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LITERATURE REVIEW

Update on Associated Risk Factors, Diagnosis, and Management of Recurrent Urinary Tract Infections in Children

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Recurrent urinary tract infection (rUTI) continues to challenge pediatric care providers. The diagnosis of an rUTI can be difficult, especially in young febrile children. Antibiotic resistance rates continue to rise, which limits oral treatment options. Prophylactic antibiotics are used commonly to manage rUTI, but their use increases the risk of rUTI with antibiotic-resistant strains without significantly reducing renal scarring. Alternative therapies for rUTI include probiotics and anthocyanidins (eg, cranberry extract) to reduce gut colonization by uropathogens and prevent bacterial adhesion to uroepithelia, but efficacy data for these treatments are sparse. The future of rUTI care rests in addressing the following contemporary issues: best diagnostic practices, risk factors associated with rUTI, and the prevention of recurrent infection. In this review, we summarize the state of the art for each of these issues and highlight future studies that will aim to take an alternative approach to managing rUTI.

Keywords. antibiotic resistance; diagnosis; probiotics; recurrent UTI.

Urinary tract infection (UTI) is one of the most common types of infection in children [1]. A subset of children experience recurrent UTI (rUTI) and pose a management challenge for all clinicians. In this review, we focus on the risk factors for rUTI and strategies for preventing and better managing it.

EPIDEMIOLOGY OF UTI

Although the exact cost of rUTI management is not known, the aggregate hospital costs of all pediatric UTI management exceeds $520 million every year [1, 2]. In children, the rate of rUTI after the first episode is 13.6% (ie, incidence rate of 0.12 per person-year) [3]. rUTI is associated with school absenteeism, a need for parental leave, frequent visits to health care providers, and a likely increase in healthcare costs.

GUIDELINES FOR DIAGNOSING rUTI

rUTI is defined as an onset of UTI symptoms after resolution of a previous UTI. The rate of renal scarring increases significantly after the third UTI [4].

Diagnosing recurrent episodes is similar to that of the sentinel episode and should involve reviewing clinical features and the results of urinalysis and bacterial culture [5]. Clinical features include dysuria, urinary frequency, irritability, fever, nausea, and poor feeding. The presence of nitrites and leukocyte esterase in a urinalysis and presence of white blood cells (WBCs) as determined by microscopy are the most widely used parameters for diagnosis [6]. The conversion of dietary nitrates to nitrites by uropathogens in the bladder takes approximately 4 hours. Therefore, the traditional nitrite test is not sensitive for children, particularly infants, who empty their bladders frequently [7]. The leukocyte esterase test is approximately 94% sensitive when used in the context of clinical UTI; however, its specificity is low (74%) [6].

A comparison of enhanced urinalysis (manual microscopic examination of uncentrifuged urine) and automated urinalysis was conducted on 703 urine samples collected by clean catch or catheterization from children aged 0 to 19 years (median, 10 months) [8]. A positive enhanced urinalysis result was defined as ≥10 WBCs/mm^3 and the presence of any bacteria per 10 oil immersion fields on a Gram-stained smear. A positive automated urinalysis result was defined as ≥2 WBCs per high power field (hpf) and the presence of any bacteria detected by the machine. The positive predictive values (PPVs) and sensitivities for pyuria were similar between the 2 methods. However, the sensitivities and PPVs for bacteriuria to detect a single organism culture of ≥50 000 colony-forming units (CFU)/mL were superior in the enhanced urinalysis. When pyuria as determined by automated urinalysis was combined with bacteriuria as determined by Gram-stain

