

“Nice to know” Updates in Pediatric Urinary Tract Infections

Pediatric Infectious Disease (2022): 10.5005/jp-journals-10081-1381

Source: del Carmen RCD, Oviedo GIN, Londono-Ruiz JP, Tobar IFG. 1153. ESBL Producing *E. coli* urinary tract infections in children: is carbapenem always necessary? *Open Forum Infect Dis* 2021;8(1):S667–S668. DOI: 10.1093/ofid/ofab466.1346

Extended-spectrum β -lactamases (ESBL) producing *Escherichia coli* are not an uncommon concern in daily practice. Carbapenems, especially meropenem/ertapenem are the choice for treatment in some hospitals, but aminoglycosides or trimethoprim and sulfamethoxazole are options for carbapenem saver. The aim of this study was to compare the clinical outcomes in ESBL producing *E. coli* UTI in children treated with ertapenem or amikacin. In the amikacin group, the median length of stay was 7.2 days [interquartile range (IQR 4–9)] and in ertapenem group was 9 days (IQR 6–10). No significant adverse effects were documented in any group. The use of amikacin in ESBL producing *E. coli* UTI in children has similar clinical outcomes like that of ertapenem. The researchers conclude by saying that the use of amikacin could decrease hospitalization time.

Source: Mina-Riascos SH, Fernández N, García-Perdomo HA. Effectiveness and risks of endoscopic management compared to vesicoureteral reimplantation in patients with high-grade vesicoureteral reflux: systematic review and network meta-analysis. *Eur J Pediatr* 2021;180(5):1383–1391. DOI: 10.1007/s00431-021-03948-w

The purpose of this study was to determine the effectiveness and safety of endoscopic management compared to ureterovesical reimplantation in pediatric patients with high-grade vesicoureteral reflux (VUR) in terms of UTI. The interventions were subureteric bulking agent endoscopic injection (polytetrafluoroethylene, hyaluronic acid, collagen, dextranomer/hyaluronic acid, and polyacrylate polyalcohol copolymer) vs vesicoureteral reimplantation (Cohen, Politano–Leadbetter, Glenn–Anderson, and Lich–Gregoir), and the primary outcome was urinary infections. A total of 1448 renal units who underwent surgical treatments for the correction of high-grade VUR were included.

The study showed no differences in UTI episodes after VUR correction in children undergoing endoscopic management compared with vesicoureteral reimplantation.

Source: Meena J, Kumar J. Adjuvant corticosteroids for prevention of kidney scarring in children with acute pyelonephritis: a systematic review and meta-analysis. *Arch Dis Child* 2021;106(11):1081–1086. DOI: 10.1136/archdischild-2020-320591

Acute pyelonephritis in children may result in permanent kidney scarring that is primarily caused by inflammation during acute infection. Antibiotic (ATB) therapy alone is not enough to significantly reduce kidney scarring, and adjuvant corticosteroid therapy has shown a significant reduction in inflammatory cytokines in urine, prompting its evaluation in randomized controlled trials. A few clinical trials showed a trend toward a reduction in renal scarring, but did not have an adequate sample size to show a significant effect. Therefore, the authors planned to synthesize the available evidence on the role of corticosteroids as adjuvant therapy in reducing kidney scarring. Three randomized trials (529 children) were included. Corticosteroids were found to be effective in lowering the risk of kidney scarring as compared with a placebo. They also found no significant increase in the risk of bacteremia and/or hospitalization in the corticosteroid group.

This systematic review and meta-analysis, with low to moderate quality evidence, suggests that short duration “adjuvant corticosteroid therapy” along with routine ATB therapy in acute febrile UTI (fUTI) may significantly reduce the risk of kidney scarring without any significant adverse effects.

Source: Da Dalt L, Bressan S, Scozzola F, Vidal E, Gennari M, La Scola C, Anselmi M, Miorin E, Zucchetta P, Azzolina D, Gregori D, Montini G. Oral steroids for reducing kidney scarring in young children with febrile urinary tract infections: the contribution of Bayesian analysis to a randomized trial not reaching its intended sample size. *Pediatr Nephrol* 2021;36(11):3681–3692. DOI: 10.1007/s00467-021-05117-5

This randomized control study aimed to evaluate the effect of oral dexamethasone in reducing kidney scars in infants with a first fUTI. Children aged between 2 and 24 months with their first presumed UTI, at high-risk for kidney scarring based on procalcitonin levels (≥ 1 ng/mL), were randomly assigned to receive dexamethasone in addition to routine care or routine care only. Kidney scars were identified by kidney scan at 6 months after the initial UTI.

