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Review Article

Recent advances in recurrent urinary tract infection from pathogenesis and biomarkers to prevention

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Abstract

Recurrent urinary tract infection (UTI) might be one of the most common problems in urological clinics. Recent research has revealed novel evidence about recurrent UTI and it should be considered a different disease from the first infection. The pathogenesis of recurrent UTI might include two mechanisms, bacterial factors and deficiencies in host defense. Bacterial survival in the urinary bladder after antibiotic treatment and progression to form intracellular bacterial communities might be the most important bacterial factors. In host defense deficiency, a defect in pathogen recognition and urothelial barrier function impairment play the most important roles. Immunodeficiency and urogenital tract anatomical abnormalities have been considered the essential risk factors for recurrent UTI. In healthy women, voiding dysfunction and behavioral factors also increase the risk of recurrent UTI. Sexual intercourse and estrogen deficiency in postmenopausal women might have the strongest association with recurrent UTI. Traditional lifestyle factors such as fluid intake and diet are not considered independent risk factors now. Serum and urine biomarkers to predict recurrent UTI from the first infection have also attracted a wide attention recently. Current clinical evidence suggests that serum macrophage colony-stimulating factor and urinary nerve growth factor have potential predictive value for recurrent UTI. Clinical trials have proven the efficacy of the oral immunoactive agent OM-89 for the prevention of UTI. Vaccines for recurrent UTI are recommended by the latest guidelines and are available on the market.

Keywords: *Biomarker, Recurrence, Urinary tract infection*

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Introduction

Urinary tract infections (UTIs) were first documented in Egypt in 1550 BC, and are still among the most common bacterial infections in the world [1]. The prevalence of UTI seems to be a J-shaped distribution, with higher frequency among very young children which gradually increases with age [2]. It is estimated to affect 150 million people each year worldwide, with an annual incidence of 12.6% in women and 3% in men [2,3]. Although most UTIs can be effectively treated by antibiotics, UTI recurrence is a common problem and sometimes may be very troublesome. Recurrent UTIs, which include relapses and reinfection, are traditionally defined as ≥2 uncomplicated UTIs in the past 6 months, or ≥3 infections within the preceding year [4]. UTI can recur easily in young immunocompetent women with anatomically normal urinary tracts. In one study, 27% of young college-age women with their first UTI experienced at least one recurrence within the following 6 months, and in another study, 53% of women over 55 years old reported UTI recurrence [5,6]. Although recurrent UTIs usually are not life-threatening, the high incidence significantly increases health-care costs and has a negative impact on patients' life quality [7,8].

The risk factors, pathogenesis, and prophylaxis of UTI have been well investigated since the early 20th century. In the recent years, research on UTI recurrence has also attracted a wide attention. Rather than treating recurrent UTI with antibiotics alone, if symptoms relapse, the current guidelines suggest aggressive management, such as avoidance of risk factors or medical prophylaxis [9,10]. Although most clinical and laboratory studies have focused on the first UTI, new evidence suggests a distinct pathogenesis in recurrent UTI. Thus, the aim of the current review is to update clinicians on the latest evidence on recurrent UTI, including the pathogenesis, risk factors, biomarkers and prevention, and present recent advances in research.

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Pathogenesis

There are two possible pathways in the pathogenesis of recurrent UTI; frequent repeat ascending infections and chronic/persistent infections in the bladder. Each pathway also might result from two possible mechanisms; bacterial factors and deficiencies in host defense.