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analysis, the PPVs and sensitivities were similar to those of the enhanced urinalysis. Therefore, combining these 2 methods might increase sample throughput without decreasing their sensitivity and PPV. Another study also found that urinalysis results can be influenced by concentration of the urine [9]. The results of a Chaudhari et al study [9] suggested that urine concentration alters diagnostic criteria and that 3 WBCs/hpf when urine is dilute (specific gravity, <1.015) or 6 WBCs/hpf when urine is concentrated (specific gravity, >1.015) should be considered a positive result. A urine culture that results in a single pathogen with ≥100 000 CFU/mL from a midstream sample or ≥50 000 CFU/mL from a sample obtained via catheter or suprapubic collection is considered diagnostic for UTI when associated with appropriate symptoms and a suggestive urinalysis result. A single pathogen culture that results in ≥10 000 CFU/mL in infants with symptoms consistent with a UTI and evidence of inflammation in urinalysis can also be considered diagnostic for UTI [10].

PREDISPOSING FACTORS ASSOCIATED WITH rUTI

Figure 1 provides an overview of the predisposing factors associated with rUTI.

Bowel and Bladder Dysfunction

Bowel and bladder dysfunction (BBD) is an underdiagnosed yet common pediatric condition [11]. BBD is a combination of lower urinary tract symptoms (LUTSs) and bowel disorders, including constipation and/or encopresis, in patients with no known neurological abnormality [12]. Overactive bladder that results from detrusor overactivity is the most common form of LUTSs in children and is marked with increased frequency of daytime urination and nocturia with or without incontinence [12]. Voiding postponement, another common LUTS, occurs when a patient delays urination (associated with withholding maneuvers such as leg-crossing and the "pee-pee dance"), which leads to urgency and incontinence because of the overfilled bladder [12, 13]. Such patients frequently also have constipation because of delayed stooling habits. Other LUTSs include underactive bladder caused by detrusor underactivity, which results in the need to strain during urination, dysfunctional voiding caused by habitual contraction of the bladder sphincter and pelvic floor, and bladder neck dysfunction, which refers to delayed or impaired bladder opening that results in reduced urine flow despite increased bladder pressure [12]. These conditions together can result in postvoid urine retention, which provides a rich medium for bacterial replication and adherence and increased risk of rUTI [14].

A review of 2 longitudinal studies, the Randomized Intervention for Children With Vesicoureteral Reflux (RIVUR) trial [15] and the Careful Urinary Tract Infection Evaluation (CUTIE) study [16], found that the most frequent urinary symptoms in children with BBD were urgency (85%), withholding

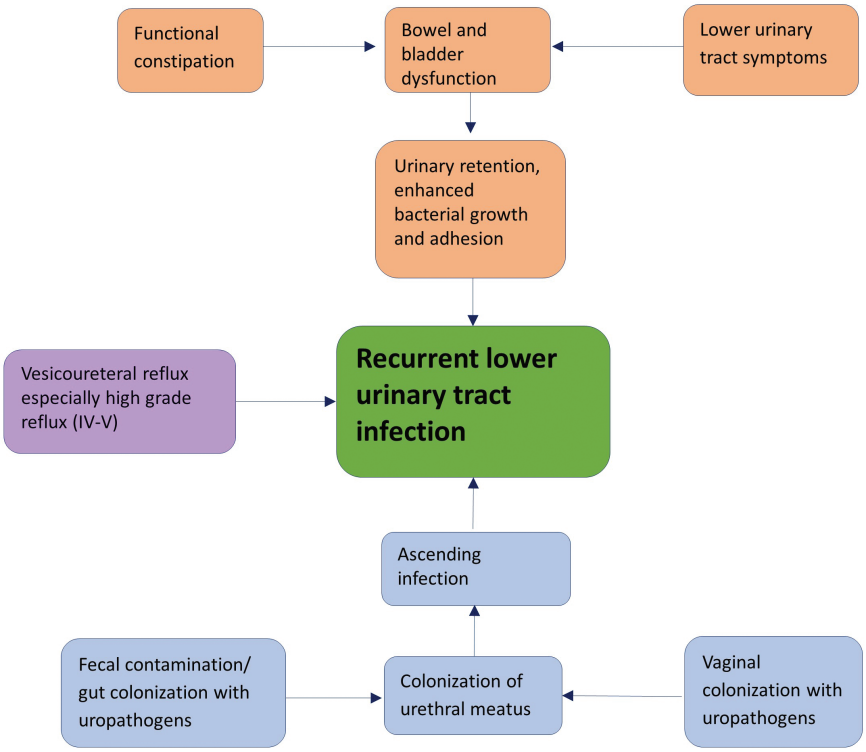

Figure 1. Overview of risk factors associated with recurrent urinary tract infection.

