Review Article

Tzu Chi Medical Journal 2021; 33 (1): 13–21

Recurrent urinary tract infection in women and overactive bladder – Is there a relationship?

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Submission : 05-Mar-2020
Revision : 02-Apr-2020
Acceptance : 08-Apr-2020
Web Publication : 29-Jun-2020

Abstract

Overactive bladder (OAB) in women has similar symptomatology with other common urologic diseases such as recurrent urinary tract infection (UTI). Recent evidence showed that chronic low-grade bacterial bladder colonization might exacerbate OAB symptoms and could be the etiology of recurrent UTI. The high prevalence of lower urinary tract dysfunction is associated with OAB. Women with urgency urinary incontinence refractory to antimuscarinic therapy had more bacteria and a more diverse urinary microbiome. The bacterial reside in the superficial urothelial cells to form intracellular bacterial community and outbreak when the host innate immunity is low. Women with recurrent UTI are found to have highly prevalent voiding dysfunction and detrusor overactivity. These functional abnormalities will further damage the urothelial barrier integrity and create vulnerable to uropathogen invasion. The defective urinary microbiota is less common in women with recurrent UTI, suggesting that the normal flora in the urine might inhibit uropathogen growth and invasion. The defective urothelial barrier function, deficient basal proliferation, and deficient maturation might be owing to chronic suburothelial inflammation, resulting in activation of sensory nerves (causing OAB) and failure elimination of intracellular bacterial communities (causing recurrent UTI). Precision diagnosis and multidisciplinary treatment of the underlying pathophysiology of OAB and recurrent UTI is necessary.

Keywords: *Lower urinary tract dysfunction, Microbiota, Overactive bladder, Pathophysiology, Urinary tract infection*

Introduction

Overactive bladder (OAB) is a symptom syndrome characterized by urgency with or without urgency urinary incontinence (UUI); urgency is the core symptom in the OAB symptom syndrome [1]. Urgency is a subjective storage symptom which might be caused by bladder hypersensitivity, low compliance, or detrusor overactivity (DO) [2]. The key symptom of OAB is urgency, and is usually associated with frequency and nocturia, with or without urge incontinence [1]. In the diagnosis of OAB, pathological conditions such as bladder outlet obstruction (BOO), diabetes mellitus, neurogenic voiding dysfunction, and urinary tract infection (UTI) should be ruled out, and confirmed profound impairment of quality of life by OAB. Patient with DO is more likely to have abnormal sensation, lower volume for strong desire and urgency, and more urgency urinary incontinence (UUI) episodes [3]. Sensory urgency might share the common pathophysiology with DO. Sensory urgency may be an earlier form of DO [4,5].

Etiology of refractory overactive bladder

Refractory OAB might have more severe symptoms or have underlying pathophysiology not resolved after initial medication. The possible pathophysiology of refractory OAB includes occult neurogenic bladder, such as minor stroke, early dementia, Parkinsonism, and brain lesion; bladder outlet obstruction (BOO) such as bladder neck dysfunction (BND), small prostate, urethral stricture; and urethral incompetence-related OAB; aging process and urothelial dysfunction; chronic bladder inflammation; central sensitization; and autonomic dysregulation [6].

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Access this article online

Quick Response Code:

Website: www.tcmjmed.com

DOI: 10.4103/tcmj.tcmj_38_20

How to cite this article: Ke QS, Lee CL, Kuo HC. Recurrent urinary tract infection in women and overactive bladder – Is there a relationship? Tzu Chi Med J 2021; 33(1): 13-21.

Because OAB in women has similar symptomatology with other common urologic diseases such as recurrent UTI, the majority of women with OAB are often diagnosed as UTIs and empirically treated without performing a urine culture as a routine care. In fact, when urine cultures are obtained, less than half of the women have a positive urine culture, suggesting that empiric treatment of UTIs without cultures commonly lead to a misdiagnosis of UTI [7]. However, more and more evidence showing chronic low-grade bacterial bladder colonization might exacerbate OAB symptoms and may explain why the current OAB treatment strategies are not always successful. For OAB refractory to conventional medication such as antimuscarinics and beta-3 adrenoceptor agonist, mirabegron, using newer technologies such as 16S RNA sequencing and extended culture techniques, might find organisms that might be responsible for persistent OAB symptoms [8].