Bacterial factors

UTIs might be caused by Gram-negative or Gram-positive bacteria, and the most common causative pathogen is *Escherichia coli* [11]. In studies using pulsed-field gel electrophoresis, 52%–77% of recurrent UTIs were caused by an *E. coli* strain which was identical to the primary infecting strain [12,13]. Since the 1960s, several specific strains of *E. coli* had been found to be significantly increased in recurrent UTIs [14,15]. Adherence of vaginal isolates in different *E. coli* strains was associated with recurrent UTI [16]. *E. coli* with DNA papG coding for a P-fimbriae was also significantly associated with recurrent UTIs [17]. In a prospective study, 148 women with a total of 558 recurrent UTIs were recruited, and the *E. coli* isolated from urine culture was routinely serologically classified for 131 O groups [18]. The ten most common O-serogroups accounted for 76% of recurrent UTIs, and nearly 50% of recurrent UTIs were caused by the three most common groups (O4, O6, and O75). In the genetic aspect, phylogenetic classification was also associated with recurrent UTIs [19]. Virulence factor genes KpsM II K2 and agn43a were independently associated with persistence or relapse of UTIs. Patients with frequent recurrent UTIs might just be infected by a special strain of *E. coli*.

Another possible mechanism for frequent recurrent UTIs is the survival of bacteria in the bladder through progression of intracellular bacterial communities (IBCs). Early studies showed that *E. coli* could replicate intracellularly, form a loose collection of bacteria, and then escape into the bladder lumen [20,21]. In 2004, Justice *et al*. used time-lapse fluorescence videomicroscopy and discovered that *E. coli* could form a complex of IBCs within the superficial umbrella cells of the bladders in mice [22]. IBCs in the bladder could form 4–16 h after bacterial infection, and then develop a persistent quiescent intracellular reservoir 2 weeks later [23]. These IBCs could be quiescent for extended periods despite antibacterial therapy, and then re-emerge to cause recurrent UTI. These IBCs are difficult to detect in urine specimens, but immunofluorescence evidence showed 18% of women with acute uncomplicated cystitis presented IBCs in the bladder [24]. In an animal study, higher numbers of IBCs were also predictive of persistent bacteriuria after acute cystitis [25]. In addition, a recent study revealed that bacteria in the IBCs had highly upregulated lacZ and yeaR genes, which contributed to utilizing a galactoside for metabolism and oxidative stress resistance, respectively [26]. Since studies propose that most recurrent UTIs are caused by *E. coli* strains which are identical to the primary infection, IBCs and a quiescent intracellular reservoir might play important roles in the pathogenesis of recurrent UTIs.

Deficiencies in host defense

It is well known that patients with immunodeficiency tend to have frequent, recurrent, and severe UTIs [27]. However, recurrent UTIs in some immunocompetent patients might also be caused by host defense deficiencies. The host defense in lower UTI consists of two main mechanisms; innate immune responses and urothelium barrier function [28]. The innate immune response in the bladder comprises different inflammatory cells and cells with recognition receptors, such as toll-like receptors (TLRs), which can recognize pathogens and induce a robust inflammatory immune response. TLRs are essential for the activation of immune responses and may be associated with recurrent UTI. In a cross-sectional study, genotyped polymorphisms were investigated in women with a history of recurrent UTIs [29]. Polymorphism of TLR2 G2258A, a variant associated with decreased lipopeptide-induced signaling, was associated with an increased risk of bacteriuria. TLR5 C1174T, which encodes a variant that abrogates flagellin-induced signaling, was associated with an increased risk of recurrent UTI in adult women [30]. On the contrary, TLR polymorphism including TLR4 A896G and TLR1 G1805T might have potential roles in protection from recurrent UTI [30]. Patients with specific TLR polymorphisms may have deficiency of pathogen recognition in the bladder, which then leads to higher prevalence of recurrent UTIs.

