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The Role of the Urinary Microbiome in the Prevention of Pediatric Urinary Tract Infections: A Narrative Review

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Urinary tract infections (UTIs) are a common condition in children and often lead to hospitalization. A considerable proportion of children with UTIs (up to 30%) experience at least one recurrence, placing them at risk for long-term complications such as renal scarring. Since the concept of the microbiome was first introduced in 2001, increasing attention has been given to the role of the urinary tract microbiome in maintaining urinary tract homeostasis. Dysbiosis of the urinary microbiome has been recognized as a factor associated with an increased risk of various urinary tract diseases, including UTIs. However, the specific role of the urinary microbiome in the pathophysiology of pediatric UTIs remains incompletely understood. The present review examines recent studies on the urinary microbiome in children and summarizes current strategies for modulating the urinary microbiome to prevent UTI recurrence in the pediatric population.

Keywords: Urinary microbiome, Urobiome, Urinary tract infection, Pediatric urobiome

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HIGHLIGHTS

This study explores the vital roles of the urinary microbiome in pediatric urinary tract infection. It highlights the concurrent nonantibiotics prophylaxis strategies which modulating urinary microbiomes in children.

INTRODUCTION

Urinary tract infection (UTI) is common in the general population. Approximately 50%–80% of women experience acute uncomplicated cystitis at least once in the lifetime, and the recurrence rate ranges from 30% to 44%, often within 3 months [1].

For children, UTI is also one of the most frequent infections [2], resulting in frequent hospitalization and a high economic burden [3]. The prevalence of UTI is approximately 7.0% in febrile infants aged <24 months and 7.8% in older children, accounting for 5%–14 % of pediatric emergency room visit [4]. Among the pediatric patients with prior UTI, the rate of UTI recurrence within the first 6 to 12 months ranges from 12% to 30%, with risk of long-term morbidity [5-7]. Moreover, recurrent UTI could induce renal scaring, resulting in chronic renal insufficiency [8]. Therefore, it is necessary for clinicians to understand the pathophysiology of UTI recurrence and proper strategies to prevent recurrence of UTI in

children.

Since the concept of microbiome was first suggested by Lederberg and McCray [9], multiple studies have demonstrated that gastrointestinal, vaginal and urinary microbiome are associated with homeostasis of urinary tract [10], and the imbalance of microbiome could result in urinary disease, including UTI. However, there are only a few studies on the role of microbiome in pathophysiology and prevention of pediatric UTI. Therefore, the current review aimed to characterize the role of urinary microbiome in pediatric UTI based on the recent literature, and to summarize contemporary strategies modulating microbiome to prevent UTI recurrence in children.

DIAGNOSTIC TECHNIQUES FOR URINARY MICROBIOME IN CHILDREN

From the 1950s, standard urine culture supported the paradigm that urine is sterile except in the case of infection [11]. Conventional urine culture has been the gold standard diagnostic test for UTI since the 1950s, which utilizes 5% sheep blood agar and MacConkey agar, aerobically incubated at 35℃ for 24 hours [12]. The cutoff value of ≥105 CFU (colony-forming unit)/mL has been universally suggested across all bacterial species to define UTI, but with the issue of oversimplification [13]. Indeed, the validity of the standard urine culture is questionable with approximately 90% of false-negative rate [12]. Moreover, the detection ability of urine culture is rather limited, favoring aerobic and fast-growing Gram-negative uropathogens [14,15]

However, with novel techniques to diagnose UTI in a culture-independent manner, such as whole-genome sequencing, and next-generation sequencing including 16S ribosomal RNA sequencing, the notion that normal urine is sterile has become obsolete [15,16]. Indeed, the Human Microbiome Project, the first large-scale mapping of the human microbiome, clearly showed that microbiome of various anatomical sites contribute to multiple and diverse human health and disease states [17]. With high concordance with urine culture in children, 16S ribosomal RNA analysis provides an additional detective value in children with equivocal culture analysis [18].

Furthermore, to overcome a methodological challenge which is the inability of the culture-independent genomic sequencing technique to differentiate DNA from live versus dead bacteria [16,19], an enhanced quantitative urine culture (EQUC) protocol, using multiple culture media and incubation conditions to cultivate bacteria which do not grow under standard conditions, was developed [14,20]. The EQUC protocol provides the 84% detection of uropathogens compared to 33% by the conventional standard urine culture [20].

