

Advances in non-surgical treatments for urinary tract infections in children

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Abstract

Objective With growing antibiotics failure due to emerging resistance of bacteria, non-surgical management of pediatric UTI plays a more important role because of its non-invasive characteristics and little adverse effects.

Methods We searched the Pubmed for management of UTI in children other than surgical correction and antibiotics using terms: risk factor, prepuce/phimosis, steroid cream/steroid, behavioral therapy, urotherapy, biofeedback/pelvic floor exercise, adrenergic antagonist, anticholinergics, diet/dietary, dysfunctional voiding/dysfunctional elimination syndrome, constipation, dietary, clean intermittent catheterization, probiotics/lactobacillus, cranberry,

vitamin supplement, breastfeeding, breast milk, with infant/child/children/pediatrics/pediatrics and urinary tract infection.

Results The proposed non-surgical management of pediatric UTI included behavioral modification (timed voiding and adequate fluids intake), topical steroid for phimosis, nutrient supplements (breast milk, cranberry, probiotics, and vitamin A), biofeedback training for dysfunctional voiding, anticholinergics for reducing intravesical pressure, alpha-blockers in dysfunctional voiding and neurogenic bladder, and intermittent catheterization for children with large PVR.

Conclusion The published reports usually included small number of patients and were lacking of randomization and controlled group. Further well-designed studies are warranted to support the concepts of non-operative management for pediatric UTI.

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Introduction

The mainstay of treatment for acute phase urinary tract infections (UTI) in children lied in antibiotics treatment. However, up to 30% of children with UTI have recurrence of UTI after antibiotics treatment, with most episodes recurred within 6 months after first episodes [1]. Long-term chemo-prophylaxis with antibiotics resulted in growing antibiotics failure due to resistance. Therefore, non-surgical management of pediatric UTI plays a more important role because of its non-invasive characteristics and little adverse effects. As such, we did a review for non-operative management for UTI in children.

Methods

We performed a literature search in Pubmed from January 1990 to February 2011 using the terms risk factor, prepuce/phimosis, steroid cream/steroid, behavioral therapy, urotherapy, biofeedback/pelvic floor exercise, adrenergic antagonist, anticholinergics, diet/dietary, dysfunctional voiding/dysfunctional elimination syndrome, constipation, dietary, clean intermittent catheterization, probiotics/lactobacillus, cranberry, vitamin supplement, breastfeeding, breast milk, with infant/child/children/pediatrics/pediatrics and urinary tract infection. Studies included in the review were limited to human trials published in English. The major end point of this review was the episodes of UTI development and recurrence in children. The improvements in voiding parameters such as decreased voiding pressure and decreased post-void residual urine were the surrogate end point of the review. With little randomized controlled trial performed, evidence from RCTs was given precedence.

Results of literature searching

The literature search identified relevant references published in Pubmed. Finally, two Cochrane Database Systemic Review, five randomized controlled trial, and three randomized crossover study were listed in Table 1. The remaining studies included were non-randomized case controlled study, and mostly were uncontrolled case series. A meta-analysis of the studies was not performed due to the heterogeneity of the trials and the diversity of the dosage and methods applied.

Topical steroids for phimosis

In boys, physiologic phimosis is an important factor either in the development or recurrence of UTI [2]. Children with non-retractile prepuce had significantly higher rate of recurrent UTI than those with retractile prepuce [3]. Neonatal circumcision had been confirmed to be effective in reducing the risk of UTI [4]. There was a reduction of 90% UTI in circumcised boys when compared with uncircumcised boys. However, complications including hemorrhage and infection occurred in 2% of patients underwent circumcision. One meta-analysis suggested clinical benefit of circumcision is likely only in boys at high risk of UTI [4].

Jorgensen and Svensson [5] first introduced the topical application of steroid treating phimosis; several authors subsequently reported success rates ranging from 67 to 95%, and little adverse effects. The fear that topical steroids would affect the cortisol level in the children was not observed [6] and may be prevented by moderately potent topical steroids with equal efficacy to highly potent steroids

[7]. In a small scale, prospective, randomized study by Lee et al. topical use of hydrocortisone twice daily on non-retractile prepuce for 2–4 weeks reduced the rate of recurrent UTI in the following year in infants with UTI (7.1% in the treatment group vs. 29.6% in the control group) [8]. Further studies evaluating neonatal application of steroid on foreskin to reduce the risk of UTI in healthy infants are warranted. The major shortcomings of topical steroids lied in children with pathological phimosis, thick scarred prepuce, or severe balanoposthitis are less beneficial, and circumcision should be considered in these patients [9].