The urothelium in the urinary tract is the first-line barrier against pathogens and toxic substances. The urothelium can secrete pro-inflammatory cytokines and protective glycoprotein plaques such as uroplakin and Tamm–Horsfall protein (THP) on the bladder surface as anatomical barriers [28,31]. The urothelium's antibacterial adherence mechanism is fundamental in host defense, and it had been proven to be less potent in patients with recurrent UTI [32]. Uroplakins are the essential structural components of the urothelium and a deficiency compromises the urothelial permeability barrier [31]. Uroplakins also serve as the urothelium receptor for Type 1-fimbriated *E. coli* and play a role in bacterial adhesion [31,33]. Decreased or entirely absent uroplakin expression in the urothelium has been found in patients with recurrent UTI [34]. On the other hand, animal studies showed that urinary THP has the potential to prevent bacteria from interacting or aggregating in the urothelium [35,36]. However, clinical evidence is still lacking. The levels of urinary THP in patients with recurrent UTI were not significantly different from healthy controls in previous studies [37-39]. In our recent immunofluorescence study, we found increased mast cell and apoptotic activity, and decreased E-cadherin expression in the urothelium of patients with recurrent UTI [40]. Current evidence supports the idea that urothelial dysfunction impacts the pathogenesis of recurrent UTI. Further clinical and laboratory studies are necessary to elucidate the mechanism.

Risk factors

Patients with recurrent UTI should undergo a comprehensive investigation to identify the possible risk factors [9,10,41]. The evaluations should include a history review and a physical examination to rule out urogenital anatomical anomalies, immunodeficiency, voiding dysfunction, and health behavioral problems [9,10,41]. Urinary tract abnormalities, including obstruction and calculi, are well-known causative factors in UTI [10]. A high

residual urinary volume (RU) was significantly associated with recurrent UTI in male patients, even in the patients without lower urinary tract symptoms [42,43]. An RU of 180 mL or greater had the best specificity and sensitivity in predicting bacteriuria in asymptomatic adult men [42]. In women, the role of large RU in recurrent UTI is controversial. Postmenopausal women with recurrent UTI had a significantly increased RU and reduced urine flow compared with age-matched controls [44,45]. A urodynamic study also found increased abdominal strength in voiding which constitutes a risk factor for recurrent UTI in women [46]. The ideal cutoff point for the maximum abdominal pressure in the voiding phase was 28 cmH_2O. However, in young healthy nonpregnant women, the RU was not different between patients with recurrent UTI and controls [47]. Most current guidelines suggest that increased RU is an independent risk factor for recurrent UTI, and RU should be measured before management [9,10,41].

Behavioral risk factors should be considered first in young women who have recurrent UTI. Sexual intercourse is the strongest behavioral risk factor in recurrent UTI [48]. The risk is even increased in any lifetime sexual activity and any sexual activity during the past year [48]. The odds ratio of recurrent UTI was high as 10.3 in young women with intercourse >9 times in the past month. In addition, any new sex partner and spermicide use in the past year also increased the risk. Voiding habits also might be a risk factor. Histories of hesitating to excuse oneself to urinate and voluntary deferral of micturition for 1 h were found to be associated with recurrent UTI in women [49,50]. The role of psychological factors in recurrent UTI has also attracted attention in the past years. Hunt and Waller used several different personality questionnaires and suggested that the neurotic personality type might be related to recurrent UTI [51]. However, because of the relatively small amount of further research, it is difficult to draw any clear conclusions concerning the role of psychological factors in recurrent UTI. The role of dietary habits in recurrent UTI is also not clear. Only drinking soft drinks was found to be moderately associated with recurrent UTI, and further evidence is still lacking [50]. Increasing fluid consumption is often recommended for patients with UTI; however, clinical studies showed contradictory results on the influence of fluid intake on the risk of recurrent UTI [52]. For postmenopausal women, the most significant risk factor is estrogen deficiency [10,41]. Lack of estrogen could cause thinning of the vaginal epithelium and decreased amounts of glycogen, predisposing women to introital colonization with *E. coli* [53]. The main vaginal flora usually changes from Lactobacilli to uropathogen such as *E. coli* after estrogen loss at menopause, leading to UTI recurrence [54]. The possible risk factors for recurrent UTI are listed in Table 1.

