World J Urol (1999) 17: 359–363

Gregor Reid

Potential preventive strategies and therapies in urinary tract infection

Abstract There are perhaps five strategies either presently advocated or under investigation for prevention of recurrent urinary tract infection (UTI): antibiotics, including natural peptides; functional foods; vaccines; probiotics; and miscellaneous, including avoidance of spermicides and maintenance of good hygiene. It is not possible to state the proportion of patients using antibiotics versus foods such as cranberry or using alternative approaches such as avoidance of spermicides. The majority of women who are referred to specialists will be prescribed long-term, low-dose antibiotics. However, given the magnitude of the problem, it is safe to state that large numbers of women are at least experimenting with alternative remedies such as drinking of cranberry juice or ingestion of herbal remedies with a view to enhancing their immune response. Vaccine development remains a long way from human use and has yet to be developed for organisms other than *Escherichia coli*. The use of probiotics to restore the normal vaginal flora and provide a competitive bacterial barrier to pathogens is close to becoming available as an alternative preventive approach. The next decade should see the introduction of new methods for reduction of the high incidence of UTI and better management of recurring urogenital infections.

Key words Prevention of UTI · New therapeutics · Functional foods · Peptides · Vaccines · Probiotics

Given the vast number of cases of urinary tract infection (UTI) occurring each year and the high recurrence rate, it is critical that preventive methods be available. For the most part, current prevention involves the use of antibiotics. In complicated cases, for example, indwelling-catheterized male and female patients, antibiotic therapy is given daily to prevent an infection that could subsequently lead to bacteremia and death.

In uncomplicated cases where the woman has a normal urinary tract and is using a diaphragm and spermicide for contraception, the latter could be playing a role in increasing the risk for UTI by disruption of the normal flora and growth by uropathogens [25, 35, 36, 42]. Under that scenario, alternative birth control methods may have to be considered. In uncomplicated cases where the woman has a normal urinary tract and is not using spermicides, no conclusive association has been found between recurrent UTI and the use of pantyhose, hygiene, bicycle riding, bathing, drinking coffee or tea, or the use of tampons [38]. If there is a clear association between sexual intercourse and onset of UTI, single-dose antibiotic therapy can be taken immediately following intercourse [63]. This is self-directed therapy that provides sufficient antibiotic levels in the bladder to stop any uropathogens, that may have entered during intercourse, from multiplying and infecting the woman.

In the situation where the infection cycle has no known cause and the patient suffers two or more symptomatic UTIs in a 12-month period, long-term antibiotic prophylaxis is the urologist's current treatment of choice. This use of antibiotics represents the method used most to manage recurrent UTI. Antibiotics such as nitrofurantoin (50 mg), trimethoprim-sulfamethoxazole (40/200 mg), norfloxacin (200 mg), and even cephalexin (125 mg) have been prescribed at low doses taken daily for between 6 months and 5 years in an attempt to break the clustering cycle of infection [4, 18, 21, 53, 62]. The combination of trimethoprim and sulfamethoxazole has also been used thrice weekly [39]. Once again, this approach represents treatment of the patient with antibiotics in amounts that prevent bacterial multiplication and infection in the bladder.

Other nonantibiotic remedies have been used with some effect, namely, methenamine hippurate (1 g twice

G. Reid
H414, Lawson Research Institute, 268 Grosvenor Street,
London, Ontario N6A 4V2, Canada
e-mail: gregor@julian.uwo.ca,
Tel.: +1-519-6466100 ext 65256, Fax: +1-519-6466110

daily) and povidone-iodine urogenital washes (twice daily) [12], but patient compliance and efficacy have not been sufficient to make these the treatments of choice.

Although there has been no evidence of increased adverse effects during long-term antibiotic therapy, few studies have examined the impact on the normal urogenital flora, and few have undertaken quality-of-life surveys or patient-preference questionnaires. It has clearly been shown that antibiotic use leads to increased presence of drug-resistant organisms in the rectum, perineum, and urethra [19, 49]. Also, depending upon the antibiotic, many patients subsequently suffer from yeast vaginitis as a result of disruption of the normal intestinal and vaginal flora. Societal trends in health care show a definite movement toward the use of natural remedies and away from chemotherapeutic regimens. Thus, in the future, more and more caregivers and patients will be less willing to rely solely upon antibiotic therapy for treatment and prevention of UTI.

Since each UTI leads to 2–3 days of symptomatic illness (and chronic UTI can cause long-lasting pain and discomfort) and to loss of several days of work and requires about 1 week for full recovery, patients are eager to prevent a recurrence. Thus, the motive for prevention exists.

