

## Recurrent urinary tract infections in children: Preventive interventions other than prophylactic antibiotics

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### Abstract

Urinary tract infection (UTI) is one of the most common

childhood infections. Permanent renal cortical scarring may occur in affected children, especially with recurrent UTIs, leading to long-term complications such as hypertension and chronic renal failure. To prevent such damage, several interventions to prevent UTI recurrences have been tried. The most established and accepted prevention at present is low dose long-term antibiotic prophylaxis. However it has a risk of break through infections, adverse drug reactions and also the risk of developing antibiotic resistance. The search is therefore on-going to find a safer, effective and acceptable alternative. A recent meta-analysis did not support routine circumcision for normal boys with no risk factors. Vaccinium Macrocarpon (cranberry), commonly used against UTI in adult women, is also effective in reducing the number of recurrences and related antimicrobial use in children. Sodium pentosanpolysulfate, which prevents bacterial adherence to the uroepithelial cells in animal models, has shown conflicting results in human trials. When combined with antibiotic, *Lactobacillus acidophilus* (LA-5) and *Bifidobacterium*, by blocking the *in vitro* attachment of uropathogenic bacteria to uroepithelial cells, significantly reduce in the incidence of febrile UTIs. Deliberate colonization of the human urinary tract of patients with recurrent UTI with *Escherichia-coli* (*E. coli*) 83972 has resulted in subjective benefit and less UTI requiring treatment. The non-pathogenic *E. coli* isolate NU14 Deltawaal is a candidate to develop live-attenuated vaccine for the treatment and prevention of acute and recurrent UTI. Diagnosing and treating dysfunctional elimination syndromes decrease the incidence of recurrent UTI. A meta-analysis found the lack of robust prospective randomized controlled trials limited the strength of the established guidelines for surgical management of vesicoureteral reflux. In conclusion, several interventions, other than antibiotic prophylaxis, for the prevention of recurrent UTI have been tried and, although showing some promise, they do not provide so far a definitive effective answer. Finding suitable alternatives still requires further high quality research of those seemingly promising interventions.

**Key words:** Kidney; Recurrence/prevention; Urinary tract infections; Vesico-ureteral reflux; Vaccinium macrocarpon; Circumcision; Vaccination; Constipation; Lactobacillus

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**Core tip:** Antibiotic prophylaxis against urinary tract infection recurrences is associated with adverse drug reaction and development of resistance. Although showing some promise, alternative interventions, such as Vaccinium Macrocarpon (cranberry), *Lactobacillus* and Probiotics, circumcision, surgical management of vesicoureteral reflux, deliberate colonization of the urinary tract with *Escherichia-coli* (*E. coli*) 83972, treating constipation and dysfunctional voiding, administration of synthetic substitutes that reproduce natural surface glycosaminoglycan(s) anti-adherence effect on uroepithelial cells and *E. coli* isolate NU14 Deltawaal as a candidate for developing a live-attenuated vaccine, do not provide so far a definitive effective answer. Further high quality research is still required.

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## INTRODUCTION

Urinary tract Infection (UTI) is one of the most common childhood infections<sup>[1,2]</sup>, affecting round 1.7% of boys and 8.4% of girls by the age of seven years<sup>[3]</sup>. A third to one half of affected children will suffer from at least one recurrence<sup>[4]</sup>. While in infancy this infection is mostly secondary to hematogenous dissemination, it usually occurs as an ascending infection in older children, where the common organism involved include Gram negative bacteria such as *Escherichia-coli* (*E. coli*), *Klebsiella*, *Proteus*, *Enterobacter*, *Pseudomonas* and *Serratia* species<sup>[5]</sup>. Permanent renal cortical scarring may occur in 15%-65% of affected children<sup>[4]</sup>, especially in recurrent UTI and its long-term complications include hypertension and chronic renal failure which may result in end stage renal disease<sup>[6]</sup>. Contrary to previous beliefs, acquired renal scarring correlates best with recurrent UTI rather than the presence of vesicoureteral reflux (VUR). In a bid to prevent long-term damage with recurrent UTI several interventions have been tried, aiming at one or more of the factors that facilitate the development of UTI.