URINE SAMPLING IN CHILDREN

To assess urinary microbiome, proper urine sampling should be performed. As the bladder capacity of children is smaller than that of adults, urine sample collection should be carefully considered in pediatric cohorts. Furthermore, the nature of urine as a low microbial biomass sample provides methodological challenges to evaluate urinary microbiome [21,22]. For nontoilet-trained children, noninvasive sampling (midstream urine, adhesive bags, or nappy pads) showed a high prevalence of contamination in urine cultures [23]. Therefore, there are 3 techniques to obtain urine samples in current research on pediatric urinary microbiome; clean-catch midstream urine, transurethral catheterization and suprapubic aspiration. Although suprapubic aspiration provides the "cleanest" urine sample, it has not been recommended in pediatric cohorts due to its invasiveness and ethical considerations, especially in healthy children [22]. Therefore, clean-catch midstream urine and transurethral catheterizations account for approximately equal proportions of current urine sampling techniques cohorts [24].

In toilet-trained children with urinary continence, midstream voided urine is usually sufficient, recognized as the dominating urine sampling technique in infant [23]. Meanwhile, either first voided or midstream urine samples showed no significant differences regarding 16S ri-

bosomal RNA analysis [25].

URINARY MICROBIOME IN "HEALTHY" CHILDREN

Using 16S ribosomal RNA sequencing analysis, up to 200 difference genera of urinary microbiome have been detected, including previously unidentified microbial taxa [26-29]. Several studies which examined urinary microbiome in pediatric cohorts, defined "healthy" children as those who are asymptomatic for UTI and have urinary continence. Approximately 83.0%–90.5% of healthy children have urinary microbiome, but there is no consensus regarding the taxonomy of healthy urine microbiome [24].

The origin of urinary microbiome is still not entirely elucidated. Kinneman et al. [27] demonstrated that even the urine samples from infants and young children younger than 48 months contain urinary microbiome. The most common species identified in urine samples were tissierellaceae, prevotellaeae, veillonellaceae, enterobacteriaceae, and comamonadaceae, while the 5 most common genera were *Prevotella*, *Peptoniphilus*, *Escherichia*, *Veillonella*, and *Finegoldia* [27]. Robertson et al. [30] suggested that the composition and function of human microbiome in the first 1,000 days are primarily determined by birth mode, maternal microbiome, exposure to antibiotics, and feeding practices in early life. Indeed, the fetus is considered to be sterile during normal pregnancy, gaining bacteria through maternal transmission at delivery [31]. The composition of infant microbiome matures within 2–3 years after birth [30,31].

There are several studies evaluating the microbiome of prepubertal "healthy" children after toilet training [32-35]. Kassiri et al. [32] revealed that the predominant genera from urine sample in prepubertal "healthy" boys were different with those in adults, suggesting that the development of the urinary microbiome starts in early life and becomes more stable in adulthood. Recently, Kelly et al. [33] demonstrated that the predominant taxa of urinary microbiomes in prepubertal children do not include taxa which are common in adults (e.g. *Lactobacillus* in females and *Staphylococcus* in males) and the diversity of urinary microbiome increased with age, mainly in boys.

According to sex, the composition of urine microbiome differed significantly, probably due to differences in sex-specific anatomy and sex hormones levels in the prepubertal period [34]. Recently, Kelly et al. [33] showed that alpha diversity of urinary microbiome was significantly higher in prepubertal girls compared to boys. Another case-control pilot study which included toilet-trained prepubertal female showed that the composition of urinary microbiome did not differ according to bladder and bowel syndrome [35].

URINARY MICROBIOME IN CHILDREN WITH URINARY TRACT INFECTION

To date, there are few studies are on the urinary microbiome in children with UTI. Kinneman et al. [27] demonstrated that the episode of UTI significantly decreased alpha diversity of urinary microbiome in not toilet-trained children. They also showed that the usage of antibiotics within 2 weeks prior to urine sampling significantly reduced the diversity of urinary microbiome. In contrast, Forster et al. [36] suggested that alpha diversity was higher in febrile children with UTI. Although there were differences in the predominant microbial taxa between children with and without UTI, there was no significant difference in beta diversity between the 2 groups. A recent pilot study conducted showed that the recurrence of UTI reduced urinary microbiome diversity. When comparing the diversities of urinary microbiome according to the numbers of UTIs, the diversity was significantly reduced in patients who experienced 3 and more episodes of UTIs. Meanwhile, prophylactic use of antibiotics did not result in the elimination of the urinary microbiome [33].