maneuvers (80%), and daytime wetting (63%) [17]. The most common bowel disorders were painful defecation (39%) and having fewer than 3 bowel movements per week (8%). Overall 22% of the patients evaluated in both studies combined met the criteria for constipation. The results of this review also suggested that BBD is an independent risk factor for rUTI and therefore should be considered part of the clinical evaluation.

Constipation, also a component of BBD, occurs in up to one-third of girls with rUTI [18]. Constipation causes urinary stasis as a result of compression of the bladder and elongation of the urethra by fecal retention, which reduces urinary flow and promotes pathogen adherence [19]. Some children with constipation are found also to have renal pelvic dilation even in the absence of anatomical abnormalities or infection [20].

Vesicoureteral Reflux

A retrospective analysis found that grades IV and V vesicoureteral reflux (VUR), age between 2 and 6 years, and Caucasian race are associated with rUTI [3], whereas lower grades of VUR are not. However, another prospective cohort study found a higher rate of recurrence in children with any grade of VUR than in those with no VUR [16]. Among children with any grade of VUR, those who were less than 24 months old or were diagnosed with constipation were at a higher risk of rUTI.

Gut Colonization With Uropathogens

The gastrointestinal and vaginal tracts are well established reservoirs of uropathogens [21]. Czaja et al [22] found a significant increase in gut-derived uropathogens in the periurethral area in women in the days that preceded a UTI episode. Another study noted that rUTI in infants are usually caused by the same organism as that which caused the previous episode, which suggests a local reservoir for the bacterial strain [23].

Male Circumcision and Female Vaginal Microbial Colonization

Other predisposing factors include uncircumcised status in male neonates and antibiotic use. Among healthy male infants less than 3 months old, there is a greater than 10-fold increase in the incidence of UTI among those who are uncircumcised [3, 24]. Normal vaginal colonization with H_2O_2-producing strains of *Lactobacillus* occurs well before the onset of menarche [25]. The use of antibiotics can alter the normal vaginal flora and result in a predominance of enteric bacteria and an increased risk of rUTI [26].

MICROBIOLOGY

Uropathogenic *Escherichia coli* (UPEC) causes 70% to 80% of all UTIs [1, 3]. Other organisms involved in UTI are enteric bacteria such as *Klebsiella* spp, *Proteus* spp, and *Enterococcus* spp and vaginal colonizers such as *Ureaplasma* spp and *Mycoplasma* spp [3]. *Pseudomonas aeruginosa* is an uncommon uropathogen, but it has been associated with rUTI, VUR, and other renal abnormalities and therefore should be considered a possible cause of infection in this population [27]. Clonal evaluation of uropathogens from urine and rectal swabs in patients with a UTI has shown that the gut is a major reservoir of these bacteria [28]. In addition, colonization of the periurethral area by UPEC increases in the days that precede an rUTI [22].

STRATEGIES FOR PREVENTING rUTI

Figure 2 provides an overview of the recommended management of rUTI.