These factors include: (1) microbial growth in the urogenital tract; (2) foreskin facilitating peri-meatal bacterial growth; (3) bacterial adhesion to the uroepithelial cells; (4) bioflora favoring pathogenic urobacteria; (5) insufficient urothelial cytokine secretion; (6) urinary

stasis; and (7) vesicoureteral reflux. The interventions considered included therefore: (1) long term antibiotic prophylaxis; (2) circumcision in male children; (3) cranberry and glycosaminoglycans; (4) lactobacillus and probiotics products; (5) vaccination; (6) management of dysfunctional elimination syndrome; and (7) vesico-ureteral reimplantation<sup>[4]</sup>.

## PREVENTIVE INTERVENTIONS

### Antibiotic prophylaxis

This is currently the most established and accepted prevention of UTI recurrences at present<sup>[7]</sup>. However, this policy is of limited efficacy with little or no clinical benefit at all in various trials<sup>[8-10]</sup>. Although compliance to treatment is reported to be 91%, only 31% of children have antibiotic metabolites identified in the urine<sup>[11]</sup>. Furthermore, the risk of break through infections is estimated to be between 25% and 38%<sup>[12,13]</sup>. Antibiotic usage is not without risk. Approximately 10% of children on long-term antibiotic therapy develop adverse reactions that range from common gastrointestinal symptoms to bone-marrow suppression and rarely Stevens Johnson Syndrome<sup>[14,15]</sup>. Also worrisome is the growing evidence of antibiotic resistance developing with excessive use of long-term antibiotics<sup>[16]</sup>.

Considering all those concerns with antibiotic prophylaxis, there is a growing need to re-evaluate the other suggested alternative interventions to prevent UTI recurrences. We look at the currently available evidence behind these alternative interventions.

### Circumcision

Although for a long time the absolute indications for circumcision have been phimosis secondary to xerotica obliterans and recurrent balanoposthitis, prevention of UTI in boys has been added after a brief report that showed that the foreskin was a risk factor for UTI in male infants<sup>[17]</sup>. Several studies have since supported the benefits of neonatal circumcision, especially as the complication rate was found to be only 1.6%, consisting mainly of haemorrhage, inappropriate penile appearance, ring impaction or stenosis<sup>[18]</sup>. When compared to 3000 uncircumcised newborns where the rate of UTI is 2%, no UTI was found in any of the other 3000 circumcised neonates up to 15 mo after the procedure<sup>[18]</sup>. Circumcision significantly reduced the incidence of UTI in male children by 90%<sup>[19,20]</sup>, however it is limited to one particular group of sex, and the incidence of UTI in boys is only 1% of total UTI population. With previous studies suggesting that uropathogen's attachment to the foreskin, by providing an environment for bacterial colonisation, made the foreskin a risk factor for UTI, a study was conducted on children with low grade VUR and showed that, when compared to antibiotic prophylaxis alone, circumcision associated with antibiotic prophylaxis resulted in a significant decrease in bacterial colonisation rate<sup>[21]</sup>. In a cohort of infants with antenatal hydronephrosis, circumcision

provided a significant reduction in the frequency of UTI frequency when comparing the periods before and after circumcision<sup>[22]</sup>.

The support for neonatal circumcision to prevent recurrent UTI is still being challenged. In a study of ritually circumcised Jewish male neonates, there was a high prevalence of UTI, suggesting that the procedure puts the infants at an increased risk of UTI<sup>[23]</sup>. It has been suggested that the differences in UTI incidence between circumcised and non-circumcised boys is not due to the procedure, but could instead be attributed to several confounding factors such as prematurity, low birth weight, perinatal anoxia, lack of breast feeding, poor hygienic practices, low parental education, prenatal maternal UTI, history of a UTI in a first degree relative, history of fever in the mother at the time of delivery, previous infections, previous course of antibiotics, method of urine collection, and diagnostic standards used<sup>[24]</sup>. Furthermore, no effect on the incidence of postoperative UTI was found with circumcision performed during anti-reflux surgery<sup>[25]</sup>.