Behavioral modification

Clinically, we usually encourage children with UTI and poor fluid intake to have more fluid, although relevant studies remain scarce. It is assumed that more fluid intake may result in shorter stasis time of urine in the bladder and better-wash out of bacteria in the bladder. Infrequent voiding, poor fluid intake, functional stool constipation, and dysfunctional voiding were more frequently disclosed in girls with recurrent UTI than in control girls [10, 11]. When managing children with UTI, frequency/volume chart may help physicians and parents monitor the voiding frequency and fluids intake in these children.

Increased post-void residual urine (PVR) has long linked to the development and recurrence of UTI [12]. Infrequent voiding may result in longer time of bacteria multiplication in the bladder and increased PVR that was frequently observed in urinary bladder over-distension. Bladder over-distension is defined as bladder capacity (voided volume + PVR) larger than 115% expected bladder capacity. At a bladder capacity reaching over-distension, more than one-third of micturition resulted in abnormal uroflow pattern and PVR >20 ml [13]. Timed voiding schedule is advised in infrequent voiders to decrease the urinary stasis time and to avoid bladder over-distension. However, optimal amounts of fluids intake are not known.

Besides, good toilet postures also play a role, which enables optimal relaxation of the pelvic floor muscle and hence reduces dysfunctional voiding and PVR. In postures with adequate bilateral foot support, the relaxation was observed in 94% recorded from the pelvic floor muscles. EMG amplitudes from the pelvic floor and adductor muscles were significantly higher in postures with unsupported legs compared with postures with supported legs [14].

Early toilet training

Voiding dysfunction with incomplete bladder emptying is deemed as an important risk factor for development and

Table 1 Summary of randomized controlled trials, randomized crossover trials and Cochrane Reviews

References	Intervention	Subjects and design	Findings and significance
Ferrara et al. [47]	Cranberry Probiotics Control	Prospective randomized controlled trial Inclusion criteria: UTI due to <i>E. coli</i>	Concentrated cranberry juice can significantly prevent the recurrence of symptomatic UTIs in girls
Yilmaz et al. [55]	200,000 IU vitamin A in addition to antibiotics	Prospective randomized controlled study	Vitamin A-supplemented group reduced from 3.58 to 0.75 per 6 months, and in the subsequent 6 months, the infection rate was 1.75 per 6 months
Lee et al. [51]	Probiotics <i>Lactobacillus acidophilus</i> 10(8) CFU/g 1 g b.i.d. versus antibiotics prophylaxis	Prospective randomized controlled study	The incidence of recurrent UTI did not differ significantly between the two groups ($P > 0.05$). The development of new renal scar was not significantly different between the two groups ($P > 0.05$)
Lee et al. [8]	Topical steroid + physiotherapy versus vaseline	Prospective randomized controlled study	The recurrent rate of UTI was 7.1% (2/28) in the infants with retractile prepuces, which was significantly less than the rate (29.6%; 8/27) in infants with non-retractile prepuces ($P < 0.05$)
Dani et al. [50]	Seven days of <i>Lactobacillus GG</i> versus placebo	A multicenter prospective, randomized-controlled study	Seven days of <i>Lactobacillus GG</i> supplementation starting with the first feed is not effective in reducing the incidence of UTIs, NEC, and sepsis in preterm infants
Schlager et al. [59]	New sterile catheter for intermittent catheterization and reuse of a clean catheter for intermittent catheterization	A prospective, randomized, crossover trial	A new, sterile catheter for each void did not decrease the high frequency of bacteriuria in patients with neurogenic bladder on intermittent catheterization
Schlager et al. [45]	Cranberry versus placebo	Double-blind, placebo-controlled, crossover study	Cranberry concentrate had no effect on bacteriuria in children underwent CIC
Foda et al. [46]	Cranberry juice versus water	Randomized single-blind cross-over study	Liquid cranberry product, on a daily basis, at the dosage employed, did not have any effect greater than that of water in preventing UTI in this pediatric neuropathic bladder population
Jepson et al. [43]	Cranberries for preventing urinary tract infections	Cochrane review	There is some evidence that cranberry juice may decrease the number of symptomatic UTIs over a 12-month period, particularly for women with recurrent UTIs. Its effectiveness for other groups is less certain
Moore et al. [29]	Long-term bladder management by intermittent catheterization in adults and children	Cochrane review	Intermittent catheterization is a critical aspect of healthcare for individuals with incomplete emptying who are otherwise unable to void adequately to protect bladder and renal health. There is a lack of evidence to state that incidence of UTI is affected by use of sterile or clean technique, coated or uncoated catheters, single (sterile) or multiple use (clean) catheters, self-catheterization or catheterization by others, or by any other strategy