Diagnosis and Treatment of BBD

Standardized questionnaires for diagnosing BBD in a primary care setting are available. Two such questionnaires were developed by Farhat et al [29] (Dysfunctional Voiding Score System) and Afshar et al [30] (Vancouver Symptom Score for Dysfunctional Elimination Syndrome). Both of them are based on quantitative and qualitative assessments of constipation, daytime and nighttime wetting, urgency, and difficulty in voiding or defecating. If BBD is suspected in a patient with rUTI, physicians can recommend maintenance of a urination and stooling diary, typically for 7 to 14 days, to provide objective data regarding frequency of urination, fluid intake, voided volume, presence of incontinence, frequency and physical characteristics of bowel movements, and any associated encopresis [31, 32]. Some authors have recommended maintaining a diary for 48 to 72 hours only for increased compliance [13]. An objective measurement of bowel movements can be made using the Bristol stool chart [33].

Treatment of BBD should include managing constipation with adequate hydration, an increase in fiber intake, and use of stool softeners [34]. Polyethylene glycol 3350 is the most commonly used stool softener, and it has been found to be effective and safe in the pediatric population [35]. Some LUTS, such as overactive bladder and voiding postponement, can be managed by behavioral changes, including using a combination of adequate hydration, timed voiding, and pelvic floor training using Kegel exercises or diaphragmatic breathing [36, 37]. Immediate-release (IR) (Ditropan) and extended-release (ER) (Ditropan XL) formulations of oxybutynin, an antimuscarinic agent, are also approved for use in children with overactive bladder. Although IR oxybutynin has been in clinical use for many years, pediatric data have been extrapolated largely from studies of adults [38]. ER oxybutynin was shown to have a greater efficacy than the IR form in studies with a relatively limited sample size [39, 40]. Some of this effect might be related to better adherence because of fewer adverse effects such as gastrointestinal disturbances, dry eyes and mouth, sleep difficulty, and blurred vision [40]. Referral to a pediatric urology specialist