DYSBIOSIS OF URINARY MICROBIOME AND URINARY TRACT INFECTION

While the advantages of bacteria from the host are rather clear, including nutrient supply, pH and oxygen, it is still unclear what benefits the urinary microbiome provide to the host. However, several roles of urinary microbiome in the homeostasis of the urinary tract have been suggested. For instance, commensal microbiome might compete with uropathogens for common resource, enhance immune system of the host and create a barrier [37].

Although there is no consensus how to define 'healthy' urinary microbiome, the imbalance of urinary microbiome might be associated with the presence of UTI. Indeed, the imbalance or disruption of the host microbiome, termed dysbiosis may result in disease susceptibility and pathophysiology of skin, respiratory tract, or gastrointestinal disease in children [38].

In urologic field, dysbiosis of the urinary microbiome is suggested to be related to an increased risk of UTI [39], nephrolithiasis [40], and lower urinary tract symptoms/benign prostatic hyperplasia [41]. For pediatric cohort, dysbiosis of microbiome is also reported to be associated with urinary diseases [42-45].

Conventionally, *Escherichia coli* was recognized as the most predominant pathogen of primary UTI (approximately 80%) in pediatric cohort [46], followed by *Klebsiella*, *Enterobacter*, *Proteus* and *Citrobacter* [2,47]. However, whole-genome sequencing revealed that there were no differences in the genomic content of virulence factors genes between strains isolated from patients and healthy individuals. Therefore, *E. coli* is suggested to be part of the commensal urinary microbiome, and their uropathogenicity might be the result of an imbalance in urinary microbiome composition [48]. Kinneman et al. [27] showed that pediatric patients with UTI showed significantly reduction of alpha diversity compared with children without UTI.

MODIFICATION OF THE URINARY MICROBIOME TO PREVENT PEDIATRIC URINARY TRACT INFECTION

Considering that dysbiosis of urinary microbiome is related with UTI [43,44], the strategies of modifying urinary microbiome could be a potential option for prophylaxis against UTI in children. Those strategies could be divided into 2 classes; antibiotic prophylaxis and non-antibiotic prophylaxis [43,49].

1. Antibiotics Prophylaxis for Pediatric UTI

Although low-dose continuous antibiotic prophylaxis has been attempted to prevent recurrent UTI and subsequent complications [50], its efficacy is controversial. Storm et al. [51] suggested that long-term antibiotic prophylaxis failed to decrease the frequency of UTI or prevent renal scarring, but increased the risk of antibiotic resistance, impacted the microbiome, and induced potential long-term side effects. The updated Cochrane Systematic Review in 2019 demonstrated that antibiotics may provide limited or no significant benefit to reduce recurrent UTI compared to placebo or no treatment, but causing the risk of antibiotic resistance of approximately 2.5 times higher [50].

Another systematic review concluded that continuous antibiotic prophylaxis in children is not recommended due to its limited efficacy and the risk of antimicrobial resistance, but could be suggested for those with significant obstructive uropathies until surgical correction [52]. Meanwhile, another multicenter randomized trial demonstrated that continuous antibiotic prophylaxis presents a small but significant advantage in prevent a first event of UTI in UTI-naïve infants with grade III or severe vesicoureteral reflux. However, the authors also reported that continuous antibiotic prophylaxis showed an increased prevalence of non-*E. coli* organisms and antimicrobial resistance [53].

Considering the controversial efficacy of antibiotic prophylaxis and the probability of antibiotic resistance, a variety of novel strategies have been tried to prevent UTI

in pediatric population [43,54].

2. Nonantibiotics Prophylaxis for Pediatric UTI

Table 1 summarized the concurrent studies which evaluated the therapeutic effect of nonantibiotics prophylaxis, comparing that of conventional antibiotic prophylaxis in pediatric population [55-69].

