Review article

Child Kidney Dis 2016;20:1-5
DOI: http://dx.doi.org/10.3339/jkspn.2016.20.1.1

ISSN 2384-0242 (print)
ISSN 2384-0250 (online)

Antibiotics and Probiotics Prophylaxis for Recurrent Urinary Tract Infection in Children

Jung Won Lee, M.D., Ph.D.

Department of Pediatrics, Ewha Womans University School of Medicine, Seoul, Korea

Corresponding author:
Jun Won Lee, M.D., Ph.D.
Department of Pediatrics, Ewha Womans University School of Medicine , 1071, Anyangcheon-ro, Yangcheon-gu, Seoul, 07985, Korea
Tel: +82-2-2650-5275
Fax: +82-2-2650--5358
E-mail: happymaniajw@hanmail.net

Received: 2 February 2016
Revised: 29 March 2016
Accepted: 12 April 2016

Since many years, continuous low dose antibiotic prophylaxis (CAP) has been used for children at a risk for recurrent urinary tract infection (UTI), especially those with vesicoureteral reflux (VUR). The incidence of recurrent UTI has been shown to be higher in children with VUR with bladder and bowel dysfunction (BBD) than in those with VUR without BBD. Therefore, CAP has been recommended for children with BBD and VUR because of the increased risk of UTI. However, the use of CAP has become highly controversial because of bacterial resistance developed due to antibiotic over-usage.

The preventive effects of probiotics have been proved in various adult urogenital infections, and the antimicrobial activities of lactobacilli against uropathogens have been demonstrated in previous in vitro studies. However, a critical assessment of their efficacy in children with UTI is lacking. The importance of the use of urogenital probiotics is that it is a natural approach that replenishes the depleted normal flora to create a better environment to fight off uropathogens. Probiotics have a great potential, particularly today with the increasing threat of antibiotic-resistant microorganisms.

Key words: Antibiotics, Probiotics, Prophylaxis, Urinary tract infection, Children

Introduction

Urinary tract infection (UTI) is the most common bacterial infection in children, and recurrent pyelonephritis may lead to renal scarring with the risk of later hypertension, proteinuria, and end-stage renal disease. The incidence of recurrent UTI within 12 months of an initial UTI is approximately 12-30%[1].

Primary vesicoureteral reflux (VUR) is the most well-known risk factor for recurrent UTI and renal scarring and current preventive strategies have been focused mainly on children with VUR[2].

For several decades, continuous low-dose antibiotic prophylaxis (CAP) has been given to children at risk for UTI, especially those with VUR[2,3].

However, this strategy has recently been challenged. Several large, prospective, randomized controlled studies have shown little or no benefit of CAP in terms of reducing the incidence of febrile UTI or renal scarring[4-8]. The emergence of resistant microorganism has been raised concerns about the long-term use of antibiotics. Instead, urogenital normal flora has been known to

play a important role to inhibit uropathogens and prevent UTI[9]. In 1994, World Helath Organization (WHO) deemed probiotics to be the next-most important immune defense system when commonly prescribed antibiotics are rendered useless by antibiotics resistance[10].

Antibiotic prophylaxis for recurrent UTI

For many years, antibiotic prophylaxis has been given to children at risk for UTI, especially those with VUR.

However, recently, the preventive effect of antibiotic prophylaxis against recurrence of UTI as well as renal damage and long-term complication has been questioned[4-8].

Garin et al.[5] studied 218 patients aged 3 months to 17 years with grade I-III VUR. They concluded that there was no difference in the incidence of UTI, pyelonephritis, or renal scarring between the prophylaxis and control groups. Roussey-Kesler et al.[6] randomized 225 children aged 1 month to 3 years with grades I-III VUR to daily trimethoprim-sulphamethoxazole or no prophylaxis, and followed for 18 months. The results failed to show a significant difference in the incidence of occurrence of UTI between the two groups. Pennesi et al.[7] included 100 children with grades II-IV VUR, diagnosed after a first episode of acute pyelonephritis. There was no difference in the rate of recurrence of acute pyelonephritis (36% in the antibiotic group vs 30% in the no-treatment group, P=0.50) and renal scarring (40% in prophylaxis vs 36% in no prophylaxis, P=0.4). Montini et al.[8] studied 338 children aged 2 months to 7 years, including 128 grades I-III VUR, and the patients are divided into antibiotic prophylaxis or no prophylaxis. There were no significant difference in the recurrence rate of UTI, or that of scarring produced by recurrent UTI, after 12 months of follow-up. They concluded that antibiotic prophylaxis is not indicated for children following a first febrile UTI with no or mild VUR (grade I to II).

Despite the uncertain benefit of CAP, some studies continued to pursue the question of which antibiotic is better.

Craig et al.[11] randomly assigned 576 children with a history of at least one UTI, including 243 children with VUR to antibiotic group or placebo group. Recurrence of UTI was 13% in the antibiotic group and 19% in the placebo group. This result indicated that CAP was associated with a modest reduction in the risk of symptomatic UTI in predisposed children. The Swedish reflux trial compared three groups (antibiotic prophylaxis, endoscopic treatment or surveillance) that were observed for 2 years. Their cohort included children aged 1 to 2 years with grades III-IV VUR. Antibiotic prophylaxis was associated with a significant decrease in recurrent UTI compared with surveillance group (19% vs 57%). In boys, there were few recurrence with no difference between treatment groups. On the other hand, recurrence in girls were more frequent in those with surveillance group than prophylaxis or endoscopic therapy [12]. There was a strong association between recurrent febrile UTI and the development of new renal damage in girls, supporting the concept that acquired renal scar is more prevalent in girls while congenital renal scar is mostly seen in boys.