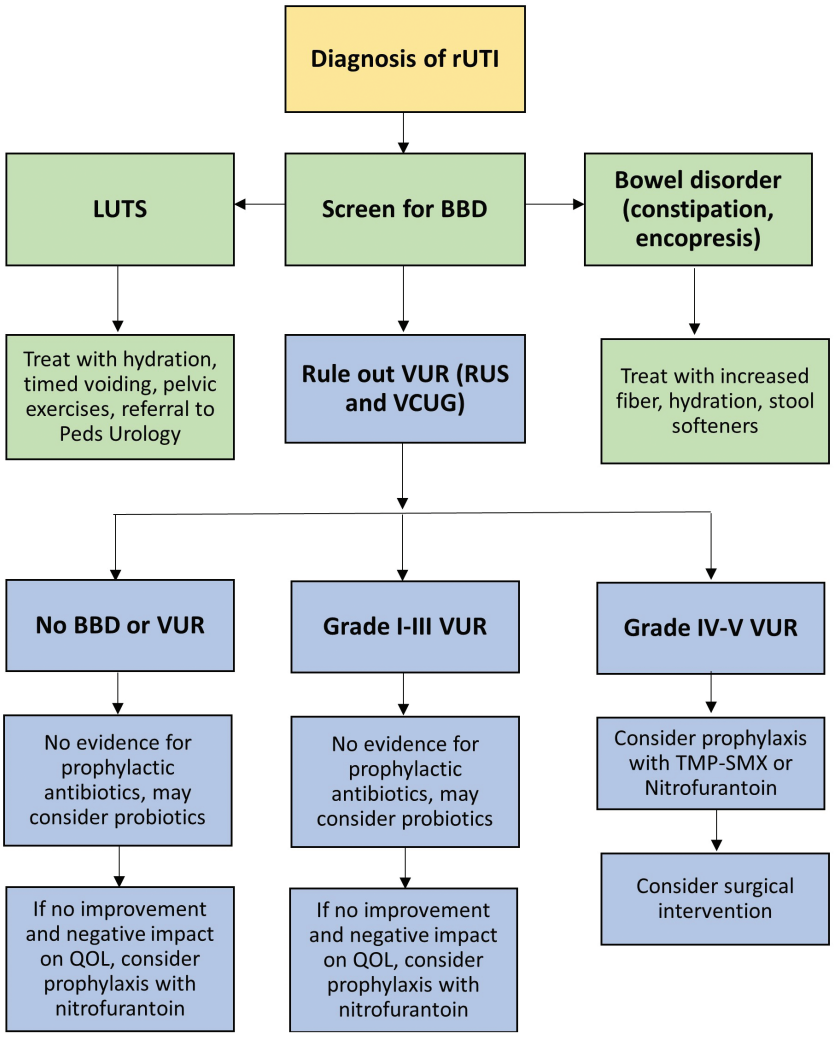

Figure 2. Recommended management of recurrent urinary tract infection. Abbreviations: BBD, bowel and bladder dysfunction; LUTS, lower urinary tract symptoms; QOL, quality of life; RUS, renal ultrasound; rUTI, recurrent urinary tract infection; TMP-SMX, trimethoprim-sulfamethoxazole; VCUG, voiding cystourethrogram; VUR, vesicoureteral reflux.

for voiding cystometry and/or biofeedback therapy using urodynamic studies should be considered also [41].

Antibiotics

Traditional strategies for preventing the recurrence of UTI, especially in children, have relied on prolonged use of antibiotics. However, several studies that compared prophylactic antibiotic use with a "just-in-time" approach found a limited effectiveness of prophylaxis in reducing renal scarring, which is the primary justification for its use, especially among patients with no or low-grade VUR [42, 43]. The RIVUR clinical trial randomly assigned more than 600 children to receive either trimethoprim-sulfamethoxazole (TMP-SMX) or placebo for 2 years and found an approximately 50% reduction in the rate of rUTI, irrespective of the severity of VUR, with a number needed to treat of 8 (ie, 5840 antibiotic doses to prevent a single recurrence) [15]. However, 63% of recurrences in the prophylaxis group were a result of TMP-SMX–resistant *E coli* vs 19% in the placebo group, which is concerning given the rapid rise in antimicrobial resistance in recent years. Prophylaxis did not reduce the incidence of renal scarring [44]. The Swedish reflux trial, which enrolled 203 children with grade III or IV VUR, also found a significant decrease in the rate of rUTI among girls who received TMP-SMX prophylaxis and in those who underwent endoscopic treatment compared to those who underwent clinical observation [45]. However, the authors also reported that prophylaxis did not reduce the incidence of renal scarring, and antimicrobial resistance increased significantly in the treatment group. A recent meta-analysis of 7 studies with a total sample size of 1427 participants revealed no significant difference in renal scarring in the antibiotic prophylaxis and control groups [46]. It is important to note also that these studies focused on antibiotic prophylaxis in children with VUR and not children with a history of rUTI.

Conclusive data to support the use of prophylactic antibiotics, even in neonates with known antenatal hydronephrosis or children with neurogenic bladder, are lacking [47, 48]. Subinhibitory concentrations of certain antibiotics, such as ciprofloxacin and gentamicin, might in fact result paradoxically in upregulation of bacterial cell surface adhesins in common uropathogens such as *E coli* and *Staphylococcus saprophyticus*, which results in denser biofilm formation [49].

Nitrofurantoin, a drug with minimal systemic absorption, has been shown to have an efficacy similar to that of TMP-SMX in prophylaxis against rUTI [50]. However, the use of nitrofurantoin results in a risk of subsequent resistance that is significantly lower than that with the use of TMP-SMX. Adverse effects occurred more frequently in children treated with nitrofurantoin than in those treated with TMP-SMX but consisted predominantly of gastrointestinal symptoms. Therefore, in this era of rising antimicrobial resistance, it might be prudent to use nitrofurantoin as the prophylactic antibiotic of choice when necessary.