1) Human breast milk

Breastfeeding is suggested to play a key role in the induction and education of pediatric immune system, protecting children [70]. Indeed, breastfeeding might be a cost-free, natural prophylaxis against pediatric UTI, particularly during the first 6 months of life [71]. Breastfeeding during this period is known to affect the diversity of the gut microbiome, with greater *Bacteroides* and *Bifidobacterium* [30]. Furthermore, as human breast milk contains high level of immunoglobulins [72], human breast milk could provide antibacterial effect by preventing bacterial adherence to the gastrointestinal mucosa and urothelium [73].

The presence of the human milk oligosaccharides (HMOs) might explain how breastfeeding could prevent pediatric UTI. HMOs are the third most important component in human breast milk, improving the gastrointestinal barrier and promoting a *Bifidobacterium*-rich gastrointestinal microbiome, which provides protection against infection [74]. Moreover, HMOs act as soluble decoy receptors for surface adhesins of a variety of pathogens, blocking uropathogens from urothelium [75].

However, the protective effect of human breast milk against UTI *in vivo* remains rather controversial. Lin et al. [76] suggested that HMOs could protect bladder epithelial cells from cytotoxicity and proinflammatory effects by uropathogenic *E. coli* (UPEC). In contrast, a prospective study in 2018 failed to show any correlation of breastfeeding with the number of UTI episodes within 5 years [77].

2) Cranberry products

Oral intake of cranberry products, primarily in juices, have been used as a folk medicine for centuries to prevent and treat UTI [78]. Although no definitive mechanism how cranberries prevent UTI has been established, several hypotheses have been proposed. Recently, anthocyanidins and proanthocyanidins, which are tannins (polyphenols) are suggested to explain the antimicrobial mechanisms of cranberries [54]. The isolated A-type proanthocyanidin oligomers purified from cranberries inhibited adhesion of P-fimbriated UPEC adhesion to uroepithelial cells [79], depending on the concentration of cranberry products and the number of cultures the bacteria were exposed to cranberry products [80]. In addition to proanthocyanidins, other phenolic components such as myricetin and quercetin [81], or xyloglucan oligosaccharides [82] are also suggested as potential inhibitor against the adhesion of P-fimbriated UPEC to bladder epithelium. Moreover, cranberry products could also modulate human gut microbiome [83] and probably preventing dysbiosis of gut microbiome, which could partially explain the mechanisms how cranberries prevent UTI [84].

To the best of our knowledge, there are 2 meta-analyses evaluating the efficacy of cranberries to prevent UTI recurrences in the pediatric cohort. A meta-analysis including 23 studies with 3,979 patients showed that cranberry products as adjuvant therapy could substantially decrease the recurrence rate of UTI in susceptible population, including children [85]. Another meta-analysis concluded that cranberry products could reduce the risk of UTI recurrence in children with a normal urinary tract, which was as effective as antibiotic prophylaxis [86]. In terms of safety issue, cranberry is very safe for most children, but intaking large amounts could cause diarrhea [87].

3) Probiotics

Probiotics are defined as "live microorganisms which could provide a health benefit on the host when administered in adequate amounts, confer" [88]. Probiotics, mostly containing *Lactobacilli*, is also recognized as a potential prophylaxis against symptomatic UTI recur-

Table 1. Summary of studies on the therapeutic effect of nonantibiotics prophylaxis