Functional foods

It has long been the belief among women that certain foods can prevent the recurrence of infection. Examples of such are cranberry juice, antioxidants, garlic, and *Echinacea* [21, 29, 31, 61]. The mechanisms of action are believed to include stimulation of the immune response, changes in urinary pH, and prevention of growth and adhesion of pathogens. The most comprehensive scientific and clinical studies with respect to the urinary tract have been undertaken on cranberry supplements. There is clear evidence to show that components of cranberry, namely, tannins and fructose, can bind to type 1 fimbriated *Escherichia coli* and reduce their ability to adhere to uroepithelial cells, thereby lowering the risk for UTI [26, 40, 56, 61]. What remains to be resolved is the issue that the proanthocyanidins (which bind to the organisms) are metabolized before they reach the bladder, thereby implying that other factors in the cranberry are involved in reducing the risk of *E. coli* infection.

The cranberry effect is not explained by lowering of the urinary pH. Indeed, UTI can occur in patients with low urinary and vaginal pH [45]. It has recently been shown that cranberry intake produces a urine whose pH is not significantly lowered [20]. The latter study also showed that vitamin C, not cranberry juice, reduced the risk for infection with *Enterococcus faecalis*, one of the main causes of UTI [46]. Interestingly, it was found that increasing the water intake produced a urine that acted as an excellent substrate for adhesion of enterococci and *E. coli* to surfaces [20]. It has long been purported that increased water intake flushes bacteria out of the bladder. Indeed, mathematical modeling experiments undertaken in 1965, before it was appreciated that pathogens attach to bladder walls, have proven that when there is a small amount of residual urine, frequent voiding is not sufficient to flush out pathogens because of their rapid reproduction [7]. Thus, the basis for increased water intake should be reexamined. Rather, this treatment may dilute antibacterial factors in the urine, such as Tamm-Horsfall glycoprotein, and thereby increase the risk of infection. Further studies in this area are warranted.

Vaccines

The search for vaccines to prevent UTI began in earnest in the late 1970s following the identification of various *Escherichia coli* adhesins, including type 1 and P fimbriae. Initial studies using in vitro and animal models were promising, with antibodies against fimbriae and receptor analogues reducing bacterial binding [2, 44, 58, 64]. More recent efforts have utilized molecular approaches to create vaccines against *E. coli*, but, again, experiments have been confined to the test tube [30]. However, thus far these approaches have failed to work effectively in vivo, and much remains to be done to prove that they will have a place in clinical care. Two problems have to be overcome: the failure of a vaccine to affect a large number of uropathogenic species (of which there are about 20 that cause UTI [46]) and the development of a vaccine that can be effective once the infection cycle has begun (it does not seem very likely that a UTI vaccine would become part of the essential immunization strategies for every female in society).

There have been some developments with respect to a combination vaccine, primarily in European companies; for example, Urovac has been developed by Solco in Switzerland. A more comprehensive discussion of this vaccine approach is covered elsewhere in this special edition. This vaccine, containing killed whole cells of various uropathogens, was given intramuscularly (three times in 1 week and then at 12 months), and an apparent reduction in UTI was said to be due to increased levels of urinary IgA antibodies [54]. Oral and vaginal vaccines have also been tested, the latter using killed uropathogens [65]. However, results have been indifferent and the mechanisms of any action remain in question.

Natural peptides

Antimicrobial peptides were first identified in the cecropia moth [27], where they act as an alternate immune system specific for insects. Subsequently, antimicrobial peptides have been found in a number of higher organisms, including humans, where they may also play an important role in innate immunity, particularly at mucosal surfaces [6, 9], as well as participating in control of the natural microflora balance [5]. They seem to act against potential host pathogens [8].

Recently, two peptides, FALL-39 [1] and cecropin P1 [31] were found to have activity against uropathogens but not against *Lactobacillus* strains [57].

Exciting developments in antimicrobial peptide application are likely to occur quite far into the future (5–10 years). This could involve simply the creation of a new line of antimicrobials or the more complicated cloning of antimicrobial peptides into the urinary system (e.g., bladder, kidney) or into the normal flora that colonize these areas. With the combination of biomaterials and host cells being eventually used to make new organs, the incorporation of antimicrobial peptides into the cells in the mucosal lining could help reduce the risk of infection.

Probiotics

In the 1970s, Dr. Andrew Bruce, Chief of Urology at Queens University in Canada, observed that the flora of the urogenital tract was abnormal in patients with recurrent UTI as compared with healthy women [10]. This led to an investigation of the role of the flora, particularly lactobacilli (and, more recently, bifidobacteria [28]), in maintaining urogenital health and reducing the risk of infection. Some key publications then documented the factors that appeared critical for the successful competition between lactobacilli and uropathogens ascending from the rectum and perineum [13, 44, 55, 59]. These are summarized in Table 1. The more difficult question is: which factors are the most critical for successful clinical improvement? On the basis of our understanding to date, the critical elements appear to be the ability to adhere to cells and inhibit the attachment and growth of uropathogens [43].