Probiotics

Given the rise in antimicrobial resistance and evidence of the adverse effects of long-term use of antibiotics on the commensal flora, probiotics such as *Lactobacillus* spp and the yeast *Saccharomyces boulardii* have garnered new interest as long-term therapy for rUTI. Probiotics are generally thought to exert their effect though the production of antimicrobial products [51, 52], competition with uropathogens for iron (which is essential for several bacterial functions) [53], and occupation of the epithelial space to prevent adherence of uropathogenic bacteria [54].

Over the past decade, several studies measured the effects on rUTI of probiotics with or without antibiotics. In 1 trial, 120 children with established VUR who had undergone TMP-SMX prophylaxis in the preceding year were randomly assigned to receive *Lactobacillus acidophilus* or to continue TMP-SMX prophylaxis during the second year of follow-up [55]. The rates of rUTI were similar between the 2 groups. In a follow-up trial, 128 infants diagnosed with primary VUR were randomly assigned to receive either the probiotic *Lactobacillus acidophilus* or TMP-SMX for 1 year [56]. The rates of rUTI in the probiotic and antibiotic prophylaxis groups were not statistically different. In a retrospective study of 191 infants with acute pyelonephritis and normal urinary tract anatomy, including no VUR, prophylaxis with *Lactobacillus* led to an 8.2% incidence rate of rUTI in the 6-month follow-up period, which was similar to the 10% rate in the antibiotic group and significantly lower than the 20.6% rate in the no-prophylaxis group [57]. All of the infants with rUTI in the antibiotic group were infected with a TMP-SMX–resistant strain of bacteria, compared to 25% in the probiotic group and 41% in the no-prophylaxis group, which further shows the negative consequences of chronic antibiotic prophylaxis.

S boulardii is a nonpathogenic yeast that is able to establish itself in the colon rapidly and has antagonistic activity against pathogens [58, 59]. In children, once-daily treatment with 5 billion CFU of *S boulardii* was effective in significantly decreasing the burden of gut colonization with *E coli* [60]. Because gut colonization with uropathogens increases the risk of rUTI, *S boulardii* might play a role in reducing recurrent episodes.

Cranberry Juice

Recent work found that cranberry extract prevents adhesion of UPEC to uroepithelial cells in a dose-dependent manner [61]. This effect is mediated by the following 2 main components of cranberry: fructose, which inhibits UPEC adherence by type 1 fimbriae, and anthocyanidins, which inhibit adherence by pyelonephritis fimbriae (p-fimbriae) [62].

Among clinical trials performed specifically in the pediatric population, cranberry products modestly reduced the incidence of rUTI in children with normal urinary anatomy. In a review of 8 trials that used cranberry juice or products for rUTI prophylaxis in healthy children or infants, only 4 trials found a significant reduction in the incidence of rUTI [63]. Most of these studies included <50 patients. However, 1 study enrolled 263 children between the ages of 1 and 16 years with normal urinary anatomy or grade I or II VUR [64]. The total number of UTI episodes per year was significantly lower in the cranberry group than in the placebo group, but the proportions of children who had >1 recurrence were the same. Most studies have concurred that cranberry juice and preparations are safe for use in all age groups [65]. Poor palatability of the cranberry products might have an adverse effect on compliance.

Authors of studies in adult patients have recommended a daily dose of 300 mL of cranberry juice to achieve a reduction in the incidence of rUTI [66]. A pediatric study that showed the effectiveness of cranberry juice used a dose of 5 mL of juice per kilogram of body weight, up to 300 mL, per day for a 6-month period [64].

Male Circumcision

Bacterial colonization in the foreskin (prepuce) has been associated with UTI in male infants less than 3 months of age [67]. Circumcision decreases the risk of UTI, especially among neonates [68]. A study of 2000 circumcised and 1000 uncircumcised neonates over a 15-month period reported no UTI episodes in the circumcised group, whereas 2% of those in the uncircumcised group experienced a UTI [69]. A 2012 American Association of Pediatrics policy statement also indicated that the health benefits of elective circumcision of male infants (reduction in the incidence of UTI and sexually transmitted disease) outweigh the associated risks [70].