recurrence of UTI in children [15]. Hellstrom et al. [16] had empirically suggested early initiation of toilet training (TT) in children at risk of developing UTI because children had less bladder sphincter dyssynergia and less post-void residual urine after toilet training [17, 18]. A longitudinal study from Vietnam found that children who were potty trained very early, the dyscoordination between bladder and sphincter disappeared at age of 9 months [16]. A cross-sectional study disclosed that rate of abnormal voiding function was comparable between TT before and after 18 months of age [19]. Late toilet training may result in

higher rates of lower urinary tract symptoms. A cohort study in the UK showed that initiating toilet training after 24 months was associated with problems attaining and maintaining bladder control [20]. However, there is a lack of prospective randomized studies to confirm the efficacy of early TT in reducing episode of recurrent UTIs.

Biofeedback relaxation of pelvic floor

Children with increased sphincteric activity during detrusor contraction, i.e., dysfunctional voiding, have a higher rate

of UTI recurrence [21, 22]. Biofeedback relaxation of pelvic floor is helpful in improving voiding symptoms and urodynamic parameters in children with dysfunctional voiding [23]. In a study of girls with recurrent UTI underwent a training program including voiding and drinking schedule, pelvic floor relaxation biofeedback, instructions on toilet behavior, and biofeedback uroflowmetry, the program was effective in preventing recurrence of UTI in 35 of 42 (83%) children [24]. In a prospective, randomized study comparing pelvic floor exercise and biofeedback therapy in treating children with dysfunctional elimination syndrome, both groups of patients showed low rate of relapsed UTI (3.8% and 10%). Children received biofeedback therapy had significantly reduced PVR. Children with voiding dysfunction and vesicoureteral reflux usually have a high breakthrough infection rate of 34–43% [25]. Of 37 children with previous history of UTI, VUR and non-neurogenic voiding dysfunction underwent biofeedback training program only 19% had breakthrough UTI during a mean follow-up of 21 months [26]. Similarly, breakthrough infection was reduced to 10% after combined conservative medical and computer game assisted pelvic floor muscle retraining program in a mean follow-up period of 24 months [27].

Clean intermittent catheterization for large PVR

Since the first introduction of clean intermittent catheterization (CIC) by Lapidus et al. [28], CIC has gained wide acceptance in treating neurogenic bladder to improve emptying of the bladder, achieve continence, prevent upper tract damage, and avoid symptomatic UTI. During the catheterization procedure, some bacteria may be introduced into the bladder, and therefore, the most common complication of CIC is UTI. A long-term follow-up study of 14 children underwent CIC, 70% out of urine samples were positive for bacteremia, but only five symptomatic UTIs were observed during the 323 patient-weeks. Therefore, the author concluded that CIC may cause asymptomatic pyuria while reduced the possibility of febrile UTI in children with neurogenic bladder [28]. The factors affecting UTI were catheterization frequency and the avoidance of bladder overfilling. The compliance of CIC was good. In a 5-years follow-up in 86 children with congenital neurogenic bladder, only 4 (4.6%) discontinued the CIC program because of discomfort associated with introducing the catheter. A recent Cochrane review [29] concluded that there is a lack of evidence to state that incidence of UTI is affected by use of sterile or clean technique, coated or uncoated catheters, single or multiple use catheters, self-catheterization or catheterization by others, or by any other strategy.