Study	Patients' characteristics	No. of patients	Intervention	Control	Duration of follow-up (mo)	Significant findings
Cranberry products versus placebo						
Foda et al. [55] (1995)	Children aged 1–18 yr with neuropathic bladder requiring CIC	40	15 mL/kg/day of cranberry cocktail (30% cranberry concentrate)	Placebo	12	No significant difference in the rate of UTI.
Schlager et al. [56] (1999)	Children aged 2–18 yr with neuropathic bladder requiring CIC	15	60 mL of cranberry concentrate (300 ml juice)	Placebo	3	No significant difference in the rate of bacteriuria.
Ferrara et al. [57] (2009)	Girls aged 3–14 yr	28 vs. 29	7.5 g of cranberry concentrate + 1.7 g of lingonberry concentrate in 50-mL water - daily	Control	6	Cranberry group showed fewer rate of symptomatic UTI (18.5% vs. 48.1%, p<0.05)
Afshar et al. [58] (2012)	Children aged with 5–18 yr	20 vs. 20	2 mL/kg of cranberry juice every day	Placebo	12	Cranberry group showed 65% reduction in the risk of UTI (p=0.045)
Salo et al. [59] (2012)	Children aged with 1–16 yr	129 vs. 134	5-mL/kg cranberry juice up to 500 mL for 6 mo	Placebo	12	No significant difference in the recurrence of UTI (p=0.21) Cranberry group showed significantly fewer days of microbials (-6 days per patient-year, p<0.001)
Wan et al. [60] (2016)	Boys aged with 6–18 yr	28 vs. 39	120 mL of cranberry juice once daily	Placebo	6	Cranberry group showed lower incidence of UTI. (25% vs. 35.9%)
Dotis et al. [61] (2018)	Children aged with 2–18 yr	30 vs. 35	Cranberry extract 250 mg every day	Routine care	12	Cranberry group showed 1ower percentage of UTIs, fewer days/year on antibiotic treatment and lower percentage of initiation of antimicrobial prophylaxis (p<0.05)
Cranberry products versus antibiotics prophylaxis						
Uberos et al. [62] (2012)	Children aged with 1 mo–13 yr	75 vs. 117	Cranberry 0.2 mL/kg	TMP 0.2 mL/kg/day	12	No significant difference in the recurrence of UTI. No significant difference in the rate of antimicrobial resistance.
Probiotics versus placebo						
Dani et al. [63] (2002)	Newborn infants with a gestational age <33 wk or birthweight <1,500 g	295 vs. 290	7 Days of *Lactobacillus GG* supplementation starting with the first feed	Placebo	2	Probiotics group showed a fewer rate of UTI (3.4% vs. 5.8%), but not significantly.

(Continued)

Table 1. Summary of studies on the therapeutic effect of nonantibiotics prophylaxis (Continued)

Study	Patients' characteristics	No. of patients	Intervention	Control	Duration of follow-up (mo)	Significant findings
Sadeghi-Bojd [64] et al. (2019)	Children aged with 4 mo–5 yr	91 vs. 90	Probiotic mixture (*Lactobacillus acidophilus*, *Lactobacillus rhamnosus*, *Bifdobacterium bifidum*, and *Bifdobacterium lactis*)	Placebo	18	Probiotics group showed a superior UTI-free rate at 18 mo to placebo group (96.7% vs. 83.3%)
Lee et al. [65] (2016)	Children aged with 1–24 mo	73 vs. 50	*Lactobacillus acidophilus* (10^8 CFU/g bid)	TMP/SMX (2/10 mg/kg qhs)	6	Probiotics group showed lower rate of recurrent UTI (8.2% vs. 20.6%, p=0.035)
Ferrara et al. [57] (2009)	Girls aged with 3–14 yr	28 vs. 29	100 mL of *Lactobacillus GG* drink on 5 days a month	Control	6	No significant difference in the rate of symptomatic UTI (42.3% vs. 48.1%, p>0.05)
Probiotics versus antibiotics prophylaxis						
Lee et al. [66] (2007)	Persistent primary VUR (all grades) after TMP-SMX prophylaxis for 1 yr	60 vs. 60	*Lactobacillus acidophilus* (10^8 CFU/g bid)	TMP/SMX (2/10 mg/kg qhs)	12	No significant difference in the recurrence of UTI (18.3% vs. 21.6%, p=0.926)
Lee et al. [67] (2015)	Children aged with 1 wk–1 yr	64 vs. 64	*Lactobacillus acidophilus* (10^8 CFU/g bid)	TMP/SMX (2/10 mg/kg qhs)	12	Probiotics group showed a slightly lower rate of recurrent UTI (32.8% vs. 40.6%) but not significantly (p=0.348)
Lee et al. [65] (2016)	Children aged with 1–24 mo	73 vs. 50	*Lactobacillus acidophilus* (10^8 CFU/g bid)	TMP/SMX (2/10 mg/kg qhs)	6	No significant difference in the rate of recurrent UTI (8.2% vs. 10.0%, p=0.532)
Probiotics plus antibiotics versus antibiotics alone						
Mohseni et al. [68] (2013)	Children aged 3–15 yr with recurrent UTI and VUR (all grades)	41 vs. 41	Probiotic yoghurt (0.25 mL/kg from 100 ml yoghurt containing 10^7 CFU/mL of *Lactobacillus acidophilus* and *Bifidobacterium lactis*) +nitrofurantoin 1 mg/kg/day	Nitrofurantoin 1 mg/kg/day	36	No significant difference in the recurrence of UTI (39% vs. 50%, p=0.4) Probiotics + antibiotics groups showed a lower rate of febrile UTI (0.00±0.00 vs. 0.13±0.40, p=0.03)
Madden-Fuentes et al. [69] (2015)	Children aged 4–13 yr	10 (retrospective)	Ciprofloxacin (20 mg/kg bid) + 250 mg of *Saccharomyces boulardii* daily for 1 yr	NA	9	Number of UTI decreased after therapy Of the 8 patients with known compliance, 7 (88%) were free of recurrent UTIs.