The concept of probiotics is simple in some ways, but the critical issues are selection of the optimal strains, verification of the necessity for and mechanisms of certain factors in the interference with pathogens, and clinical proof that there is merit to the theory. Short-cutting these steps may result in the use of strains for clinical trials that are likely to fail [3]. A number of lactobacilli have been found to have probiotic potential. The actual definition of probiotics has evolved from sole referral to a "microbial feed supplement," implying oral intake and intestinal benefits [15], to a broadened definition as a biotherapeutic agent that comprises "a living microorganism(s) administered to promote the health of the host by treating or preventing infections owing to strains of pathogens" [14]. In the latter case the definitive reference to infections may also be too narrow, as certain probiotics have been shown to have other attributes such as lowering of cholesterol levels and reduction of the risk for cancer [16, 17]. With respect to the use of lactobacilli as probiotics for urogenital health and prevention of UTI, the definition of Elmer et al. [14] fits quite well.

Verification of the efficacy of probiotics in preventing UTI is in some ways difficult because current preventive methods do not use vaginal preparations. Thus, a trial would need to compare daily long-term, low-dose administration of oral antibiotics versus the weekly use of a vaginal suppository.

With respect to the level of *lactobacillus* colonization desired, the healthy adult has about 10^7–10^9 anaerobic/microaerophilic bacteria and 10^6–10^8 aerobic/facultative anaerobic bacteria per gram of discharge [23, 60]; this constitutes between 1 and 4 *Lactobacillus* species per healthy woman ([60]; Reid, unpublished data). Even with insertion of exogenous lactobacilli, which produce hydrogen peroxide, the total flora appears to reach an equilibrium that does not significantly exceed the counts found in healthy women. Although a number of factors are responsible for maintaining a flora that is capable of resisting uropathogens, particularly the properties of the lactobacilli that are colonizing, the total numbers required have not been defined. One study has shown a correlation between protection from UTI and the pres-

Table 1 Lactobacillus probiotic properties important in the restoration and maintenance of a healthy urogenital flora, which reduces the risk of recurrent UTI

Properties	Reference
Ability to adhere to uroepithelial and vaginal cells using lipoteichoic acid, proteins, and hydrophobic and hydrophilic surface structures, including fimbriae	Reid et al. [47] Reid et al. [50] McGroarty [32]
Exclusion of uropathogens from cells and materials	Reid et al. [47] Hawthorn and Reid [22]
Production of factors, including acids, hydrogen peroxide, and bacteriocins, that inhibit the growth of pathogens	Reid et al. [48] McGroarty and Reid [33, 34] Hillier et al. [24]
Production of biosurfactants that inhibit adhesion of uropathogens to surfaces	Velraeds et al. [66, 67]
Ability to resist spermicidal and other antimicrobial agents	McGroarty et al. [35]
Ability to coaggregate and form a normal, balanced flora	Reid et al. [48]
Capability to survive, grow, and multiply in a host with and without prebiotics	Bruce et al. [11] Reid et al. [51, 52]
Create an environment, even if it means enhancement of indigenous flora rather than domination by exogenous strains, that confers improved well-being in the host without causing major side effects	Reid et al. [52, 53]
Associated with easy use and good patient compliance and acceptability	Reid et al. [53]

ence of at least 10^4 effective lactobacilli/ml on a vaginal swab [52].

Another indirect attribute of lactobacillus probiotic therapy is that restoration of the normal flora, rather than destruction caused by antimicrobial agents, can reduce the risk for vaginal candidiasis, a common problem following antibiotic therapy for UTI. Few *Lactobacillus* strains have been shown to have specific anti-yeast properties. In about 60% of healthy women, *Candida albicans* is part of the normal flora; thus, coexistence per se is not an infectious problem. However, it is believed that domination by lactobacilli and coaggregation to form a balanced flora can prevent *Candida* from infecting the host. In studies of women highly prone to recurrent candidal vaginitis the restoration of *lactobacillus* numbers with prebiotics (nutrients to stimulate lactobacilli) and probiotics resulted in no case of candidiasis [52]. In a study using mice that were highly susceptible to candidiasis, the oral instillation of a probiotic cocktail containing strains of *L. acidophilus*, *L. reuteri*, *L. casei* GG, and *Bifidobacterium animalis* had profound effects in protecting against *C. albicans* [68]. Although further studies are warranted, there does appear to be a role for lactobacilli in the prevention of yeast vaginitis.

In summary, the next decade should see the introduction of a number of new methods to improve the management of complicated and uncomplicated UTI. Emphasis will be placed on the use of natural substances, including functional foods and probiotics, as well as on methods to stimulate the host's immune and antimicrobial defenses. These new approaches will represent the biggest advances made since the advent of antibiotics for treatment of UTI. Furthermore, they will help to deplete the enormous financial costs of patient care associated with UTI and reduce the burden of illness in this very large patient population.

Acknowledgement The ongoing collaboration with Dr. Andrew W. Bruce as well as his enthusiasm for urological research is much appreciated.

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