Non-surgical management of recurrent urinary tract infections in women

Paul A. Bergamin[1,2,3], Anthony J. Kiosoglous[1,2,3]

[1]Department of Urology, Royal Brisbane and Women's Hospital, Queensland, Australia; [2]Queen Elizabeth II Jubilee Hospital, Brisbane, Australia; [3]School of Medicine, University of Queensland, Brisbane, Australia

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Correspondence to: Anthony J. Kiosoglous, FRACS. Department of Urology, Royal Brisbane and Women's Hospital, Level 8, Ned Hanlon Building, Queensland, Australia. Email: anthony.kiosoglous@health.qld.gov.au.

Abstract: One in three women will experience a clinically significant urinary tract infection (UTI) by age twenty-four and almost half will have at least one in their lifetime. Recurrent UTIs (rUTIs) are defined as having greater than two infections in a 6-month period, or three infections over twelve months, with complete resolution for at least two weeks. These may be due to relapse from incomplete treatment (persistence) or re-infection (new source). It may be difficult to distinguish between the two, where the same organism is cultured. There are several risk factors for rUTIs including an impairment of the body's immune system and virulence factors. Reversible or treatable causes are sought and excluded in the patient's initial review. Patient's with rUTI are often complex and difficult to manage. The long-term management options in women are multimodal and should focus on prevention of relapse and recurrence. Behavioural factors include adequate hydration, care with sexual hygiene, reducing one's body mass index (BMI) and post-void residual (PVR) volume. There are several non-antimicrobial options for rUTIs which have become a multi-billion-dollar business. Unfortunately, there are numerous studies which fail to show any major benefit or having conflicting data. Vaccines are currently being explored as a prevention strategy, delivered through injection, intra-nasal sprays, or vaginal suppositories, which are made from combinations of heat killed uro-pathogenic strains. There are no widely available vaccines at present due to limited clinical success. It is well established that appropriate antibiotic therapy results in higher rates of symptom relief and bacterial eradication in women with uncomplicated cystitis. There are several options for antimicrobial use which have been shown to be highly effective in reducing the risk of rUTI in women. The pain and discomfort of the UTI must be balanced with the cost and risk of developing resistance when using antimicrobials. Continuous prophylaxis, pre- and post-coital voiding, and self-starting are the three commonly accepted options for prophylaxis. The choice between these will depend upon patient preference, cultures and previous pattern of infection. Intra-vesical instillation of hyaluronic acid and chondroitin sulphate have been used for glycosaminoglycan (GAG) layer replenishment for many indications, including interstitial cystitis, overactive bladder syndrome, radiation cystitis and prevention of rUTI. At present, intra-vesical therapies are reserved for only those with the most unresponsive rUTIs. The principles of treating rUTI are to break the cycle and to treat any reversible causes. With our ever-expanding research knowledge, there are now many useful products that may be used for the successful treatment of rUTI. A management plan including a combination of a non-antimicrobial and selective antimicrobial regime for a minimum of six months should be considered. It is a prudent clinician that clearly defines this management plan, with reassurance of a finite period of therapy.

Keywords: Urinary tract infections (UTIs); prophylaxis; non-antimicrobial

Introduction

Urinary tract infections (UTIs) are common in females, the elderly, the immunosuppressed, and patients with catheters. One in three women will experience a clinically significant UTI by age twenty-four and almost half will have at least one in their lifetime (1). They occur commonly in women with anatomically and physiologically normal urinary systems. The various types of UTIs include pyelonephritis (kidneys), cystitis (bladder) and urethritis (urethra). We will be limiting this chapter to the bladder.

Recurrent UTIs (rUTIs) are defined as having greater than two infections in a 6-month period, or three infections over twelve months, with complete resolution for at least two weeks (2). These can be due to relapse from incomplete treatment (persistence of bacteria) or re-infection (new source). It may be difficult to distinguish between the two, where the same organism is cultured. In one study 27% of women with a UTI were found to have a recurrence within 6 months, and 3% had two recurrences (3). Providing the genitourinary tract is anatomically and functionally normal, the progression from cystitis to pyelonephritis, even without treatment, is only 2% (4).