The researchers could randomize 48 children, of whom 42 had a UTI and 18 had outcome kidney scans (instead of 128 planned). Kidney scars were found in 0/7 and 2/11 patients in the treatment and control groups, respectively. The probability that dexamethasone could prevent kidney scarring was 99% in the setting of an informative prior probability distribution (which fully incorporated in the final inference the information on treatment effect provided by previous studies) and 98% in the low-informative scenario (which discounted the prior literature information by 50%). The probabilities that dexamethasone could reduce kidney scar formation by up to 20% were 61% and 53% in the informative and low-informative scenarios, respectively.

The researchers conclude that dexamethasone is highly likely to reduce kidney scarring, with a more than 50% probability of reducing kidney scars by up to 20%.

Source: Li X, Yu Q, Qin F, Zhang B, Lu Y. Serum vitamin D level and the risk of urinary tract infection in children: a systematic review and meta-analysis. *Front Public Health* 2021;9:637529. DOI: 10.3389/fpubh.2021.637529

This thought-provoking systematic review and meta-analysis aimed to evaluate the association between serum vitamin D concentration and the risk of UTI in children. Human studies reported the serum vitamin D level in children with UTI and healthy controls were collected from PubMed, Scopus, Embase, and Cochrane databases. The strictly standardized mean difference (SSMD) and 95% confidence interval (CI) were calculated to evaluate the relationship between serum vitamin D levels and the risk of UTI. The results of the analysis showed that serum vitamin D levels in children with UTI were significantly lower than in healthy control children (SSMD: 0.891, 95% CI: 0.707–1.075, $p < 0.000$; SSMD: 0.797, 95% CI: 0.500–1.094, $p < 0.000$, respectively). It can be concluded that there is a significant negative relationship between serum vitamin D levels and the risk of UTI in children.

Source: Scott Wang HH, Cahill D, Panagides J, Logvinenko T, Nelson C. Top-down versus bottom-up approach in children presenting with urinary tract infection: comparative effectiveness analysis using RIVUR and CUTIE data. *J Urol* 2021;206(5):1284–1290. DOI: 10.1097/JU.0000000000001931

The initial imaging approach to children with UTI is controversial. Along with renal/bladder ultrasound, some advocate voiding cystourethrogram (VCUG), that is, a bottom-up approach, while others advocate dimercaptosuccinic acid (DMSA) scan, that is, a top-down approach. Comparison of these approaches is challenging. In the Randomized Intervention for Children with Vesicoureteral Reflux/Careful Urinary Tract Infection Evaluation trials, however, all subjects underwent both VCUG and DMSA scans.

The objective of this study was to perform a comparative effectiveness analysis of the bottom-up vs top-down approach. The authors assumed that all children with VUR received continuous antibiotic prophylaxis (CAP). Outcomes of the study included recurrent UTI, number of VCUGs, and CAP exposure. The authors assumed a 25% VUR prevalence in children with initial UTI with sensitivity analysis using 40% VUR prevalence.

The authors, in the simulated cohort, found a slightly higher yet statistically significant recurrent UTI in the top-down compared with the bottom-up approach. On the other hand, the bottom-up approach resulted in more VCUG. Top-down resulted in fewer CAP exposed patients and lower overall CAP exposure. Sensitivity analysis was performed with 40% VUR prevalence with similar results. So, in short, the top-down approach was associated with slightly higher recurrent UTI and compared to the bottom-up approach, it significantly reduced the need for VCUG and CAP.

Source: Meena J, Thomas CC, Kumar J, Raut S, Hari P. Nonantibiotic interventions for prevention of urinary tract infections in children: a systematic review and meta-analysis of randomized controlled trials. *Eur J Pediatr* 2021;180(12):3535–3545. DOI: 10.1007/s00431-021-04091-2

A considerable proportion of children experience a recurrence of UTI following the first episode. While low-dose ATB prophylaxis has been the mainstay for the prevention of UTIs, recent evidence raised concerns over their efficacy and safety. Hence, this study aims to systematically synthesize evidence on the efficacy and safety of nonantibiotic prophylactic interventions for UTIs. Randomized controlled trial (RCTs) comparing any nonantibiotic interventions with placebo/ATBs for the prevention of UTIs in children were considered eligible. Around 16 trials evaluating 1426 participants were included. Cranberry was as effective as ATB prophylaxis but better than placebo/no therapy in reducing UTI recurrence. Probiotic therapy was more effective in reducing UTI recurrence when compared with placebo. While probiotic therapy was not better than ATB prophylaxis in preventing UTI, the authors comment that they have a lower risk of ATB resistance.

Low-quality evidence suggests that cranberry products and probiotics could reduce the risk of UTI recurrence when compared with a placebo in children with a normal urinary tract.