To clear the confusion, a meta-analysis of 12 studies on circumcision and UTI prevention was conducted and, although the procedure seemed to be more beneficial to boys with recurrent UTI (only 11 needed to prevent 1 UTI) and boys with grade III or more VUR (four needed to prevent one UTI), it was calculated that overall, 111 circumcisions would be required to prevent one UTI, costing £55000 in the United Kingdom. The study concluded that a decision to carry out routine circumcision for normal boys with no risk factors was not supported by that meta-analysis<sup>[26]</sup>. In addition, although, in its policy on circumcision in 1989, the American of Paediatrics concluded that newborn circumcision decreased the rate of UTI from 1% to 0.1%, it modified the guideline in 1999 stating that routine circumcision was not necessary in all newborns<sup>[27]</sup>.

#### **Preventing bacterial adhesion to the uroepithelial cells**

**Vaccinium macrocarpon (Cranberry):** *Vaccinium macrocarpon*, also called large cranberry, American cranberry and bearberry, is a cranberry of the subgenus *Oxycoccus* and genus *Vaccinium*. It is one of the most commonly used and acceptable preventive agent against UTI in adult women, and has also been tried in pediatric age groups where it was associated with a much better compliance than oral antibiotics and without significant side effects<sup>[15,28]</sup>.

The mechanism of action of cranberry resides in the action of proanthocyanidine it contains on mannose-resistant P-fimbriated *E. coli*, strains that cause cystitis and pyelonephritis<sup>[29]</sup>. The proanthocyanidine containing "A" type linkage prevents the adhesion of proteinaceous fibres or fimbriae [heteropolymeric fibers carrying a Gal (alpha 1-4) Gal-specific PapG adhesin at its distal end and located on the bacterial cell] to the specific carbohydrate receptors on uro-epithelial cells<sup>[30-32]</sup>. This effect occurs at a concentration as low as 75 µg/mL<sup>[33]</sup>.

Data on the effectiveness of cranberry in the preven-

tion of UTI in adults is encouraging but still incomplete. In premenopausal women, while cranberry juice did not significantly reduce UTI risk compared with placebo, the reduction in urinary P-fimbriated *E. coli* strains supported the biological plausibility of its activity<sup>[34]</sup>. In renal transplant patients, a combination of cranberry juice and L-methionine reduces by more than 50% the incidence of UTI and also decreases the prevalence of symptomatic pyuric patients<sup>[35]</sup>. A Cochrane review of 10 good quality randomised controlled trials in over 1000 women suggests that cranberry juice decreases the number of symptomatic UTIs over a 12-mo period<sup>[36]</sup>.

The evidence of efficacy is still less clear in children. Some studies have shown promising results in paediatric UTI prevention<sup>[37]</sup>. However, in a double-blind randomized placebo-controlled trial involving 255 children, while cranberry juice did not significantly reduce the number of children who experienced a recurrence of UTI, it was effective in reducing the actual number of recurrences and related antimicrobial use<sup>[38]</sup>. A recent Cochrane review showed that while cranberry juice decreases the number of symptomatic UTIs in women, there is still lack of such evidence in children<sup>[36]</sup>. It is also likely that its acidic nature reduces its palatability in children<sup>[36]</sup>.

#### **Glycosaminoglycans and sodium pentosanpolysulfate:**

The transitional epithelial cells at the surface of the urinary bladder secrete and bind to their surfaces one or more glycosaminoglycans that markedly reduce the ability of microorganisms to adhere to the mucosa, a prerequisite to cause a UTI<sup>[39]</sup>. Comparing the prevalence of UTI in intact mucin deficient rabbit bladders with those treated with sodium pentosanpolysulfate (PSP, a similar but synthetic substitute for the surface glycosaminoglycan), UTI were more frequent in mucin deficient bladders after exposure to bacteria. This suggests that the natural surface glycosaminoglycan(s) and the synthetic substitutes that reproduce their antiadherence effect appear to be protecting factors<sup>[40]</sup>. In human trials, the results have been conflicting. While no significant effect of sodium PSP was found compared to placebo in patients with interstitial cystitis and painful bladder disease<sup>[41]</sup>, another study in patients with interstitial cystitis has shown a significant benefit from treatment with sodium PSP<sup>[42]</sup>. So far, no studies on its role in preventing UTI in children have been performed.