Figure 1 shows the possible pathophysiology for the relationship between OAB and recurrent UTI.

Bladder inflammation in overactive bladder

Bladder inflammation is commonly found in patients with OAB, interstitial cystitis (IC), systemic diseases such as diabetes mellitus, end-stage renal disease, or congestive heart failure, and lower urinary tract disorders (LUTD), resulting in bladder storage symptoms such as urgency and frequency [6]. In previous studies of IC, chronic inflammation leads to increase of urothelial cell apoptosis, lower adhesive protein E-cadherin, and lower tight junction protein zonula occludens-1 expression [9]. The chronic inflammation in the IC bladders also inhibits the basal cell proliferation, causing defective apical cell maturation and impaired barrier function [10]. Further study of apoptotic markers such as Bad, Bax, and caspase 3 all increased in the IC bladder tissues, and the inflammatory signals such as p38 mitogen-activated protein kinase and tumor necrosis factor alpha (TNF-α) were upregulated [11].

Chronic inflammation is also found in a large proportion of patients with OAB [12]. A multiplexed analysis of plasma samples among healthy volunteers, OAB, IC, and UTI revealed interleukin 4, TNF-α, macrophage inflammatory protein-1β, serum amyloid A, and Tie2 can reliably differentiate OAB relative to controls and can be used to distinguish OAB from the other conditions [13]. Chronic neural plasticity due to chronic inflammation and activation of sensory receptors may change the sensory afferent activity via influencing antinociceptive activity and result in bladder oversensitivity or provoking DO. The urinary nerve growth factor (NGF) levels in patients with OAB, IC, or other bladder oversensitivity have been found to elevate, suggesting that these different LUTDs might share common pathways in the increase of bladder sensation [14-16].

Bladder and urinary NGF, cytokines, and serum C-reactive protein have been found to increase in patients with OAB, as well as in patients with IC [16-18]. Chronic inflammation of the bladder wall is involved in both OAB and UTI. However, tight junction protein zonula occludens 1 and adhesive protein E-cadherin are downregulated in IC, but not in OAB, compared with the controls, suggesting that urothelial barrier dysfunction is not involved in the pathophysiology of OAB [19]. In a study of urothelial dysfunction in women, increased urothelial cell apoptosis, defective E-Cadherin, and increased chronic inflammation are noted in women with recurrent UTI compared to controls, suggesting that defective urothelial barrier function could be a cause of recurrent UTI [20]. Elevated levels of urinary inflammatory biomarkers including monocyte chemotactic protein-1, macrophage inflammatory protein, and epidermal growth factor, which suggest that inflammation is involved in pathogenesis of OAB [21].

In a longitudinal study of female OAB, Chuang *et al*. found that the OAB symptoms changed with time [22]. Among the patients with urodynamic DO at baseline, 25.7% turned to