Surgical Intervention

Surgery to correct VUR plays a significant role in preventing rUTI. The success rate for endoscopic surgery for VUR grades II, III, IV, and V ranges from 60% to 90% and depends on the

VUR grade and the absence of associated BBD [71]. The success rate for open neoureterocystostomy or ureteral reimplantation, the gold standards for surgical intervention, is 95% irrespective of VUR grade or BBD [72]. In addition, children with low-grade VUR (grades I–III) have an approximately 40% chance of spontaneous resolution within their first year of life [73].

FUTURE AND ONGOING RESEARCH

Vaccines

Two vaccines are available currently in Europe for use in treating rUTI, Solco-Urovac (Legacy Pharmaceuticals, Switzerland) and Uro-Vaxom (Om-pharma, Portugal). Solco-Urovac is a whole-cell inactivated vaccine used as a vaginal suppository that contains 6 *E coli* strains and 1 strain each of *Proteus mirabilis*, *Morganella morganii*, *Enterococcus faecalis*, and *Klebsiella pneumoniae* [74]. An intramuscular formulation of Solco-Urovac was used in a trial on 10 otherwise healthy girls (5–11 years of age) with rUTI [75]. These girls were vaccinated 3 times at weekly intervals and then received a booster 6 months later. The total number of UTI episodes among all the participants decreased from 34 in the 6 months before enrollment to 13 over the 1-year follow-up period. Uro-Vaxom is an oral capsule that contains a lyophilized mixture of membrane proteins from 18 UPEC isolates. In a randomized controlled trial in 112 women, participants were given either the vaccine or a daily placebo for 3 months and were followed for another 3 months [76]. By the end of the 6-month study period, 67% of the participants in the vaccine group had no episodes of rUTI, whereas this rate was 22% in the placebo group [76]. Uro-Vaxom is currently part of the European Association of Urology guidelines for alternative treatment of UTI in adults. Both these vaccines are not licensed for use in the United States.

Ideal strategies for vaccinating against rUTI would be to target bacterial factors involved in the establishment and maintenance of bladder colonization. Vaccines that target FimH, the type I pilus adhesin that plays a critical role in bacterial adhesion to urothelial cells, have shown some promise. In 1 study, the FimH antigen copurified with its chaperone protein, FimC, was used to vaccinate cynomolgus monkeys, which resulted in significant protection against infection with type I pili expressing UPEC [77]. This vaccine is being developed by Sequoia Sciences (St. Louis, Missouri) [78].

Small-Molecule Inhibitors of Pathogenic UPEC Factors

Several small-molecule inhibitors of pathogenic UPEC factors have been developed. They generally act to decrease bacterial virulence, which enables the host immune system to eradicate the bacteria. Mannose derivatives, called mannosides, inhibit the binding of FimH adhesin on type I pili to the mannosylated receptors on the uroepithelial cells by the formation of a FimH–oligomannose complex [79]. These molecules were found to be effective in the treatment of chronic infection in a murine model and had synergistic activity with conventional antibiotics such as TMP-SMX. Other small molecules in development target the chaperone–usher pathway (CUP) pili [80], which are ubiquitous among UPEC strains and play a major role in adhesion and in evasion of host immunity.

CONCLUSIONS

Pediatric rUTI continues to pose a significant challenge to medical providers and the healthcare system. Accurate diagnosis is vital for preventing the inappropriate use of antibiotics. BBD increases residual urine and urinary stasis, which allow for greater bacterial adherence and rUTI. Therapeutic management of rUTI traditionally has included the use of prophylactic antibiotics; however, there is strong evidence that this approach does not prevent renal scarring but does increase the risk of antibiotic resistance, which suggests that alternative strategies, including the use of probiotics and management of BBD, might be more prudent. With a better understanding of the etiology and pathogenesis of rUTI, researchers are investigating agents that can interfere with bacterial adhesion and intracellular growth.

Notes

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