UTIs are caused by micro-organisms, most commonly bacteria. rUTIs are believed to occur from vaginal or bowel sources of flora (5). Recent studies have shown that some *Escherichia coli* strains are able to invade the urothelial bladder lining and form quiescent intracellular bacterial reservoirs, which can then act as a source of bacterial persistence and thus recurrence (6). Reduction in oestrogen, usually associated with post menopausal females, leads to a change of the vaginal flora (7). The incidence of anaerobic gram-negative rods was significantly higher (40% *vs.* 7%) in this group of women. *Lactobacillus* in women with atrophic vaginitis constituted only 11.2% of vaginal communities, in contrast to healthy women which had lactobacillus species significantly more abundant (P<0.0001) and on average constituted 53.2% (8).

Clinical features of UTIs most commonly include urinary frequency, urgency, dysuria, suprapubic pain, and malodorous smelling urine. Up to 90% of infections of the bladder are from *E. coli*. Other common pathogen species include Staphylococcus, Enterococcus, Proteus, and Klebsiella. The bacterial strain identified can often give clues as to the source. For example, Staphylococcus *aureus* commonly occurs from haematogenous spread, whereas Enterococcus species usually migrate from the gastrointestinal system (9,10).

Predisposing factors for UTIs can be divided into several ways. Biological and genetic risk factors have been shown to increase susceptibility to UTIs (11-15). Virulence factors include adhesins (P fimbriae, mannose-resistant adhesins and type 1 fimbriae), the aerobactin system, haemolysin, K-capsule and resistance to serum killing (16).

Our normal immune defense mechanisms against bacterial pili (facilitates bacterial ascension) may be impaired due to many factors and can increase the propensity for colonisation. These factors include immunosuppression from diabetes, malnutrition or drugs such as chemotherapy agents and steroids. Genetic mutations affecting the innate immune system are also being increasingly identified as risk factors for rUTIs in both children and adults (17). It has been mentioned above that low oestrogen states such as atrophic vaginitis in post-menopausal women can alter recurrence rates of UTIs (7). Alternatively, foreign bodies such as urinary stones, suture material, or mesh, can act as a nidus to infection. There are several behavioural risk factors which may be easily optimised and are critical to lowering recurrence rates. These will be explored further in the chapter.

Anatomical and physiological variations are another source of risk. For example, the distance from the female urethra to anus is inversely proportional to the risk of developing a UTI (18). There was a significant difference between cases and controls for mean distance from urethra to anus (4.8 *vs.* 5 cm, P=0.03). Surprisingly, this study found no predisposition for urethral length or urine voiding characteristics.

High post-void residual (PVR) volumes can act as a reservoir for organisms, resulting from incomplete eradication of infected urine, volumes down to 20mls have been shown to be clinically significant in patients with rUTIs (19,20). Common causes of urinary stasis include hypo- or a contractile bladder and bladder outlet obstruction (including high tone non-relaxing sphincters, urethral strictures, vesical diverticulum, cystoceles). Other causes include neuropathic bladders and fistulae (colo-vesical and vesico-vaginal).

A detailed history and examination are required to rule out potential differential diagnoses and reversible and treatable causes, such as sexually transmitted diseases, fistulae and urothelial carcinoma. Symptoms alone can predict UTI in over 90% of cases (21). Directed investigations such as urine cultures, urine cytology, ultrasound and flexible cystoscopy can be utilised to look for complicating features but in the absence of suggestive

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features on history or examination they are generally low yield (22). Significant bacteriuria is defined somewhat arbitrarily as >10^5 cfu/mL, an important consideration for patients with convincing rUTIs whose mid-stream urine specimen growths do not reach this threshold (23).

One must also consider that previously uncommon infections are increasing in frequency due to migration policies and globalisation. These infections include bacterial (e.g., Mycobacterium *tuberculosis*) or parasitic (e.g., Schistosomiasis *haematobium)*. It is recommended that these difficult to eradicate infections should be managed in a multi- disciplinary team approach including urologists and infectious disease physicians.