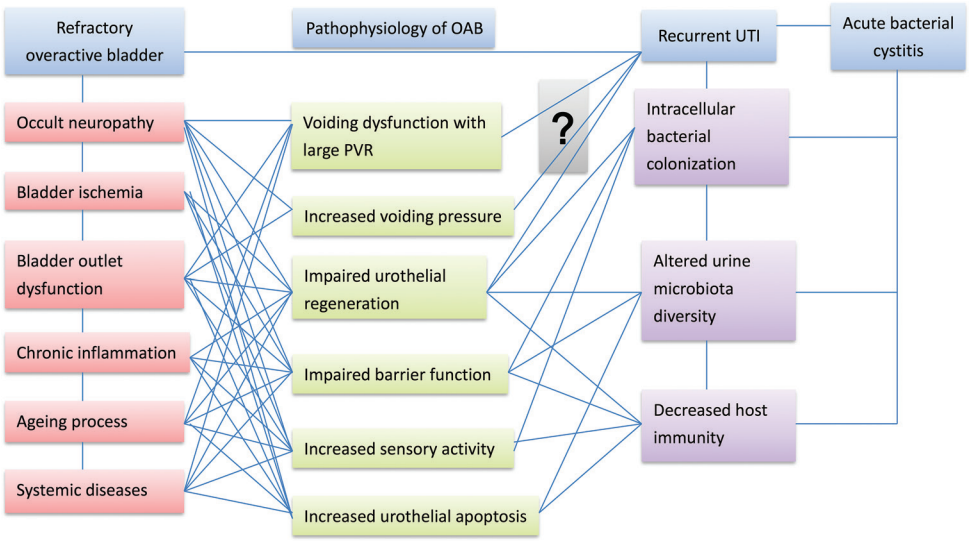

Figure 1: Possible pathophysiology for the relationship between overactive bladder and recurrent urinary tract infection. The lines between lower urinary tract condition and pathophysiology have possible relationship but some of them have not been proven

normal, 17.1% became increased bladder sensation, and only 57.1% of patients remained to have DO after 5 years. This study indicated that OAB is a reversible symptom syndrome, possibly because of its inflammatory nature [23]. When local or systemic condition resolved after treatment with time, the bladder condition will also change. Serum C-reactive protein levels were significantly higher in patients with OAB ($P = 0.012$) or IC ($P = 0.049$) than that in controls. No statistically significant difference in C-reactive protein level was noted between patients with OAB and IC ($P = 0.43$). These data support the association between chronic inflammation of the urinary bladder in patients with OAB and IC [18].

Overactive bladder and urine microbiota in women

OAB is a syndrome with different etiologies including LUTDs and systemic diseases. In women with acute bacterial cystitis, OAB symptoms are predominant with or without micturition pain. Therefore, in the clinical diagnosis of OAB, we should exclude many identifiable diseases including UTI. Recent clinical studies found that urinary microbiota have association with the treatment outcome of UUI. Thomas-White found women with UUI had more bacteria and a more diverse urinary microbiome. The responders to solifenacin treatment are more likely to have fewer bacteria and a less diverse community at baseline than nonresponders. The nonresponders had a more diverse bacterial community including bacteria not typically found in responders [24]. Using 16S ribosomal RNA gene sequencing to confirmed urinary bacterial DNA in 182 women with UUI. Among them, 51.1% of the participants' urine samples were sequence positive. The sequence-positive participants were younger, had a higher body mass index, had a higher mean baseline daily UUI episode, responded better to antimuscarinic treatment, and were less likely to experience UTI [25].

Current evidence suggests that chronic low-grade pathogenic bacterial bladder colonization may exist in urine, which is usually not cultured but can be identified using new technologies. The microorganisms in urine may be important in the etiology of refractory OAB or may exacerbate OAB symptoms [8]. In addition, the existence of a core urinary microbiome for the human urinary tract has been considered to have a potential relationship with LUTDs [26]. Decrease of urine microbiome diversity has been found to correlate with UUI symptom severity [8]. Certain *Lactobacillus* species may play a role in maintaining a healthy bladder milieu, and higher bacterial diversity in the absence of *Lactobacillus* dominance was associated with UUI and resistance to anticholinergic treatment [27].

In clinical practice, patients with UTI often have OAB and UUI symptoms. The OAB symptoms can potentially be influenced by UTI-associated bacteria, or the microbiome in the urine [28]. Extracellular ATP released by the bacteria may increase bladder sensation and facilitate detrusor contractility, resulting in OAB symptoms. Organisms such as *Escherichia coli* and *Gardnerella vaginalis* induce calcium influx and detrusor contraction, whereas *Lactobacillus crispatus* and *Lactobacillus gasseri* do not [28]. In an analysis of 39 women who had refractory UUI and coexistent recurrent UTI, a diverse urinary microbiota was identified in nine severely affected women, using bacterial 16S RNA profiling, suggesting that persistent bladder colonization might exist and exacerbate the bladder OAB condition [29]. Based on these evidence, patients with OAB refractory to antimuscarinic therapy might have subclinical UTI, in which the pathogen might not be cultured by the routine methods. The imbalance of microbiota in the urine might play an important role in refractory OAB.