Table 1: Possible risk factors for recurrent urinary tract infection

Immunodeficiency
Diabetes mellitus
Organ transplants
Chronic renal insufficiency
Urinary tract abnormality
Urinary calculi
Urinary tract obstruction
Vesicoureteral reflux
Voiding dysfunction
Increased residual urinary volume
Reduced urine flow
Increased abdominal strength in voiding
Behavioral factors
Sexual intercourse
New sex partner
Spermicide use
Voluntary deferral of micturition
Others
Drinking soft drinks
Estrogen deficiency

Biomarkers

Although many risk factors have been reported in research, clinical patients with recurrent UTI often do not have any identifiable risk factors. Moreover, evidence about some behavioral risk factors is controversial due to unreliable questionnaire estimations [55]. Objective urine or serum biomarkers for predicting recurrence in patients with a first UTI is important and clinically useful. In the past decade, many possible biomarkers have been investigated in animal and human studies.

Serum biomarkers for recurrent urinary tract infection

Serum antibodies were the first possible biomarkers found in recurrent UTI. Women with recurrent UTI who had complete antibiotic therapy were recruited in a 2001 prospective study [56]. The levels of serum antibody immunoglobulin (Ig) G, IgM, and IgA in the study patients were significantly higher than those in healthy controls. Hannan *et al*. investigated serum cytokines in mice with acute bacterial cystitis. The levels of serum hormone granulocyte colony-stimulating factor (CSF) and interleukin-5 (IL-5) at onset were significantly higher in the mice with redevelopment of cystitis than those without reinfection [57]. The research group further investigated serum cytokines in women with uncomplicated acute cystitis and tried to identify candidate serum biomarkers from 48 different cytokines [58]. Macrophage CSF was found to be significantly elevated in patients who subsequently developed recurrent UTI. An elevated prostate-specific antigen (PSA) level is well known in the diagnosis of prostate cancer, but it also might have a potential protective role in recurrent UTI [59]. In a retrospective study, male patients with a PSAlevel higher than 4 ng/mL at UTI onset were less likely to have recurrent UTI than those with PSA <4 ng/mL (13% vs. 70%, respectively, $P < 0.01$) [59]. A bacterial challenge study revealed a significantly decreased frequency of *E. coli* invasion in PSA-positive prostate epithelium, which suggests a protective role for PSA in recurrent UTI [60]. In addition, the mean serum levels of Vitamin D among premenopausal women with recurrent UTI were significantly lower than those of controls (9.8 ± 4 ng/mL vs. 23 ± 6 ng/mL; respectively, $P < 0.001$) [61]. Vitamin D is important for innate immunity,

mainly by increasing neutrophilic phagocytic function and motility [61]. Deficiency of serum Vitamin D also might be a biomarker for recurrent UTI.

Urinary biomarkers for recurrent urinary tract infection

Urinary biomarkers for lower urinary tract diseases have been widely discussed for years. Nerve growth factor (NGF) is a small protein that induces survival and differentiation of neurons [62]. Urinary NGF levels were significantly increased in women with overactive bladder and were considered a possible biomarker [62]. In our recent study, we prospectively enrolled women with uncomplicated UTIs and measured urinary NGF levels at baseline and follow-up [63]. At 12 weeks, the serial urinary NGF levels in women with UTI recurrence were significantly lower than those in women without recurrence. Neutrophil gelatinase-associated lipocalin (NGAL) is an iron-transporting protein and has been regarded as a promising biomarker in acute kidney injury [64]. In young patients with a first UTI recurrence, the urinary NGAL levels were significantly decreased [65]. This might result from reduced TLR4 expression and reflect-defective innate immunity [65]. In a cross-sectional survey of different urinary cytokines in asymptomatic women with a history of recurrent UTI, urinary IL-8 was significantly higher in patients with bacteriuria, and was associated with higher serum neutrophil levels [29]. Urinary IL-8 levels might have a predictive value in recurrent UTI in women. The above-mentioned serum and urinary biomarkers not only have potential predictive value, but also might involve the systemic or regional pathomechanism in patients with recurrent UTI.

Further prospective clinical trials are necessary to confirm the predictive efficacy. In summary, the possible biomarkers for recurrent UTI are listed in Table 2.