Intensive bowel regimen for constipation

Constipation is a common problem among children with prevalence rate ranging from 0.7 to 29.6% [30]. Rome III criteria defined that children with more than two of the following symptoms were diagnosed to have functional constipation: (1) ≤ 2 defecation per week, (2) ≥ 1 fecal incontinence/week, (3) history of retentive posturing or stool retention, (4) painful or hard bowel movements, (5) large fecal mass in the rectum, and (6) large stool obstructing the toilet [31]. It is postulated that chronic retention of fecal mass above anal verge makes children maintain a high anal sphincter tone. The high anal tone leads to pelvic floor activity and impairs emptying function of bladder and elevated PVR which is an important factor in developing UTI [32]. Another theory is that constipation may increase the uropathogenic organism in the gastrointestinal tract and then leads to more UTI [33]. Previous studies have documented correlation between constipation and UTI. Romanczuk et al. [34] evaluated 180 children suffering from recurrent UTIs and found that treatment of chronic constipation may reduce pyuria, bacteremia, and enuresis among these children. In a study of 234 children treated for chronic constipation, relief of constipation was obtained in 52% of patients without urinary tract anomaly and resulted in disappearance of UTI [35]. Koff et al. [22] evaluated 143 children with primary vesicoureteral reflux and UTI, 66 had dysfunctional elimination syndrome in which 50% had constipation as the most prominent symptom. Of 66 with dysfunctional elimination syndrome, 82% needed surgical reimplantation, while only 18% had spontaneous resolution of reflux. Therefore, the importance of managing constipation and voiding dysfunction concurrently can not be overemphasized. Except by history from parents, Bristol stool form scale had been shown to be appreciated by children. In children with recurrent UTI and constipation, we should have them a bowel movement diary and a frequency/volume chart. Then, physicians and/or parents can monitor the condition from the children and supervise them. Treatment of constipation includes osmotic laxatives, stimulant laxatives, increasing fluids intake, biofeedback, and psychological intervention; all are effective in the management of constipation [36].

Nutrients supplement

Breast milk

The protective role of breast milk may be attributed to the specific contents within the breast milk, including immunoglobulin A [37], antiadhesive oligosaccharide [38], and lactoferrin [37]. The antibacterial effect and selection of low uropathogenic bacteria play the role. Marid et al.

observed that shorter duration of breastfeeding was associated with higher risk of UTI in children [39]. Recently, the same group concluded that ongoing breastfeeding and a longer duration of breastfeeding resulted in a lower risk of infection after weaning, especially in girls [40]. The protective role of breastfeeding was strongest directly after birth; then, it decreased after 7 months of age. Recently, a case–control study enrolled 6198 premature infants and showed that breast milk is associated with lower risk of getting UTIs (OR = 0.314, 95% CI 0.140–0.707) [41]. In addition to UTI, breast feeding also reduced the risk of acute respiratory infections, acute otitis media, and thrush in the first 6 months of life [42]. Since breast feeding has many benefits and bears no risk, we strongly recommended breastfeeding to prevent recurrence of UTI in children with one episode of UTI.

Cranberry

From a meta-analysis by Jepson and Craig, there is some evidence supporting the use of cranberry in reduction of UTI episodes among women with recurrent UTI, while there is scarce randomized trial evaluating the effectiveness of cranberry in children [43]. The evidence of the role of cranberry in prevention of UTI in children was still inconclusive, although cranberry juice consumption provides significant anti-adherence activity against different *E. coli* uropathogenic strains in the urine compared with placebo [44]. Schlager et al. conducted a double-blind, placebo-controlled, crossover study to determine the effect of cranberry juice on pyuria and symptomatic UTI in children with neurogenic bladder needing clean intermittent catheterization [45]. They found that cranberry concentrate had no effect on bacteriuria in the study population, although this may be partly due to host susceptibility to infection. Foda et al. conducted a randomized single-blind cross-over study to compare cranberry juice and water, and no difference in infection of the intervention periods was observed [46]. Ferrata et al. enrolled 84 girls with *E. coli* urinary tract infections [47]. They were randomized to receive cranberry, lactobacillus, and control group. Girls who received daily cranberry juices had less recurrence rate of UTIs. Another study showed that cranberry juice had comparable effects with cofactor in preventing UTIs in children with vesico-ureteral reflux [48]. Studies mentioned above only enrolled small number of children; more studies are required to elucidate the role of cranberry in prevention of pediatric UTI.