Microbiota in urine and recurrent urinary tract infection

The urine microbial ecology is different between controls and OAB patients. The bacterial growth colony count and presence of infected urothelial cells were higher in OAB patients. A correlation between symptoms and pyuria and epithelial shedding, and there was a correlated increased immune response among OAB patients. However, routine urine cultures were unable to distinguish OAB from controls, but uroepithelial cell sediment culture differs significantly [30]. Intracellular bacteria were visualized in shed urothelial cells from about 80% of OAB patients with pyuria. The basal release of ATP was significantly greater in the bladder urothelium of patients with OAB and pyuria, compared to non-OAB patients or patients with OAB but not pyuria [28]. Altered purinergic receptor P2 expression was evident in the urothelium of patients with OAB and pyuria. These results suggest the increased ATP release from the urothelium of patients with pyuria and OAB, and the ATP released by bacteria extracellularly or intracellularly might stimulate signaling pathways leading to OAB or exacerbating UUI [28,30].

E. coli could replicate intracellularly in the bladder urothelium to form a loose collection of bacteria and then escape into the bladder lumen [31,32]. *E. coli* usually form a complex of intracellular bacterial community (IBC) within the superficial umbrella cells of the bladders in mice [33] and developed a persistent quiescent intracellular reservoir 2 weeks later [34]. Immunofluorescence evidence showed that 18% of women with acute uncomplicated cystitis presented IBCs in the bladder [35]. In patients with OAB, the IBCs can be identified in the urothelial shed cells when the OAB patients had a coexistent pyuria [30].

UTI has been considered as an interaction between the pathogens and the host. The actions of bacterial attachment and invasion activate a cascade of innate host defenses leading to the death and exfoliation of bladder urothelial cells and production of inflammatory mediators [36]. Uropathogenic *E. coli* (UPEC) avoid clearance by invading and replicating within the epithelial cells. Thus, these bacteria serve as a reservoir for recurrent UTI. The persistence of uropathogenic escherichia coli (UPEC) in bladder tissue may subsequently cause recurrent acute cystitis based on a complex series of dynamic host–pathogen interactions [36,37].

Acute bacterial cystitis damages the urothelium, causing tissue edema and accumulation of large numbers of inflammatory cells in the urothelium and suburothelium. These

inflammatory cells could start a cascade of tissue inflammation involving several sensory proteins and cytokines accompanied by pain and OAB symptoms to bladder distension [20]. Local inflammatory process might be induced through the afferent and efferent nerves in the suburothelial interstitial cellular network, which integrate the transmission of signals from the urothelium to the detrusor muscles in the bladder wall [38-40].

Recurrent UTIs, which are including relapses and reinfection, are traditionally defined as ≥2 uncomplicated UTI in the past 6 months, or ≥3 infections within the preceding 1 year [41]. It has been estimated that 27% of young college women with their first UTI experienced at least one recurrence within the following 6 months, and 53% of women above the age 55 years had UTI recurrence [42,43]. Recurrent UTIs usually are not life-threatening, however, the high incidence of UTI would significantly increase health-care costs and had a negative impact on patients' life quality [44,45]. Rather than treating recurrent UTI with antibiotics only if symptoms relapse, current guidelines suggest aggressive management such as avoidance of risk factors or medical prophylaxis [46,47]. Most clinical and laboratory studies focused on the first UTI; new evidence also suggest distinct pathogenesis in recurrent UTI. Searching for the underlying defective microbial imbalance or detecting diverse pathogens is essential to eradicate UTI and provide a better therapeutic outcome for women with recurrent UTI.

Impairment of regenerative ability underlies the pathophysiology of recurrent urinary tract infection

Urinary bladder is an organ for storage and periodic emptying of urine with time. The bladder urothelium is essentially quiescent with a low turnover rate of the human bladder urothelium [48]. When there is insult to the urinary bladder such as bacterial infection, toxin, or trauma, the urothelium will regenerate readily upon the insult [49-51]. The processes of the bladder urothelial regeneration are initiated from the proliferation of progenitor cells in the basal or intermediate layers, which differentiate to the mature apical umbrella cells. In normal condition, the bladder urothelium will regenerate within 24 h upon insult and complete the urothelial repair within 72 h [52]. Altered urothelial differentiation might result in increased permeability and decreased protective function of the bladder urothelium [53].