Prevention of recurrent urinary tract infection

Prevention of recurrent UTI has attracted much interest and was investigated by researchers. The European Association of Urology guideline suggests that the prevention of recurrent UTI should include the following in this order: (1) behavioral modifications and avoidance of risk factors, (2) nonantimicrobial measures, and (3) antimicrobial prophylaxis [10]. Due to the limited context, the current review mainly focuses on nonantimicrobial treatment of recurrent UTI.

Table 2: Possible biomarkers for recurrent urinary tract infection

Serum biomarker	Urine biomarker
Granulocyte colony-stimulating factor↑	NGF↓
Macrophage colony-stimulating factor↑	NGAL↓
IL-5↑	IL-8↑
IgG, IgM, and IgA↑	
PSA↓	
Vitamin D↓	

↑: Elevated in patients with recurrent UTI, ↓: Decreased in patients with recurrent UTI, UTI: Urinary tract infection, Ig: Immunoglobulin, IL: Interleukin, PSA: Prostate-specific antigen, NGF: Nerve growth factor, NGAL: Neutrophil gelatinase-associated lipocalin

Prophylaxis with cranberry juice

Drinking cranberry juice might be the most well-known means of prevention of recurrent UTI. It has been shown to inhibit the adherence of P-fimbriated *E. coli* to urothelium, and could decrease the virulence in bacterial cystitis [66]. Early randomized controlled trials showed that cranberry juice decreased the number of symptomatic relapses over a 12-month period in women with recurrent UTIs [67]. However, further studies suggest that cranberry juice is not as effective as previously reported. The large number of withdrawals from the trials indicates that cranberry juice may not be acceptable over long periods of time. The latest Cochrane database systematic review in 2012 revealed that cranberry products, including juice, tablets, and capsules, did not significantly reduce the relapse rate for women with recurrent UTI [68]. A large double-blinded, randomized, placebo-controlled trial in 2016 again confirmed that the administration of cranberry capsules versus placebo resulted in no significant difference in UTIs over 1 year [69]. Currently, most guidelines suggest that cranberry products cannot be recommended for the prevention of UTI recurrence [10,41].

Prophylaxis with probiotics

Since the urogenital flora of healthy premenopausal women is dominated by Lactobacilli, it has been suggested that restoration of the unhealthy urogenital flora from uropathogens with Lactobacilli may protect against UTI [70]. A 1988 study revealed that intravaginal administration of Lactobacilli *(Lactobacillus casei* GR-1) twice weekly could significantly extend infection-free periods compared with pretreatment in women with recurrent UTI [71]. A recent randomized, placebo-controlled trial, on 100 young women with a history of recurrent UTI, used intravaginal *Lactobacillus crispatus* daily for 5 days and then once weekly for 10 weeks [72]. The UTI recurrence rate was significantly lower in the study group than in the control group. Various Lactobacilli administered orally have also been assessed in clinical study, but the efficacy in the prevention of UTI recurrence is controversial [73,74]. Although some studies showed promising results, pooled data from meta-analyses of available randomized controlled trials (RCTs) show no convincing benefit of *Lactobacillus* products as prophylaxis for recurrent UTI [75]. Current guidelines recommend that *Lactobacillus* should not be used outside of investigational trials [10,41].

Further research must be conducted before oral or intravaginal probiotics can be recommended as a regular prophylaxis.

Hormonal replacement prophylaxis

Estrogen loss in postmenopausal women leads to decreasing glycogen, thinning of the epithelium, and alkalization of the vagina [54]. All these changes could change vaginal flora and predispose to UTI [54]. Estrogen replacement with either topically applied vaginal cream or oral medications for recurrent UTI in women has been used since the 1980s and has shown favorable results [76,77]. In two RCTs in the 1990s, intravaginal estrogen therapy significantly decreased the incidence of UTI and decreased the vaginal pH in the study group

without severe unexpected adverse events [78,79]. The rate of *Enterobacter* colonization in the vagina was also decreased in the study group but was not changed in the control group. A recent meta-analysis of RCTs also proved the efficacy of vaginal estrogens for preventing UTI recurrence [80,81]. In contrast, these meta-analyses indicated that oral estrogens could not decrease the rate of UTI recurrence and may result in local and systemic side effects [80,81]. Current guidelines suggest that intravaginal estrogen therapy, but not oral estrogen, shows a trend toward preventing UTI recurrence [10,41]. Side effects of intravaginal estrogen might be common but usually not severe. Vaginal irritation is the main adverse effect and might occur in up to 20% of women [81].