#### **Bioflora modification**

These alternatives are based on two mechanisms: Competitive exclusion and bacterial interference.

#### **Competitive exclusion-lactobacillus and probiotics:**

The interest in studying probiotics for the prevention of UTI started after an animal study where the injection of five strains of periurethral uropathogenic organisms into the urinary bladder of female rats and then instilling an isolate of *Lactobacilli casei* GR1 from the urethra of a healthy woman resulted in decreased the development

of UTI by 84% up to 60 d later<sup>[43]</sup>. This experiment was underpinned by the concept of competitive exclusion as indigenous bacteria block the *in vitro* attachment of uropathogenic bacteria to human uroepithelial cells.

Women with recurrent UTI are believed to have pre-existing alterations in their normal vaginal microflora resulting in depletion of hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>) containing Lactobacilli which are protective against infections. Restoration of normal vaginal microflora through the use of (H<sub>2</sub>O<sub>2</sub>) containing lactobacillus probiotic has been investigated to test the hypothesis that it confers a protective effect against recurrent UTI in women. Intravaginal administration of Lactobacilli Crispatus suppository was established to be safe<sup>[44]</sup>. Vaginal suppositories of *Lactobacillus Crispatus* reduced by 50% the incidence of UTI in 50 pre-menopausal women<sup>[45]</sup>. Oral probiotic yogurt, prepared from inoculating of *Lactobacillus acidophilus* (LA-5) and *Bifidobacterium* in heated milk, combined with antibiotic, was compared to antibiotic prophylaxis alone for prevention of UTI and it resulted in a significant reduction in the incidence of febrile UTIs in the third year of administration (although there was no difference in the first two years)<sup>[46]</sup>. Several studies challenged the benefit of *Lactobacillus*: it did not provide significant prevention of UTI in sick neonates in a neonatal intensive care unit<sup>[47]</sup>. And, when compared to *Vaccinium Macroponam*, it was not more effective in preventing UTI<sup>[48]</sup>.

**Bacterial interference:** Animal studies showing the interference of *E. coli* with the growth of *Pseudomonas aeruginosa* in the bladder of male Wistar rats<sup>[49]</sup> raised the theory of bacterial interference as a therapeutic option. This was supported by the finding that asymptomatic bacteriuria, especially with *E. coli* 83972 (associated with symptom-free colonizations for long periods of time) protects against recurrent UTI. This observation has prompted clinical trials with deliberate colonization of the human urinary tract of patients with recurrent UTI which has resulted in a subjective benefit and in less UTI requiring treatment in colonized patients<sup>[50]</sup>. Similarly, UTI commonly occurs in patients with spinal cord injury as their bladder, particularly in the presence of an indwelling bladder catheter, can become colonized by a variety of organisms, including benign colonizing bacteria which are often left untreated because they may provide some protection against symptomatic infection with more pathogenic microbes. As a result, intentional colonisation of the neurogenic bladder in patients with spinal cord injury with a non-pathogenic strain of *E. coli* such as *E. coli* 83972<sup>[51-53]</sup> or *E. coli* HU21117<sup>[54]</sup> was attempted and was shown to reduce the risk of symptomatic UTI with pathogenic *E. coli* in these patients and was safe.

### Vaccination

As deletion of the O antigen ligase gene, waaL, from

the uropathogenic *E. coli* isolate NU14 results in a strain that stimulates urothelial cytokine secretion, NU14 DeltawaaL was tested as a vaccine for UTI in mice *via* instillation into the bladder as was shown to protect mice against challenge with a broad range of clinical uropathogenic *E. coli* isolates and produced immunity that lasted 8 wk. It is therefore a candidate live-attenuated vaccine for the treatment and prevention of acute and recurrent UTI by caused by uropathogenic *E. coli*<sup>[55,56]</sup>. Human trials have not been performed so far.