The child younger than 1 years had a higher incidence of renal scarring than older childrens suggesting an age related risk of scarring. CAP is recommended for the child less than 1 year of age with VUR with a history of a febrile UTI[13].

Many studies suggest that lower urinary tract dysfunction (LUTD) is an important risk factor for recurrent UTI and spontaneous resolution of primary VUR. Abnormal bladder and bowel function (BBD), and VUR are recognized to be associated with each other and linked to UTI. BBD refers to abnormalities of storage as well as emptying, and includes constipation. Accepting the relationship between bladder dynamics and VUR, they postulated that VUR could in turn be positively associated with subsequent dysfunctional elimination syndrome (DES).

Koff et al.[14] found VUR in 43% of children with DES and Chen et al.[15] found that 44.2% of patients with neither VUR nor UTI had DES symptoms compared to approximately 22.0% of those with VUR and no UTI.

The presence of VUR in children with LUTD plays an important role with regard to recurrent UTI and renal damage[16]. Van Batavia et al.[17] showed that female with LUTD have much higher incidence of UTI than males (53% vs 5%). This association was most often noted for lower urinary conditions in which urinary stasis occurs, including detrusor underutilization disorder and dysfunctional voiding.

In 2010, The American Urological association (AUA) guidelines shows that CAP is recommended for the child

with BBD and VUR due to the increased risk of UTI while BBD is present and being treated[13].

Probiotics prophylaxis for recurrent UTI

Urogenital normal microflora of a healthy woman comprise about 50 bacterial species which is dominated by lactobacillus species (107-108/mL). Disruption of the balance between urogenital lactobacilli and uropathogen was suggested to increase the incidence of UTI.

Probiotics, developed from the concept of normal flora, refer to beneficial live microorganism when ingested in adequate amounts. Lactic acid bacteria have been the common probiotic strains, because they exist naturally in human intestinal and urogenital tracts[10]. In vitro studies, lactobacillus strains impede the adherence of uropathogens by secreting biosurfactants, compete with uropathogens in the binding site on vaginal epithelial cells, and inhibit the growth of uropathogens by hydro-molecules. They also enhance the local immunity of the intestinal mucosa and improve the innate immunity and cell-mediated immunity by activation monocytes[18]. Recently, use of lactobacilli activate Toll-like receptor-2 (TLR2), which produce interlukin-10 and myeloid differentiation factor 88 (MyD88). This process downregulates inflammatory reactions caused due to uropathoges[19].

Bruce et al.[20] first showed that vaginal lactobacilli were significantly depleted in women with recurrent UTI compared to healthy women without history of UTI. And there was inverse association of urogenital lactobacilli and *E. coli* in women with recurrent UTI[21]. Intravaginal instillation of *L. rhamnosus* GR-1 colonised the vaginal epithelium and prevented the colonisation of coliform bacteria with recurrent UTI.

In a randomized, placebo controlled study of 64 women, daily oral intake of *L. rhamnosus* GR-1 and L. reueri RC-14 led to a significant reduction in uropathogens and yeast in the vagina[22].

In animal models, indigenous *L. casei* strain, instilled into the bladder, vagina and urethra before challenge with uropathogens, prevented UTI in 84% of the animals[23] and *L. casei* shirota strain eradicated *E. coli*, ostensibly by modulation of host immune response such as stimulation of natural killer cell activity[24]. Furthermore, intraurethral instillation of the indigenous *L. murinus* strain also significantly prevented *Proteus mirabilis* ascending UTI in mouse model[25].

Indeed, lactobacilli in the maternal vagina are first source of lactobacilli of newborn infants. While passing through the birth canal, maternal vaginal lactobacilli are transferred to sterile neonate gut for the first time. After that time, lactobacilli in breast milk are the second important source of infant gut lactobacilli.

In children, human breast milk, known as natural probiotics, was proven to prevent UTI in infants[26] and in preterm infants with *L. GG* supplementation, the incidence of UTI were reduced compared to the control group, although the difference was not statistically significant[27].

Gerasimov et al.[28] first reported that *L. acidophilus* successfully prevented in 6-year-old girl with recurrent UTI. There has been a prospective study in which oral lactobacillus prophylaxis was effective in preventing recurrent UTI in persistent primary VUR in children[29]. Recently, Lee et al.[30] demonstrated the lactobacillus colony counts for the stool, urine and periurethral swabs from the UTI infants were significantly lower than those for the control group ($P<0.05$) and lower urogenital lactobacillus colonization may be risk factor of UTI in infants.

Conclusion

CAP is not routinely indicated for first febrile UTI children with low grade VUR. BBD affect the critical aspects of VUR management including recurrent UTI, spontaneous resolution and surgical cure. Therefore, it is important to identify BBD to permit identification of risks in children and treatment of BBD. CAP is recommended for the child with BBD and VUR, especially, girls with a history of LUTD.

In this era of increasing bacterial resistance to antibiotic over-usage, development of alternative and yet harmless approach is of major importance. Probiotics is one of the most encouraging therapeutic alternatives for the prevention of UTI. However, there are still many questions to be resolved and promising evidence on urogenital lactobacilli provides the possible benefits and rationale for studying

lactobacilli as prophylaxis to prevent UTI in children.

In order to develop the ideal urogenital probiotics, it is essential to search the most appropriate probiotic strains to be used in reducing childhood UTI.

Conflict of Finterest

No potential conflict of interest relevant to this article was reported.

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