CIC, clean intermittent catheterization; UTI, urinary tract infection; CFU, colony-forming unit; VUR, vesicoureteral reflux; TMP, trimethoprim; SMX, sulfamethoxazole; NA, not available.

rence [89]. A multicenter randomized trial showed that cow's skim milk fermented with *Lactobacillus paracasei* CBA L74 could prevent common pediatric infectious diseases, such as acute rhinitis, tracheitis, laryngitis, pharyngitis and otitis media [90,91]. Indeed, *Lactobacilli* are prevalent in the healthy vaginal flora, performing anti-biofilm, antioxidant, pathogen-inhibition, and immunomodulation activities against vaginal infection and further UTI [92].

Several articles demonstrated the effectiveness of probiotics to prevent UTI recurrence in children. For children with normal urinary tract, probiotics were more effective than placebo at decreasing the risk of recurrent UTI after their first episode of febrile UTI [64]. Another recent randomized controlled trial showed that probiotics containing *Lactobacillus rhamnosus* PL1 and *Lactobacillus plantarum* PM1 decreased UTI of almost 50% compared to the placebo group [93].

However, the prophylactic effect of probiotics against recurrent UTI is rather controversial. According to the Cochrane Systematic Review, probiotics failed to show significant benefit in the prevention of pediatric UTI compared to with placebo or no treatment. However, as the evidence level was limited, the potential benefit of probiotics was not entirely denied [94]. Another meta-analysis also demonstrated that monotherapy of probiotics did not reduce the prevalence or recurrence of UTI in children, but showed a moderate efficacy when used as adjuvant therapy to antibiotics [95]. Meanwhile, Meena et al. [86] found that probiotics provide more beneficial effect to reduce the recurrence of UTI in children with normal urinary tract. Compared to antibiotics, probiotics failed to show significant benefit in preventing UTI, but reduced the risk of antibiotic-resistant bacteria.

There is no consensus with regard to the selection of probiotic strains, accurate dosage, mode of administration, or proper duration of therapy. Moreover, a variety of factors influencing the viability of probiotic bacteria during production, storage, and delivery until consumption time, including temperature, pH, molecular oxygen, and additives may affect the clinical outcomes of probiotics. In addition, the effects of probiotics are strain-specific, and may not be in other strains of the same bacteria [43]. In terms of safety, probiotics are considered to be safe and well-tolerated. The most frequent side effects of oral probiotics included diarrhea, nausea, vomiting, constipation, and vaginal symptoms [94].

Although probiotics are mainly administered orally in children, probiotics could be administered vaginally or as intravesical instillation. The vagina serves as a potential reservoir for uropathogens, resulting in UTI [96]. Indeed, vulvovaginitis is reported to result in UTI by modifying the perineal microbiome and increased colonization of uropathogens [97], while the loss of vaginal *Lactobacilli* raises the risk of colonization with uropathogenic microbes [89]. In addition, probiotics maintain vagina's characteristic low pH, by producing lactic acid [43]. Therefore, it would be reasonable to suggest that vaginal probiotics as an efficient method to prevent recurrent UTI. Although the preliminary observational studies have shown promising results in adults, there is a lack of studies on the efficacy of vaginal probiotics in children.