### Voiding habits

Non-neurogenic neurogenic bladder, first described in 1986<sup>[57]</sup>, is a disorder of functional bladder obstruction causing urinary retention and altered bladder anatomy that may lead to upper urinary tract dilatation and scarring<sup>[58]</sup>. Dysfunctional elimination syndromes are functional bowel and/or bladder disorders, including bladder instability, inability to effectively empty the bladder, infrequent voiding enuresis, UTI, incontinence, constipation or other voiding symptoms. They are common and often unrecognized in children with primary VUR<sup>[59]</sup>. Girls with recurrent UTI are more likely to have a high degree of dysfunctional elimination<sup>[60]</sup>. These syndromes are associated with delayed VUR resolution and an increased rate of breakthrough urinary tract infection, which may require ureteral reimplantation surgery<sup>[59]</sup>. These problems are not only important during childhood, but they may also have a negative impact on bladder and bowel function later life<sup>[61]</sup>. Objective assessment of symptoms severity, is required for screening and diagnosis purposes, confirmation of treatment results and follow up. It might also be useful for screening purposes<sup>[62]</sup>.

Diagnosing and treating constipation as well as dysfunctional voiding are required to treat this condition<sup>[63]</sup>. Correcting constipation has been shown to decrease in the incidence of recurrent UTI<sup>[64]</sup>. In children with dysfunctional elimination, treating constipation with polyethylene glycol 3350 is successful, lacks significant side effects and is associated with good compliance and persistent constipation is associated with decreased resolution of voiding symptoms<sup>[65]</sup>. Biofeedback is an effective, non-invasive method of treating dysfunctional elimination syndrome with 80% success rate<sup>[66]</sup>. Children-directed biofeedback is also promising<sup>[67]</sup> and animated biofeedback, with pelvic floor muscle exercises, coordination of breathing and pelvic floor muscle contractions has been shown to be beneficial in improving dysfunctional elimination<sup>[68]</sup>. Sacral neuromodulation has been suggested for children with dysfunctional elimination syndrome whose symptoms are refractory to maximum medical therapy but should be cautiously used as it carries a significant risk of complications<sup>[69]</sup>.

### Ureteral re-implantation

The role of surgical treatment of VUR in the prevention

of UTI recurrences is well documented. Ureteral reimplantation in 205 infants (180 boys and 25 girls) with primary VUR reduced the frequency of febrile UTI reduced from 0.23538 before surgery to 0.00894 and 0.00081 per patient per month at six and 12 mo after surgery respectively, with no development of renal scarring on DMSA scan<sup>[70]</sup>. Several studies on a large number of children have shown absence of significant difference in renal growth between surgical ureteral re-implantation and medically treated children with primary VUR, both in previously scarred and in normal kidneys up to 10 years later, and, although pyelonephritis occurred significantly less often in surgically treated children, there was no significant difference in glomerular filtration rate nor in the development of hypertension<sup>[71-73]</sup>. A systematic meta-analysis was carried out by the Vesicoureteral Reflux Guideline Update Committee of the American Urological Association established to update the management of primary vesicoureteral reflux in children. A total of 2028 articles were reviewed, data were extracted from 131 articles including a total of 17972 patients. Guidelines for managing vesicoureteral reflux in children were issued but the lack of robust prospective randomized controlled trials limited the strength of these guidelines<sup>[74]</sup>.

## CONCLUSION

Several interventions, other than antibiotic prophylaxis, for the prevention of recurrent UTI have been tried and, although showing some promise, they do not provide so far a definitive effective answer.

Cranberry juice appears to be a promising and safe alternative with no serious adverse events. However its efficacy remains questionable in the pediatric population. Few studies are available on probiotics, but their efficacy is still debated for UTI prevention. Circumcision, a largely popular choice in certain countries, lacks good quality studies to prove its safety, and effectiveness. It was found to be particularly useful for children with low grade VUR and antenatal hydronephrosis, but the presence of many confounding factors requires further larger good quality studies to establish its efficacy. Glycosaminoglycan and sodium pentosanpolysulfate, found to be useful in animal models, have not been tested yet in humans. The benefit of surgical interventions, such as ureteral reimplantation, is confined to a particular group of patients, and the statistical significance of its efficacy remains questionable. Although improving voiding habits is certainly a beneficial approach, its effectiveness in isolation remains unproven. Vaccination is an attractive emerging option, but high quality large randomised controlled trials in humans are needed to look for its efficacy in UTI prevention.

Finding suitable alternatives to oral long-term antibiotic prophylaxis for UTI prevention still requires further high quality research of those seemingly promising interventions.

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