Methenamine hippurate, trade name Hiprex™ is a non-antibiotic form of medicine used in the prevention of recurrent UTIs. Its action is via the formation of bactericidal formaldehyde from methenamine as well as the bacteriostatic effects of hippuric acid. Methenamine hippurate is effect against both gram positive and negative organisms.

A 2012 cochrane review of 14 studies (6 for symptomatic UTIs and 8 for bacteriuria) found that in patients with no renal tract abnormalities, methenamine hippurate was effective with a relative risk of 0.24 in patients with symptomatic UTI (95% CI 0.07 to 0.89) and 0.56 in patients with bacteriuria (95% CI 0.37 to 0.83). This effect was also found in short term prophylaxis of 1 week or less in patients with no renal tract abnormalities, with a relative risk of 0.14 (95% CI 0.05 to 0.38). This beneficial effect was not replicable in patients with underlying renal tract abnormalities [53].

The current licence for methenamine hippurate is for maintenance therapy to prevent recurrent UTIs after initial antibiotic treatment, for long-term use in recurrent cystitis, for patients with indwelling catheters to recue infection and blockages, as surgical prophylaxis prior to instrumentation procedures and for asymptomatic bacteriuria. The dosage is 1g twice daily for adult patients, increased to three times a day if patients have catheters [53].

New Treatments

Intravesical instillations

It has been proposed that the bladder epithelial lining relies on an intact covering layer of glycosaminoglycan (GAG) to prevent bacterial adherence to the epithelial cells beneath [54]. Therefore in the presence of a damaged GAG layer, the patient is at risk of UTIs [55].

One option to repair this layer is via the instillation of Hyaluronic Acid (HA) or Chondroitin Sulphate (CS). CS and HA are instilled into the bladder via a catheter. The patient is then often told to hold onto the agent for around two hours before recommencing normal everyday habits [56]. Results have shown patients after HA +/- CS instillation had a significantly lower rate of UTI recurrence and an increased time span to their next recurrence [57,58]. The strength of these positive benefits had a positive correlation with the number of bladder instillations performed [56, 58-60]. This treatment is limited by its invasive nature and need to attend the clinic for administration; hence it is an expensive option based on the attendance costs as well as the product costs. However clinical studies report mixed results

on effectiveness and are limited in their power by the small patient numbers [61].

There are a few commercially available instillation options. Cystistat® (Bioniche Life Sciences Inc., Belleville, Ontario, Canada) has been shown to lower rates of recurrent UTIs in a small prospective observational study with minimal side effects [62].

Ialuril® (Aspire Pharma, UK) is another instillation option, comprising of a mix of HA and CS. One previous study found that instillation weekly for 4 weeks followed by monthly for 5 months was found to decrease the rate of UTI over a 12 month period [57]. In addition, when compared to antibiotic prophylaxis or placebo, Ialuril® has been shown to be effective in decreasing episodes of recurrent UTIs [63,64].

Probiotic instillations

A health commensal flora is widely recognised as key in providing a strong defense against bacterial infections. Probiotics are already widely used both as over the counter medication as in drinks/yoghurts with minimal evidence of side effects.

In the management of recurrent UTI, intra-vesical instillations of a non-pathogenic strain of *E Coli* (83972) have been shown to significantly decrease the likelihood of developing recurrent UTIs, however these trials all involve small numbers of patients only [65,66]. Furthermore intra-vaginal instillations of *lactobacillus* (the usual commensal bacteria) have also shown promise in small studies in preventing recurrent UTIs [67]. However a Cochrane review in 2015 of 6 studies involving 352 participants found no major risk reduction in recurrent UTIs between patients treated with probiotics compared with placebo (Relative Risk 0.82, 95% CI 0.60 to 1.1). However the conclusion is weakened by the small number of patients in each study, wide confidence intervals and varying methods of administration, mentioned above [68]. Until larger trials are available, it is too early to say if intra-vesical or intra-vaginal instillations of probiotic organisms will be beneficial in the management of recurrent UTIs.

Immunomodulation vaccine therapy

To fight against uropathogens, the genitourinary tract harbours an innate and adaptive mucosal immune system, which is part of a larger common mucosal immune system made up of various different areas around the body called the mammalian lymphoid organ system. 80% of all immunocytes in the body are contributed to by this system. The immunocytes accumulate and transit though these various Mucosa-Associated Lymphoid Tissues (MALT) thus, the activation of immunocytes from one MALT site leads to the dissemination of immunity through to various other distant sites which form part of the same lymphoid organ system [69]. The sublingual mucosa has been linked to the genitourinary tract mucosa, with induction at the sublingual mucosa found to stimulating Toll-Like Receptors (TLR), leading to the subsequent activation of a broad spectrum of mucosal and systemic immune responses, which are both persistent and of high efficacy, at the site of the bladder mucosa [69-71]. The stimulation of TLR4 in particular allows the recognition of the lipopolysaccharide found on the outer membrane of the most common uropathogen E-coli. As most uropathogens share a similar antigenic structure, this polysaccharide is also found in many other gram-negative bacteria's and uropathogens, and thus can be recognised by the same pattern recognition receptor and consequently targeted by the same immune response [71].