The role of bladder urothelium is a barrier to prevent injurious stimuli, toxins, or microorganism from invasion into the stroma and upper urinary tract [54]. Chronic inflammation in the suburothelium may inhibit normal urothelial basal cell proliferation and affect apical urothelium function. The apoptotic signaling molecules, including Bax cleaved caspase-3 and Bad, were noted to increase in the recurrent UTI bladders [20]. Decrease of E-cadherin expression is also associated with recurrent bacterial cystitis in women [19,20,55].

The epithelium integrity in the urinary bladder is regulated by the proliferation and differentiation of the stem cells and progenitor cells in the basal layer. Although the urothelial cells in the bladder mucosa undergo little or no cell division in normal condition, any urothelial injury with chemicals, toxins, or bacterial infection induces rapid proliferation [51]. The basal cells of the urothelium include stem cells which can be marked by the expression of the secreted protein sonic hedgehog (*Shh)* are considered as the progenitor cells for this urothelial repair on injury [51]. The *Shh* expression in the basal cells increases on injury to the urothelium, and then stromal expression of *Wnt* protein signals increases and stimulates urothelial and stromal cell proliferation. After infection by pathogenic *E. coli*, the proliferative marker *Ki67,* increases within 24 h, and basal urothelial cell proliferation increase to increase the urothelial cell layers, this process also increases exfoliation of the infected apical urothelial cells, in which the IBCs are present.

Chronic inflammation in the bladder might affect the proliferation ability of these basal cell function and altered proliferation rate and result in defective urothelial apical cells and barrier function [56]. Similarly, in the bladders of recurrent bacterial cystitis, the basal cell proliferative function might also be affected. Decreased proliferation of basal cells result in continuing presence of IBC, and recurrent cystitis may ensue after cessation of antibiotics treatment [34]. Improvement of basal cell proliferation in diseased bladders is crucial to restore normal bladder mucosal barrier. In this regard, factors that can alter the cellular mitochondrial memory can result in decreased regenerative response and increased permeability and changes in the cells within the bladder wall.

Urothelial dysfunction is frequently encountered in patients with recurrent UTI and other bladder diseases such as OAB and BOO. Increased urothelial inflammation and urothelial cell apoptosis seem to share common pathophysiology of various LUTDs that cause similar bladder symptoms [57]. Putting these findings together, the urothelial dysfunction and underlying chronic inflammation might be the downstream pathogenesis of increased bladder sensation, bladder pain, and recurrent UTI in the LUTDs due to bladder, bladder outlet, or systemic diseases. Elimination of chronic inflammation might improve urothelial regeneration and differentiation and rebuilt the defense mechanism of the diseased bladder.

Possible etiology of recurrent urinary tract infection in women

Concerning the risk factors of recurrent UTI, patients with immunodeficiency tend to have frequent recurrent and severe UTI [58]. In addition to the virulence of pathogen and diversity of microbiota of the urine and vagina, there are two major mechanisms that may impact the occurrence of UTI or recurrent UTI. The innate immune responses and the urothelium barrier function are the utmost causing factors for recurrent UTI [59]. Toll-like receptors (TLR) could recognize pathogens and induce a robust inflammatory immune response. Patients with specific TLR polymorphism TLR4_A896G, may have deficiency of pathogen recognition in the bladder, which was found to be associated with protection from recurrent UTI, but not pyelonephritis, leading to a higher recurrent UTI prevalence [60].