Asymptomatic bacteriuria is defined as two cultures of the same bacterial strain or species, taken over 24 hours apart, which show bacteria >10^5 cfu/mL (2). Treatment of asymptomatic bacteriuria, however, does not reduce the frequency of infections nor improve outcomes (24). Populations where intervention is indicated include pregnancy (25), prior to urological procedures that may cause mucosal bleeding, and for those who are on chemotherapy. Diabetics, the elderly, and patients with indwelling catheters often do not need therapy, as they frequently have non-pathogenic strains which can remain asymptomatic for long periods (26).

Management

The management of rUTIs in women is multimodal. During active infection antimicrobials remain the mainstay and first line of therapy. Confirming cultures and antimicrobial sensitivities should guide both type and duration of therapy. The vast majority of patients will be managed as outpatients. Hospital admissions are generally reserved for patients requiring acute resuscitation from urosepsis.

The long-term management of women who suffer from rUTIs should focus on prevention of relapse and recurrence. A variety of measures will be discussed below relating to prevention of recurrences.

Behavioural

The prevention of high risk behaviours is the first step in managing females with rUTI. There are many simple measures which can influence a person's risk. Studying these modifiable risk factors has proven difficult, with analysis often complicated by data heterogeneity. For many of the suggested interventions the reality is that there are few side effects and thus little downside, and so are recommended despite inadequate and irrefutable data proving the intervention will work.

Fluid intake

It is telling that perhaps one of the commonest advice given to women to prevent rUTIs is to increase fluid intake. The concept being that if uni-directional flow of urine and reduced retrograde migration of bacteria occurs, then the risk of UTI will reduce. Studies have only provided conflicting results with this intervention, and over hydration may result in worsening of some overactive lower urinary tract symptoms in women (27-31).

Sexual hygiene

In one large case control study, a multivariate analysis revealed frequency of sexual intercourse in young women is the strongest risk factor for UTIs (18,28). Other risk factors these studies identified included spermicide usage, new sex partner in past 12 months, UTI before age 15, and having a mother with a history of UTIs (28,32-35). These studies failed to prove a significant relationship between UTI risk with pre- or post-coital voiding, frequency of urination, delayed voiding habits, wiping patterns, douching, use of hot tubs, use of tampons, use of pantyhose or tights and asking male partners to wash under their foreskin if uncircumcised to reduce bacterial load. Whilst without significant evidence to support their practices, the lack of harm associated with many of these suggestions leads to their ongoing recommendation (28,36,37). These recommendations are also a frequent occurrence in many mainstream media articles on the topic (38).

Body mass index (BMI)

BMI was shown in a cross-sectional study to be associated with UTI. Women with an elevated BMI of 30–34.9 were significantly more likely to suffer from a UTI (OR 1.22; 95% CI: 1.15–1.28). However, other BMI classifications have not shown statistical significance (39).

PVR

It is generally accepted that a PVR volume greater than 50–100 mL is an independent risk factor for rUTIs in many populations, especially post menopausal women and the

elderly (40,41). There are several conservative measures to reduce PVR with minimal risks, but with little proven evidence, include frequency of urination, double voiding, forward pelvic tilting whilst voiding, and pelvic floor exercises or relaxation techniques (28,29,31). Though there is little evidence to direct recommendations regarding the use of diaphragms and tampons and UTI risk, there is some evidence that they may harbour bacteria. Also, they may provide mechanical resistance thus reducing the bladder's ability to empty to completion, as has been shown on urodynamic studies (42).

More invasive measures to reduce residual volume include clean intermittent self-catheterisation and the use of medications which block the alpha-adrenergic receptors in the bladder neck (43,44). Finally, surgically correctable causes, not within the scope of this chapter, must be ruled out, for example urethral strictures or cystoceles.