Immunoactive agent prophylaxis

One of the possible pathogeneses in recurrent UTI is adaptive immune response dysfunction, especially in defects of pathogen recognition [28]. Thus, using a vaccine to strengthen active acquired immunity against uropathogens might be a reasonable prevention of UTI recurrence. Systemic vaccination has been used in treating women with recurrent UTI for more than a century [82]. However, due to the heterogeneity of uropathogens, therapeutic vaccination against UTI has largely been seen as ineffective in the past years [83]. Recently, there were encouraging results in some animal studies in the development of an *E. coli* vaccine [84]. Since 1994, clinical trials have been conducted on intravaginal vaccines in women with recurrent UTI [85,86]. Women using a vaginal vaccine remained free of infections for a significantly longer period than those receiving placebo. The total vaginal and urinary IgG and IgA were also significantly increased in the study groups. Nowadays, both oral and parenteral vaccines have also been shown effective in recurrent UTI, and are available on the market [87,88]. A recent meta-analysis enrolled four clinical trials of an oral vaccine (OM-89), and showed that it significantly decreased the rate of UTI recurrence with a good safety profile [81]. Headache and gastrointestinal complaints were reported most often (13%, comparable with that in the placebo group), and only one allergic reaction leading to withdrawal was reported. Now, the latest guideline recommends OM-89 for immunoprophylaxis in female patients with recurrent uncomplicated UTI [10].

Antimicrobial prophylaxis

Antimicrobial prophylaxis might be more effective, but it should be used after nonantimicrobial agents because of possible adverse effects [10]. Antimicrobial prophylaxis for preventing UTI recurrence can be given continuously for long periods of time (3–6 months), or as a single postcoital dose. A Cochrane review found that postcoital prophylaxis was just as effective as low-dose continuous antibiotic prophylaxis in the prevention of a recurrent UTI [89]. Continuous prophylaxis for 6 or 12 months significantly reduced the rate of UTIs during the prophylaxis period, with no difference between the two treatment groups after cessation of prophylaxis [90]. Postcoital prophylaxis involves taking a dose of antibiotics within 2 h of intercourse [41]. It requires smaller amounts of antibiotics than continuous prophylaxis and is associated with fewer side effects [91]. The antimicrobial prophylaxis regimens and recommended doses from the current guidelines are listed in Table 3 [10,41,92].

Table 3: Antimicrobial prophylaxis regimens and recommend doses from the current guidelines

Antimicrobial agents	Continuous prophylaxis (daily dose) (mg)	Postcoital prophylaxis (one-time dose) (mg)
Cephalexin	125-250	250
Ciprofloxacin	125	125
Nitrofurantoin	50-100	50-100
Trimethoprim/sulfamethoxazole	40/200	40/200-80/400
Norfloxacin	200	200

Conclusion

Recurrent UTI might be one of the most common problems in urology clinics, but may not attract much attention from urologists in Taiwan. Treating UTI might not be difficult, but preventing UTI recurrence sometimes might be very troublesome for both patients and doctors. Recent research has revealed many novel concepts in recurrent UTI, including the pathogenesis, risk factors, biomarkers, and prevention. Nowadays, recurrent UTI may be considered a distinct disease, and patients with recurrent UTI should be managed aggressively. Further basic science studies are needed to elucidate details in the pathogenesis, and RCTs are also necessary to clarify the efficacy of the current management.

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Conflicts of interest

There are no conflicts of interest.

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