Bladder urothelium can secrete pro-inflammatory cytokines and protective glycoprotein plaques such as uroplakin and Tamm–Horsfall protein at bladder surface and act as anatomical barriers [59,61]. Tissue-resident mast cells not only orchestrate the early innate immunity during bladder infection, but they also subsequently play a tissue-specific immunosuppressive role, which might have association with the recurrent UTI [62]. Previous studies have revealed that patients with recurrent UTI have elevated urinary NGF level, suggesting that chronic inflammation is present in the bladder of these patients after resolution of UTI [63]. It is possible that the IBC might remain in the urothelial cells after acute bacterial cystitis and cause persistent chronic inflammation of the bladder wall. Intravesical antibiotic injections to treat recurrent UTI had been tried and the results seemed promising [64].

In the analysis of urinary NGF in women with recurrent UTI, Chuang *et al*. found that serial urinary NGF levels in women with recurrent UTI were significantly lower than those who did not have UTI recurrence during the follow-up period, suggesting that the lower urinary NGF level might reflect the impaired innate immunity and associate with UTI recurrence [65]. The binding of UPEC to the urothelial cell surface is the initial step to establish UTI, preventing the bacteria from being eliminated by periodic micturition. The binding of UPEC to the urothelial cell surface is mediated by the FimH adhesin which is located at the tip of the bacterial type 1-fimbrium and its urothelial receptor. Uroplakins also serve as the urothelium receptor for type 1-fimbriated *E. coli* and play an important role in the bacterial adhesion [61,66].

Increased mast cell and apoptotic activity, and decreased E-cadherin expression in urothelium, are also noted in patients with recurrent UTI, suggesting that the chronic bladder inflammation leads to increase of urothelial cell apoptosis and decrease of junction protein expression. Chronic inflammation might reside in the bladder wall, which might contribute to urothelial dysfunction and defective barrier function, then recurrent UTI ensues. This urothelial dysfunction might occur in several different lower urinary tract diseases, such as interstitial cystitis/bladder pain syndrome, BOO, spinal cord injury (SCI), and resulting in recurrent UTI [57].

Overactive bladder and recurrent urinary tract infection in lower urinary tract dysfunction of women

Anatomical or functional abnormalities of urinary tract, including upper tract or BOO and urinary tract calculi, have been well known as causative factors of UTI [47]. A post-void residual (PVR) of 180 ml or greater had the best specificity and sensitivity in predicting bacteriuria in asymptomatic adult men [67]. The maximal abdominal pressure used in voiding during voiding cystometry was found to constitute a risk factor for recurrent UTI in women [68]. Most of the current guidelines suggested that increased PVR is considered an independent risk factor for recurrent UTI [46,47,69].

In clinical practice, OAB is frequently encountered in patients with acute bacterial infection, in association with micturition pain, gross hematuria, and frequency nocturia. Patients with recurrent UTI or persistent always suffer from intractable urgency and frequency. The symptoms of OAB and recurrent UTI usually overlap, although only less than half of the women have a positive urine culture [70]. Searching for microbiome in the routine culture negative urine is important in patients with OAB refractory to conventional OAB management [29]. However, the LUTDs should be considered first to find out the possible etiology that causes OAB or recurrent UTI.

In an analysis of 100 women with recurrent UTI, Lee and Kuo found that 90% of women with recurrent UTI had LUTDs identified by video urodynamic study, despite receiving individualized treatments based on their video urodynamic findings. The LUTD included (BND, 19%), detrusor hyperactivity with impaired contractility (DHIC, 6%), detrusor overactivity (DO, 5%), detrusor underactivity (DU, 10%), dysfunctional voiding (DV, 25%), hypersensitive bladder (6%), and poor relaxation of the pelvic floor muscle (PRPF, 20%). Only 10% of patients had normal urodynamic tracings. Interestingly, although LUTD was identified and appropriate management was given to patients, only 11.3% of patients with recurrent UTIs were free from subsequent UTIs following individualized treatment for voiding dysfunction [71]. Among patients with recurrent UTI, urodynamic DO was noted in a high percentage of patients (DHIC – 100%, DO – 100%, DV – 72%, BND – 36.8%, and PRPF – 15.8%) [71]. In another study of video urodynamic study in women with recurrent UTI, DU, detrusor sphincter dyssynergia (could be DV), and combination of both LUTD were found in 22%, 17%, and 11%; and OAB was noted in 28% of patients, respectively [72]. Most of these recurrent UTI patients had urgency frequency symptoms. These results imply that OAB is closely related with recurrent UTI, especially in patients with voiding dysfunction such as DV, BND, and PRPF. In the treatment of recurrent UTI, these functional abnormalities should be treated in advance.