Non-antimicrobial

Oestrogen

Topical oestrogens are an effective method of normalising the vaginal flora in post-menopausal women (45). Efficacy in preventing rUTIs was explored with a 2007 Cochrane database systematic review (46) which included 3,345 post-menopausal women. Two randomised studies favoured oestrogen, with a relative risk of symptomatic UTI of 0.25 (95% CI: 0.13–0.50) (47) and 0.64 (95% CI: 0.47–0.86) (48). They found that the occurrence of UTIs went from 5.9 to 0.5 episodes per year (47). The usual dose is estradiol cream 0.5 mg daily for 2 weeks then twice per week ongoing. Alternatives include oestrogen pessaries with a dose of one insert nocte for seven days then twice per week with review after six weeks of therapy. These patients will have an increase in lactobacilli and a decrease in *E. coli* colonization peri urethral. Side effects unfortunately are common (incidence 6–20%) and include breast tenderness, vaginal bleeding, spotting, discharge or irritation (46,47,49).

Cranberry

Limited evidence exists for cranberries in reducing the risk of rUTIs, importantly there are also no known adverse effects (45,50,51). Cranberries contain type A pro-antho-cyanidins whose urinary metabolites interfere with the adhesiveness of uro-pathogenic bacteria to the bladder epithelium, thus preventing adherence of bacteria to the bladder lining (52).

They are not as effective as antibiotics and have variable intestinal absorption (53). One RCT showed that both cranberry tablets and juice were able to significantly reduce the proportion of women experiencing rUTI over the 12 months compared with placebo (18% *vs.* 32%) (51). A Cochrane database systematic review updated in 2012 looked at 4,473 participants (54). It showed that there was no significant reduction in the occurrence of symptomatic UTI overall or for any subgroups tested (54). These included children, the elderly, women, pregnant women, cancer patients, neuropathic bladder patients or spinal patients. The review concluded that with additional studies included the evidence for cranberry juice in preventing UTIs was less than previously thought. There were, however, three studies that showed cranberry products were equivalent to antibiotics in preventing UTIs, with less side effects. These were limited by the lack of standardisation between tablets and powders and the limitations associated with lack of information about the active ingredient present in each sample. No recommendations were able to be made. Finally, for those wishing to take cranberries it is known that the tablets are twice as cost effective as the juice (51).

Probiotics

There are several mechanisms by which probiotics are thought to reduce the risk of UTI. These include blocking the attachment of bacteria to epithelial lining, producing hydrogen peroxide (microbicidal to uro-pathogens), reducing pH, and inducing an anti-inflammatory cytokine response in epithelial cells. A review of randomised trials found only one which demonstrated a significant reduction in rates of UTI recurrence (55). This trial in post menopausal women comparing trimethoprim-sulfamethoxazole with lactobacillus tablets found the lactobacillus had more recurrences (3.3 *vs.* 2.9 per year) and also a shorter time to recurrence (3 *vs.* 6 months) (56). It is important to note that both therapies were successful in reducing symptomatic UTI rates with probiotics inducing less antibiotic resistance. There are two proposed methods of administration of probiotics for the prevention of UTIs, oral and vaginal. The above review looked primarily at oral lactobacillus dosing, it is hypothesised that the vaginal dosing may be of greater benefit in changing vaginal flora. Lactobacillus *crispatus* was given intravaginally to premenopausal women with rUTIs and aside from being much better tolerated, also showed decreased rates of

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rUTI compared to placebo (15% *vs.* 27% of women) (57). Similarly, Lactobacillus *rhamnosus* and Lactobacillus *reuteri* have proven efficacy as an intravaginal probiotic (58). These strains given intravaginally can restore vaginal lactobacilli and compete with uropathogens, and are thought to prevent bacterial vaginosis and thus reduce the ris of UTI (45,59).