Uro-Vaxom® (Terralab, Croatia) was one of the first oral immunomodulating vaccines. Originally named OM-89 in literature, it is comprised of bacterial extracts from 8 uropathogenic *Escherichia Coli* strains and has been shown in mice models to induce the immunological defense response within the bladder [72]. Clinical studies however reported mixed results.

On taking one Uro-Vaxom® tablet daily for 3 months, followed byan observation period between 3-12 months, 4 placebo controlled studies [73-76] showed Uro-Vaxom® halved the number of UTIs in the treatment group, with a 0.61(95% CI 0.48-0.78) relative risk of developing a UTI in the treatment group [77].

However a recent multicentre double blind control trial of 451 patients showed no significant difference in UTI rates between Uro-Vaxom® and placebo [78].

A newer inactivated whole bacteria vaccine has shown more promising results. Uromune® (Syner-Med (PP) Ltd UK, Inmunotek S.L. Spain) is an immunomodulating vaccine aimed at this pathway. Uromune® is currently in the pre-license Phase III development stage and is available under the Named Patient Program in the UK. The vaccine is a sublingual suspension of inactivated whole bacteria, within which contains equal amounts of *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus vulgaris* and *Enterococcus faecalis*. Retrospective studies in Spain have reported a significant decrease in UTI recurrence in women with recurrent UTIs who have undergone treatment with Uromune® when compared with antibiotics. The absolute risk reduction was reported as high as 90.28% (87.18-93.38). The studies also reported no side effects in any of the Uromune® patients [79,80].

These results also reflect the recent prospective data from the first use of Uromune® in the UK on women with recurrent UTIs who have failed conventional treatments including long-term antibiotic prophylaxis. 85% of these patients reported no subsequent UTIs in the 12 months follow up after a 3 month course of Uromune® [81]. A RCT with Uromune® is currently in development in the UK, the results are awaited.

Other methods of vaccine therapy are also currently in development, focusing primarily on using uropathogenic *E Coli* strains alone to elucidate a host immunological response [82]. Whilst these studies are still in its infancy stage, a phase I clinical study is currently in progress on using a 4-valent prototype *E coli* bioconjugate vaccine in the prevention of recurrent UTIs, however to date, the results from this trial is still awaited [83].

Laser therapy

Similar to vaginal oestrogens, new laser therapies have now been developed which aim to provide vaginal rejuvenation by restoring the vaginal mucosa and thus reduce UTIs and other symptoms associated with atrophic vaginitis. This is done via a thermo-ablative fractional CO_2 laser which when applied directly to the vagina, has been found to repair at the cellular level the vaginal mucosa by restoring the thick squamous stratified epithelium, intracellular glycogen storage and synthesis of new components for the extra-cellular matrix. This restoration of the vaginal mucosa allows concurrent restoration of the commensal *Lactobacillus* bacterium, allowing for increase synthesis

of lactic acid and the re-establishment of the natural protective acidic pH environment within the vagina [84,85].

Furthermore, significantly decreased symptoms of vulvo-vaginal atrophy, and in particular dyspareunia, were also found in patients who underwent a course of fractional CO_2 laser [86,87].

Currently, two clinical trials for CO_2 fractionated vaginal laser therapy are underway. One multicentre prospective single blinded clinical trial, run by The Cleveland Clinic, is underway comparing the effectiveness of treatment between using vaginal oestrogen creams and CO_2 fractionated vaginal laser therapy [88]. The other trial is based in Reading, UK [89]. The results for both are awaited.

Conclusion

Recurrent UTIs pose a challenge for healthcare clinicians. Whilst the initial infection is often treated with ease by conventional antibiotic treatments, in recurrent UTIs, long-term antibiotics are often required, increasing the risk of bacterial resistance. With common uropathogens already displaying ever increasing amounts of resistance to conventional antibiotic therapy, there is an urgent need to find new ways of preventing recurrence.

Having first investigated and excluded the presence of any modifiable risk factors or pathology putting the patient at risk of recurrent UTIs, and having failed conservative management options, clinicians can now consider newer therapies which boost the natural immune systems. Vaginal oestrogen therapies, laser therapy, intra-vesical treatments, probiotics and immunomodulation vaccines have all shown promise as methods to decrease the risk of UTI recurrence without the need for antibiotic therapy.

With both the Centre for Disease Control and the World Health Organization naming antimicrobial resistance as one of the biggest threats to humanity, the development of these new therapies, which circumnavigate the need and dependence for antibiotic use, provides a direction for future research in developing novel treatments.

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