Source: Rius-Gordillo N, Ferré N, González JD, Ibars Z, Parada-Ricart E, Fraga MG, Chocron S, Samper M, Vicente C, Fuertes J, Escribano J, DEXCAR Study Group. Dexamethasone to prevent kidney scarring in acute pyelonephritis: a randomized clinical trial. *Pediatr Nephrol* 2022;37(9):2109–2118. DOI: 10.1007/s00467-021-05398-w

This is a multicentric, prospective, double-blind, placebo-controlled RCT where children from 1 month to 14 years of age with proven acute pyelonephritis (APN) were randomly assigned to receive a 3-day course of either an intravenous corticosteroid (dexamethasone 0.30 mg/kg/day) twice daily or placebo. The late technetium 99 m DMSA scintigraphy (>6 months after the acute episode) was performed to assess kidney scar persistence. Kidney scarring risk factors (VUR, kidney congenital anomalies, or urinary tract dilatation) were also assessed.

The researchers concluded that dexamethasone showed no effect on reducing the risk of scar formation in children with APN. Hence, there is no evidence for an adjuvant corticosteroid treatment recommendation in children with APN. However, the study was limited by not achieving the predicted sample size and the expected scar formation.

Source: Moghimbeigi A, Adibi A, Meibodi SMRA, Abdan Z, Sarokhani D, Fakhri M, Dehkordi AH. Prevalence of renal scarring caused by urinary tract infections in children: a systematic review and meta-analysis. *Przegl Epidemiol* 2022;76(2):190–199. DOI: 10.32394/pe.76.19

The aim of this study was to evaluate the prevalence of renal scarring after UTI in children through systematic review and meta-analysis.

In 29 studies with a sample size of 9,986 children, the prevalence of renal scarring in children was estimated at 35%. Also, the prevalence of renal scarring was 61% in girls and 34% in boys. The prevalence of unilateral renal scarring in children was 56% and bilateral renal scarring was 31%. In addition, the prevalence of scar was 54% in children with reflux and 12% in children without VUR.

According to this study, more than one-third of people under the age of 18 after UTI have renal scarring. The prevalence of this complication in girls is about two times higher than that in boys and in people with reflux, it is about four times higher than in people who do not have urinary reflux. Also, about half of people under the age of 18 suffer from unilateral renal scarring and about one-third of them suffer from bilateral renal scarring.

Source: Harper L, Blanc T, Peycelon M, Michel JL, Leclair MD, Garnier S, Flaum V, Arnaud AP, Merrot T, Dobremez E, Faure A, Fourcade L, Poli-Merol ML, Chaussy Y, Dunand O, Collin F, Huiart L, Ferdynus C, Sauvat F. Circumcision and risk of febrile urinary tract infection in boys with posterior urethral valves: result of the CIRCUP randomized trial. *Eur Urol* 2022;81(1):64–72. DOI: 10.1016/j.eururo.2021.08.024

Boys with posterior urethral valves (PUVs) have an increased risk of fUTI. This clinical RCT was conducted to determine the effect of circumcision on the risk of fUTIs in boys with PUVs. Boys, aged 1–28 days, diagnosed with posterior urethral valves, confirmed by voiding cystogram, were included. The participants were randomized to neonatal circumcision + antibiotic (CATB) prophylaxis or ATB prophylaxis alone, and followed for 2 years with a primary outcome measure of risk of presenting fUTIs in each group.

In total, 91 patients were included: 49 in group CATB and 42 in group ATB. The probability of presenting an fUTI was 20% in group ATB vs 3% in group CATB. The hazard ratio of presenting an fUTI within 2 years in the ATB group compared with that in the CATB group was 10. Around 64 children (70.3%) had a complete follow-up at 2 years of age. The authors unequivocally conclude that circumcision significantly decreases the risk of presenting an fUTI in boys with PUVs.

Source: Renko M, Salo J, Ekstrand M, Pokka T, Pieviläinen O, Uhari M, Tapiainen T. Meta-analysis of the risk factors for urinary tract infection in children. *Pediatr Infect Dis J* 2022;41(10):787–792. DOI: 10.1097/INF.0000000000003628

The aim of this meta-analysis was to investigate the risk factors for UTIs in children. All studies assessing at least one possible risk factor for the occurrence or recurrence of UTI with a clear definition of symptomatic UTI in children were included in the analysis. Circumcision decreased the occurrence of UTIs with an odds ratio (OR) of 0.1 and breastfeeding with an OR of 0.4, both with low heterogeneity. Being overweight or obese increases the risk of UTI. Both poor fluid intake and infrequent voiding were associated with recurrent UTIs. However, there were variations in the design, populations, and definitions between the studies.

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