Methenamine hippurate (MH)

MH is thought to prevent UTI by reducing urinary pH through its conversion to formaldehyde. A meta-analysis of six studies was hampered by methodologic and heterogeneity issues and found no overall significant conclusions (60). Subgroup analysis showed decreased incidence of UTI within the post gynaecologic surgery setting, involving only one week of treatment. This is a group at relatively low risk of UTI and that which is relatively easily treated with antimicrobials, thus MH would not be indicated for this purpose. Anecdotal evidence exists for its use with multidrug resistant uro-pathogens after first and second line therapies have failed, in this setting it appears safe and generally well tolerated (60). Formaldehyde is a well known human carcinogen (61). Studies have shown that exposure to formaldehyde in rat bladders led to DNA damage to the urothelium, which was repaired within four hours (62). It has been thus extrapolated from this data that with long term human use could potentially lead to urothelial malignancy.

Ascorbic acid (vitamin C)

Vitamin C can acidify urine and has been weakly associated with decreased risk of UTI (63). It also works synergistically with MH, providing an acidic environment to aid conversion to formaldehyde (64). Finally, there is data to suggest that vitamin C can also have a bacteriostatic effect within urine, mediated by reduction of urinary nitrites to reactive nitrogen oxides (65,66).

D-mannose

D-mannose is a natural sugar which may have clinical benefit, though data is limited. A randomised placebo-controlled non-blinded clinical trial has shown that a daily dose of 2 g d-mannose was superior to placebo and as effective as 50 mg nitrofurantoin in preventing UTI (67). Mannose receptors are part of the protective mucopolysaccharide layer found on uroepithelial cells lining

the urinary tract. The mechanism of action is thought to involve binding of the mannose receptors to *E. coli* pili, thus preventing both adhesion to and invasion of urothelial cells. The complex created between mannose and *E. coli* can then be washed away with voiding (2,68,69). In Australia, online orders are required as it is not locally sold at present.

UTI vaccines

Vaccines are currently being explored as a prevention strategy. There are no widely available vaccines at present due to limited clinical success. A meta analysis looked at the published data and found moderate efficacy, albeit with the requirement of booster cycles (70). These vaccinations are available in Europe currently. Several vaccines have had partial success or are under development, delivered through injection, intra-nasal sprays, or vaginal suppositories, which are made from combinations of heat killed uropathogenic strains (71-73). OM-89 [Uro-Vaxom(R)] vaccinations have been shown to be better than placebo in randomised trials with minimal side effects. EAU guidelines have recommended immunoprophylaxis in female patients with rUTIs (45,70,74). New methods are looking at a vaccine against *E. coli* type 1 fimbrial adhesion protein (FimH) (75). At present, none are widely used in Australian practice.

Antimicrobials

It is well established that appropriate antibiotic therapy results in higher rates of symptom relief and bacterial eradication in women with uncomplicated cystitis (76).

There are several options for antimicrobial use which have been shown to be highly effective in reducing the risk of rUTI in women (77,78). Prophylactic antimicrobials are indicated in those who fit the definition of rUTI. The pain and discomfort of the UTI must be balanced with the cost and risk of developing resistance when using antimicrobials. Continuous prophylaxis, pre- and post-coital voiding, and self-starting are the three commonly accepted options for prophylaxis. The choice between these will depend upon patient preference, cultures and previous pattern of infection.

Prophylactic Antibiotic Therapy. The use of long term, low dose antimicrobials, is associated with up to 95% decreased rates of infection (78-80). A Cochrane meta-analysis (81) researched 10 trials, including 430 women. It concluded that per year, the recurrence rate was reduced from 0–0.9 in the treatment group, versus 0.8–3.6 in the

placebo group. There was a relative risk of one recurrence at 0.21 (95% CI: 0.13–0.33), and a number needed to treat to prevent one recurrence of 1.85. This review noted side effects of vaginal and oral candidiasis and gastrointestinal symptoms more commonly in the antibiotic group. It noted no difference between continuous and post coital prophylaxis.