Implication of treatment of recurrent urinary tract infection and overactive bladder simultaneously

Acute bacterial cystitis is a common UTI among women. Acute bacterial cystitis damages the urothelium, causing tissue edema and accumulation of large numbers of inflammatory cells in the urothelium and suburothelium. These inflammatory cells could start a cascade of tissue inflammation involving several sensory proteins and cytokines accompanied by pain and hypersensitivity to bladder distension. Innate immunity usually could solve this inflammation and resume a normal bladder urothelial environment. However, if the inflammatory process is not resolved with time, it might lead to a chronic suburothelial inflammation [14,20]. Chronic inflammation of the suburothelium may increase urothelial cell apoptosis and inhibit basal cell proliferation and apical cell maturation, causing deficient barrier function of the umbrella cells [20]. Uropathogenic bacteria can easily adhere and invade the umbrella cells and form the IBCs [33]. When the innate immunity is low, no adequate lymphocytes can be recruited

to protect the bladder wall; the IBC will exist for long time, preparing for another outbreak (recurrent UTI) in the bladder wall. When there is residual IBC and chronic inflammation in the bladder wall, the sensory nerves can be activated by the urothelial cell release of ATP and acting on the P2X receptors, resulting in sensory urgency or OAB symptoms [28].

If the patient has voiding dysfunction such as BND, DV, or PRES, the voiding pressure is usually high enough to interrupt the integrity of the glycoprotein barrier such as uroplakin on the cell membrane of the umbrella cells [61,66]. The defective barrier of the bladder urothelium will further easily be invaded by the pathogens in the urine. Voiding dysfunction can not only cause high voiding pressure, but also result in large PVR. When the patient is a victim of diabetes mellitus, the urine sugar will be more fruitful for bacterial growth. In addition, the urinary tract harbors a variety of bacterial species and pathogenic or nonpathogenic micro-organisms, forming a special microbiome [73]. Some microbiome such as *Lactobacilli* species may inhibit the growth of UPEC [28]. Higher bacterial diversity in urine without the existence of *Lactobacillus* dominance has been found to associate with UUI and resistance to anticholinergic treatment [27]. Using special technology, such as 16S ribosomal RNA gene sequencing, a polymicrobial community in the female bladder in both healthy controls and women with UUI can be identified [26]. The increase in UUI symptom severity is also associated with a decrease in microbial diversity in women with UUI, suggesting that deficient microbiome in urine is vulnerable for uropathogenic bacterial growth and invasion, resulting in recurrent UTI in women [73].

Based on the recent evidence, the relationship between OAB and recurrent UTI is very close [69]. About 70% of OAB patients can be adequately treated with oral medication such as antimuscarinics, beta-3 adrenoceptor agonists, or in combination. If the oral medication fails, intravesical botulinum toxin injection can also benefit another 60%–70% of patients with OAB [74]. For the remaining patients who still have urinary incontinence or bladder hypersensitivity, the deficient urinary microbiota should be considered. Most of the patients with OAB have a history of acute bacterial cystitis. The residual bladder inflammation might be responsible for their OAB symptoms or recurrent UTI. If the routine urine culture cannot prove the presence of uropathogenic bacteria in the urine, more sensitive DNA sequence might be considered.