Stapleton [96] reported that vaginal probiotics containing *Lactobacillus crispatus* (Lactin-V; Osel) significantly prevented UTI recurrence in premenopausal women. The side effects included vaginal discharge, itching, or moderate abdominal discomfort. Gupta and colleagues [89] also demonstrated that either vaginal probiotics or in combination with oral probiotics could effectively prevent recurrent symptomatic UTI episodes in premenopausal women, without no serious adverse events.

Regarding intravesical instillation of probiotics, Forster et al. [98] suggested that intravesical instillation of *Lactobacillus rhamnosus* GG (LGG) could be safe route of administration, with self-resolved symptoms within one week. Groah et al. [99] also showed that intravesical LGG could be safe and well-tolerated in adult and pediatric patients with neurogenic lower urinary tract dysfunction under clean intermittent catheterization. The same authors reported that intravesical LGG alters the composition and diversity of urinary microbiome [100].

4) Intravesical instillation of glycosaminoglycan

The glycosaminoglycan (GAG) layer, which covers the urothelial epithelium of bladder, forms a barrier to prevent the adherence of uropathogens [101]. Recently, the GAG replacement therapy with intravesical instillation of combined hyaluronic acid and chondroitin sulfate is tried in the patients with recurrent cystitis, post-radiation cystitis and bladder pain syndrome, suggested as a potential prophylaxis against UTI [102,103].

However, there are only 2 studies on the effectiveness of intravesical GAG replacement therapy in children with recurrent UTI [104,105]. In 2015, a case-series first reported the efficacy of intravesical hyaluronic acid instillation in children with recurrent UTI, demonstrating that 86.7% experienced overall complete or partial response within 24 months [104]. Cicek et al. [105] showed that intravesical hyaluronic acid instillation significantly decreased mean UTIs per patient-month during a follow-up period of 16 months, among the pediatric patients with spina bifida and neurogenic bladder who undergo clean intermittent catheterization.

5) Immunostimulants and autologous bacterial lysates

Since the oral vaccine, Uro-Vaxom/OM-89 was first approved in Europe, immunostimulants have become a promising prophylaxis against recurrent UTI, providing UTI-free rates of 55%–90% [106]. A recent meta-analysis suggested that vaccines could be effective in the short term (6–12 months) at reducing recurrent UTI for adult females, but the evidence level was limited [107]. Another systemic review also showed that immunostimulants could decrease the risk of UTI recurrence compared to placebo [108].

However, a majority of previous studies on the efficacy of immunostimulants included only adult population. Only a few studies assessed the effectiveness of immunostimulants in children. A recent meta-analysis reported that immunostimulants could reduce the risk of acute upper respiratory tract infections by 39% in children, despite limited quality of evidence [109]. To the best of our knowledge, there is no previous studies on the efficacy of immunostimulants for prevention of pediatric UTI.

Autologous bacterial lysates are manufactured with the isolated bacteria from the infected site, inactivated by heat, and homogenized in a suspension, favoring immunoglobulin (Ig) G and IgM production and T-lymphocyte activation [110,111]. In adult, autologous bacterial lysates were reported to reduce UTI recurrence [112]. A prospective study also showed a promising result in children with recurrent UTI due to congenital anomalies of the urinary tract after surgical intervention, showing insufficient response to antimicrobial therapy. The autologous bacterial lysates reduced the presence of *E. coli* in the urine culture from 92.5% of patients at the beginning of the study, to 55.5% and 34% for the second and third months, respectively [113].

CONCLUSIONS

With advanced techniques such as EQUC and high-throughput molecular gene sequencing analysis, the presence of urinary microbiome is now well-known. Recently, the urinary microbiome has been recognized to play an important role in maintaining homeostasis and health of urinary tract. In childhood, starts to mature and changes with age, stabilizing in the adulthood. The imbalance or dysbiosis of the urinary microbiomes may cause a variety of pediatric urinary tract disease, including UTI. Indeed, the potential effect of manipulating urinary microbiome on the prevention of UTI seems promising. Further larger scale, well-designed, prospective studies are required to elucidate the association between the urinary microbiome and the common risk factors of pediatric UTI, including vesicoureteral reflux, obstructive uropathy, overactive bladder, or neurogenic bladder. This will enable the development of novel microbiome-based prophylactic strategies to control recurrent UTI in children.

NOTES

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