There is no conclusive evidence as to the best antibiotic choice nor optimal duration, schedule or dosage (81). Most guidelines (2) recommend an initial three to 6-month trial, with most women reverting back to the previous pattern once prophylaxis ceased. Trimethoprim-sulfamethoxazole has been studied out to five-years and is reported effective and well tolerated (82,83). Prophylactic doses range from 100 to 150 mg once daily. Nitrofurantoin has also been shown to be safe out to 12 months. It has the added benefit of being excreted preferentially in the urinary tract rather than bowel unlike many other antimicrobials (84). There are concerns regarding toxicity with nitrofurantoin use. These include hepato-toxicity, pulmonary toxicity and neuropathy, but the overall incidence is low (85). Prophylactic doses range from 50 to 100 mg once daily. Antibiotic choice should also be made with advice regarding local resistance patterns and through consultation with infectious diseases specialists and microbiologists. Resistance patterns can vary even within cities. Similarly, patients who spend significant amounts of time in urology units are also more likely to have uropathogens such as *E. coli* with higher antimicrobial resistance patterns (86). It is common practice for antibiotic rotation. However, there is no strong evidence for or against rotation of antibiotics in this situation (87,88). Long-term use with switching of antibiotic to theoretically reduce the risk of resistance or side effects is not recommended (88).

When to cease antibiotic prophylaxis should be based on severity of symptoms, physician and patient preference. Empirically it has been recommended that six months of treatment is given, followed by observation for re-infection (89). Continuous prophylaxis, whether for six or twelve months, had similar UTI rates post ceasing prophylaxis, regardless of duration.

Thus, it is preferential practice for earlier antibiotic cessation, once the initial rUTI cycle is broken (81). It is important to note that with break through UTI's, a urine microscopy, culture, and sensitivity, should be tested, appropriate antibiotic sensitivities obtained, a full dose and course of antibiotics prescribed (it may be the original treating antibiotic or a differing class), and then the low dose course resumed. The aim is not a break in antibiotic therapy.

Post-coital prophylaxis

This is recommended where there is a clear pattern of infection following sexual intercourse. It consists of a single dose immediately following intercourse. Optimal choice of antibiotic is not clear. The only controlled trial compared placebo with trimethoprim-sulfamethoxazole. It revealed an incidence rate of 0.3 versus 3.6 infections per patient year improvement (90). Other studies have compared post coital antibiotics with a single course of antibiotics. One study investigated ciprofloxacin with equivalent success, leading to decreased cost and side effects in the post coital antibiotics groups (81,91).

Self-start antibiotics

Technically not a form of prophylaxis, self-start antibiotics is another technique which most commonly appeals to those who prefer to minimise their antimicrobial intake. This method is only possible when the patient has the ability to recognise a UTI symptomatically and involves a 3-day course of antibiotics. Several studies have proven that patients can accurately self diagnose UTIs with 86–92% concordance between self diagnosis and urine cultures in an appropriately selected population (92-94). This model relies on a compliant and motivated patient who has close contact with their general practitioner. It is recommended that if there is minimal improvement after 48 hours, or symptoms are worsening, then patients should present for further assessment.

Side effects can occur from several of the above regimes. As mentioned, nitrofurantoin has been associated with pulmonary reactions, chronic hepatitis and neuropathies. These toxicities are rare and the drug should be avoided if creatinine clearance is <30 mL/min. Fluoroquinolones can cause prolonged QT interval and are contraindicated in pregnant women, women trying to conceive, and children. They are associated with a small risk of tendonitis and tendon rupture, and can exacerbate the symptoms of myasthenia gravis. All antibiotics can potentially interfere with oral contraceptives through altering gut flora, which leads to reduced oestrogen concentrations (95). Women on these medications should be encouraged to use a second line of contraception. Clostridium *difficile* diarrhoea risk is also increased following antibiotic use and patients should be warned accordingly.

One final note should be made with regards to resistance from antimicrobials. There is strong evidence that resistant

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uropathogens are selected out following the use of several antibiotics, including ciprofloxacin (96) and trimethoprim-sulfamethoxazole (56). Thus, these antibiotics are generally not used for prophylaxis. There are also adverse effects on the gut and vaginal flora (97).