Probiotics

The term probiotics is defined as “live microorganisms which when administered in adequate amounts confer a

health benefit on the host” [49]. The concept of probiotics developed from normal flora that existed in the gastrointestinal tract and genital area. The introduction of probiotics in the prevention of recurrent UTI was largely due to antibiotics failure and increased evidence of the efficacy of probiotics [49]. However, controversy exists over the efficacy of probiotics in prevention of pediatric UTI. Dani et al. [50] administered *Lactobacillus GG* in neonates with UTI, sepsis, and necrotizing enterocolitis; no significant effect of *Lactobacillus GG* in reduction of UTI was noted. A prospective, randomized controlled study compared the conventional antibiotics and probiotics in treating children with primary VUR; the incidence of recurrent UTI was comparable in both groups of children [51]. Long-term effects of probiotics in children need further evaluation. Also, which strains of lactobacillus are more helpful in preventing pediatric UTI needs further elucidation. Despite the possible clinical effects of probiotics on UTI in children, 2 cases with bacteremia of lactobacilli were reported [52].

Vitamin A

Vitamin A has an anti-inflammatory property and reduces the damage to the kidney after glomerulonephritis in animal model [53]. Ayazi et al. [54] found that children with pyelonephritis had lower rate of renal scar if adjuvant intramuscular vitamin A was given (20 vs. 68%, $P = 0.0001$) in addition to antibiotics. Yilmaz et al. [55] randomized children with UTI to receive intravenous antibiotics with and without supplements of 200,000 IU Vitamin A. In children with supplements of Vitamin A, the recurrence rate of UTI during 1-year follow-up was greatly reduced. However, the number of enrolled patients was small (12 patients for each group), and the follow-up period was short. The efficacy of long-term effects of vitamin A on preventing urinary tract infections in children needed further clarifications.

Acidification of urine

Prevention recurrent UTI with acidification of urine using methionine, methenamine hippurate, and vitamin C was seldom studied in children, and therefore, we did not discuss in our context.

Medications other than antibiotics

Alpha-blockers

Several studies had shown the effectiveness of alpha-blocker to improve voiding dysfunction and reduce PVR.

However, none of these studies correlated the alpha-blockers to reduction of UTI. In children with dysfunctional voiding or neurogenic bladder, alpha-blockers may relieve bladder outlet obstruction and improve urodynamic parameters such as uroflow rate and post-void residual urine. Yang et al. evaluated the effectiveness of doxazosin in 16 boys with low flow rate and urinary incontinence. The symptoms and flow rate improved in half of the children after medical treatment, although no placebo control group was compared [56]. In a randomized, double-blind, placebo-controlled study, doxazosin did not demonstrate a significant objective benefit (including incontinent episodes, voiding parameters, and PVR), but produced a significant subjective benefit in the treatment of urinary incontinence secondary to voiding dysfunction [57]. Yucel et al. [58] conducted a small scale, prospective, open-label, randomized study to compare the efficacy of biofeedback therapy and alpha-blockers for children with dysfunctional voiding and urinary tract infection. The peak flow rates, PVR, and urge incontinence improved in both groups without statistical difference while these patients also received behavioral therapy, anticholinergics, and antibiotics prophylaxis. There existed no long-term effects of alpha-blocker on pediatric dysfunctional voiding and UTI; further evaluation should be warranted.

Conclusions

Despite clinical importance of urinary tract infection in children, there is a lack of large scale, well designed, and randomized controlled trials on the topics about non-operative management. Although some dietary supplements were proved to be effective in adult, more works on children are warranted. Besides, further studies on the impact of early toilet training for pre-toilet-trained children, life-style modification, and the optimal fluids intake on pediatric UTI should be performed.

Conflict of interest All the authors had nothing to disclose and no conflict of interest.

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