Perspectives of treatment and prevention of recurrent urinary tract infection

Treatment of recurrent UTI should follow the following sequence: (1) correct possible LUTD, large PVR, and high voiding pressure; (2) behavioral modifications and avoidance of risk factors; (3) nonantimicrobial measures; and (4) antimicrobial prophylaxis, which should be attempted also in this order [47,75]. Antimicrobial prophylaxis should be used after nonantimicrobial therapy failure [47]. The antimicrobial prophylaxis can be used continuously for 3–6 months. For women, a postcoital antimicrobial prophylaxis was effective in the prevention of recurrent UTI [76]. Continuous antimicrobial prophylaxis for 6 or 12 months significantly both reduced the rate of UTIs during treatment failure, but did not differ between groups after cessation of prophylaxis [77]. It is possible that prolonged antimicrobial prophylaxis cannot change the host innate immunity, the underlying pathophysiology of voiding dysfunction, or the urothelial dysfunction due to patients' bladder condition. Improvement of patient's barrier function and decrease of chronic bladder inflammation might be more helpful than antimicrobial prophylaxis.

Previous studies have shown that treatment based on a single pathophysiology such as urothelial damage or neurogenic inflammation might not be enough to eradicate the cascade of pathologies that seem to be the cause of IC [38]. Platelet-rich plasma (PRP) has been found to promote angiogenesis and increase blood flow and oxygenation in the wound by the platelet-released factors [78]. PRP also contains mesenchymal stem cells that contribute to the wound healing process [79]. Platelet-recruited macrophages and neutrophils play important roles in switching to an anti-inflammatory phenotype and release anti-inflammatory factors [80]. Repeated intravesical PRP injection is well tolerated and appears to be safe and effective in medically refractive IC and provides significant symptom improvement [81]. PRP may induce inflammation in the initiation of wound healing, followed by tissue remodeling and axon regeneration, resulting in the elimination of neuropathic pain and wound healing [82]. Based on these evidence, PRP may be used in the treatment of recurrent UTI and OAB by its therapeutic mechanisms of anti-inflammation, promote urothelial regeneration, and facilitation of urothelial IBC cell exfoliation. Repeat injection of PRP into the bladder suburothelial space might provide a better bladder health and prevent UTI recurrence.

Concerning the deficient urinary microbiota in women with recurrent UTI, the treatment might be less effective simply based on antimicrobial therapy and prophylaxis. The diversity of urinary uropathogenic bacteria can be treated by prolonged antimicrobial agents to increase the bacterial diversity in urine. Lack of *Lactobacilli* may result in a less healthy bladder condition and vulnerable to uropathogen invasion [27]. Previous clinical trial using fecal microbiota transplant had shown reduced recurrent UTI episodes in patients undergoing therapy in the following 1 year, suggesting the relationship between the gut and urinary microbiota [83]. The vaginal and urinary microbiota have been found to closely interconnected [84]. Probiotics containing *Lactobacilli* species have been used to promote women's vaginal health [85]. However, the lack of bacterial diversity in the urine is difficult to treat. In this concern, a urinary microbiota transplant by the urine donation from healthy human might be considered to instill into the bladder of women with chronic recurrent or persistent UTI. Periodic bladder instillations with healthy urine might provide a chance to increase the urinary microbiota and restore the bladder defense mechanism for uropathogen invasion. In patients with OAB refractory to medication or recurrent UTI refractory to antimicrobials, this treatment modality might be an alternative trial.

Conclusion

Recurrent UTI in women is common. A high prevalence of lower urinary tract dysfunction in association with OAB is noted. The relationship between OAB and recurrent UTI is close and might have interconnected with common pathophysiology. The defective urothelial barrier function, deficient basal proliferation, and maturation might be owing to chronic suburothelial inflammation, resulting in the activation of sensory nerves (causing OAB) and failure elimination of IBCs (causing recurrent UTI). Precision diagnosis of the underlying pathophysiology of OAB and recurrent UTI is necessary. Corrective therapy and long-term UTI prophylaxis may eradicate bacteria in IBCs. Intravesical injection of PRP has anti-inflammation and facilitate urothelial regeneration, might also reduce the episodes of UTI recurrence. Clinical trial to improve urine microbiota diversity by urine or fecal microbiota transplant, or providing vaginal probiotics, might promote the bladder and vaginal health and prevent recurrent UTI or improve OAB condition.

Financial support and sponsorship

This study was supported by the grant of Buddhist Tzu Chi Medical Foundation (TCMF107-02-01) and Hualien Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation (TCRD108-01E).

Conflicts of interest

There are no conflicts of interest.

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