Intravesical

Intravesical instillation of hyaluronic acid and chondroitin sulphate have been used for glycosaminoglycan (GAG) layer replenishment for many indications, including interstitial cystitis, overactive bladder syndrome, radiation cystitis and prevention of rUTI. A total of 276 women with rUTIs were treated with intravesical hyaluronic acid and chondroitin sulfate and achieved significantly reduced rates of recurrence and increased symptomatic relief, quality of life and bladder capacity compared to standard therapy only (98). Standard therapy in this study consisted of an antimicrobial, immunoactive prophylaxis, probiotics and cranberry. Treatment involved hyaluronic acid 1.6% and chondroitin sulphate 2% with one instillation per week for the first month, fortnightly instillations for the second month and finally monthly instillations until remission of symptoms. Another smaller study showed similar outcomes with the regime of weekly instillations for 4 weeks, then fortnightly for 4 weeks, versus Bactrim alone for 6 weeks (99). A study from Damiano *et al.* looked at 57 women with rUTI and randomised them to either 50 mL of combination 1.6% hyaluronic acid and 2% chondroitin or 50 mL placebo. They found the treatment arm significantly reduced UTI rates over the 12-week course (–86.6% *vs.* –9.6%) (100). Finally, a review of 27 studies was unable to make any conclusions on its effectiveness (101). Further research is required, and due to significant cost, it is limited at this stage to multi-resistant, difficult to eradicate UTIs.

Intravesical gentamycin has been shown to be effective at reducing bacteriuria and rUTIs, however, the data is limited to case reports and case series (102). Of note, there were no clinically relevant side effects reported and it has been described as a reasonable treatment option in select patients, such as those who self catheterise.

Summary

The approach to women who present with recurrent UTI requires a full history, examination and then directed investigations. The relevant investigations include a 48-hour bladder diary, and baseline blood testing including full blood count, liver and renal function tests. Urine samples are analysed for microscopy, culture and antibiotic sensitivities, and urine cytology. Imaging will generally consist of an ultrasound of the kidneys, ureters and bladder, and a uroflow with PVR testing. If the patient fulfils the criteria for rUTIs, then initial management is often instigated, running concurrently with investigations. If there are any areas of concern with the patient's work-up, more invasive forms of investigation such as contrast imaging, urodynamics (cystometrogram), or cysto-urethroscopy, are recommended.

Initial management includes general advice regarding prevention strategies of uncomplicated rUTIs. There is a balance between the established evidence, risk factors from interventions, practicalities of treatment options and patient compliance. It is noteworthy that without treatment, 25–42% of uncomplicated UTIs in women resolve spontaneously (76), and progression to pyelonephritis occurs in only around 2% of women with untreated UTIs (4).

Behavioural and conservative interventions include advice on adequate fluid intake, sexual hygiene, weight loss, and PVR volume reduction strategies. Non-antimicrobial advice is more variable and often dependent on the level of bother, recurrence frequency and severity. Cost is also an important factor to many patients. A recommendation includes combination of probiotics, cranberry tablets and D-mannose.

Antimicrobial prophylaxis includes low dose-long continuous course of antibiotics, self-start or post-coital therapy. The choice is multi factorial, and often reflects the patient's duration and severity of symptoms. Antibiotic choice is driven by organism sensitivities, patient tolerance, and clinician preference. Nitrofurantoin 50–100 mg and trimethoprim 150 mg are two of the most common selections. With long-term antibiotic prophylaxis, it is vital to counsel patients on breakthrough infections, and to provide a management plan. If differing antibiotics are utilised, then it is recommended against overlapping therapy. Women with rUTI associated with sexual intercourse may be offered post-coital therapy as an alternative in order to minimize cost and side effects.

Overall, patients with rUTI are often complex and difficult to manage. The principles of treating rUTI is to break the rUTI cycle and to treat any reversible causes. Uniform recommendations are difficult, however, there are now a number of beneficial products. A combination of a non-antimicrobial and selective antimicrobial regime for a minimum of 6 months should be considered. Defining

a management plan and providing reassurance of a finite period of therapy, assists with patient compliance and satisfaction.

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Footnote

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