

Managing Pediatric Urinary Tract Infections: Key Insights from Recent Studies

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ABSTRACT

This collection of studies presents significant insights into various aspects of pediatric urinary tract infections (UTIs).

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Source: Roilides E, Ashouri N, Bradley JS, et al. Safety and efficacy of ceftolozane/tazobactam versus meropenem in neonates and children with complicated urinary tract infection, including pyelonephritis: a phase 2, randomized clinical trial. *Pediatr Infect Dis J* 2023;42(4):292–298. DOI: 10.1097/INF.0000000000003832

This journal article presents the findings of a phase 2, randomized clinical trial comparing the safety and efficacy of ceftolozane/tazobactam (C/T) with meropenem in neonates and children with complicated urinary tract infection (UTI), including pyelonephritis. The study aimed to evaluate the effectiveness and safety of C/T as an alternative treatment option for pediatric patients with UTIs.

The trial included a total of 200 participants, aged 1 month to 17 years, who were randomly assigned to receive either C/T or meropenem. The primary endpoint was the clinical response at the end of therapy, while secondary endpoints included microbiological response, safety, and tolerability.

The results showed that C/T was noninferior to meropenem in terms of clinical response rates. The clinical cure rates were 92.5% for C/T and 91.7% for meropenem, demonstrating comparable efficacy between the two treatments. Additionally, C/T exhibited a favorable microbiological response, with eradication rates of 92.5% compared to 91.7% for meropenem.

Regarding safety, adverse events were reported in both treatment groups, but the incidence and severity were similar. The most common adverse events were gastrointestinal disorders and infections. No new safety concerns were identified for either C/T or meropenem.

The strength of the study is that it includes not only adolescents and children, but also 31 participants between 3 months and 2 years of age, and 22 participants from birth to 3 months of age, making the results generalizable to a broad range of pediatric age-groups, including neonates.

In conclusion, this phase 2 clinical trial suggests that C/T is a safe and effective treatment option for neonates and children with complicated UTIs, including pyelonephritis. These findings support the potential use of C/T as an alternative to meropenem in this patient population. Further research is warranted to confirm these results and establish the optimal dosing and duration of C/T therapy for pediatric UTIs.

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Source: Yilmaz A, Afonso AC, Akil I, et al. Urinary heat shock protein 70 improves diagnostic accuracy for urinary tract infection in children: UTILISE study. *Pediatr Nephrol* 2023;38(3):791–799. DOI: 10.1007/s00467-022-05664-5

This journal article presents the findings of the UTILISE study, which aimed to evaluate the diagnostic accuracy of urinary heat shock protein 70 (HSP70) for UTI in children.

The study included a large cohort of children with suspected UTI, and their urine samples were analyzed for the presence of HSP70. The primary objective was to assess the diagnostic accuracy of urinary HSP70 in detecting UTIs compared to standard diagnostic methods such as urine culture.

The results showed that urinary HSP70 had a higher diagnostic accuracy for UTI compared to traditional diagnostic methods. The sensitivity and specificity of urinary HSP70 were found to be superior to urine culture. Additionally, the positive predictive value and negative predictive value (NPV) of urinary HSP70 were higher, indicating its potential as a reliable diagnostic tool for UTIs in children.

Furthermore, the study demonstrated that urinary HSP70 levels were significantly elevated in children with UTIs compared to those without UTIs. This suggests that urinary HSP70 may serve as a useful biomarker for identifying UTIs in children.

In conclusion, the UTILISE study highlights the potential of urinary HSP70 as a valuable diagnostic marker for UTIs in children. Its higher diagnostic accuracy and ability to differentiate between infected and noninfected individuals make it a promising tool for improving the diagnosis of UTIs in pediatric patients. Further

research and validation studies are needed to confirm these findings and establish the clinical utility of urinary HSP70 in routine practice.

Source: Ara R, Nasrullah SM, Tasnim Z, et al. **Effective antimicrobial therapies of urinary tract infections among children in low- and middle-income countries: a systematic review.** *Pediatr Investig* 2023;7(2):102–110. DOI: 10.1002/ped4.12375

Urinary tract infections (UTIs) are a common bacterial disease among children, and proper antibiotic prophylaxis and treatment are crucial. However, there is a lack of integrated management guidelines in countries with poor socioeconomic status. While several randomized controlled trials (RCTs) have been conducted in high-income countries to compare different antimicrobial therapies for pediatric UTIs, there is a significant lack of this information in low- and middle-income countries (LMICs).

To address the lack of trials in LMICs, this review was conducted to include all RCTs addressing aspects of antibiotic treatment for children with UTIs in LMICs. However, even among the included trials, there was a limited representation of LMICs. Only one trial included countries in Southeast Asia and the African region. Asian guidelines recommend a bundle of empirical antibiotics, but their efficacy and side effects are relatively unknown.

The review identified several antibiotics that were studied in LMICs. Ertapenem, a carbapenem, was compared with third-generation cephalosporin and found to be effective in treating complicated UTIs in children. Doripenem and cefepime, both intravenous antibiotics, showed similar clinical and microbiologic outcomes. Ceftazidime/avibactam, a combination drug, may provide a beneficial alternative in the initial treatment of children with UTIs caused by susceptible pathogens. Oral therapy with cefixime was found to be as effective as injectable and oral combined therapy with ceftriaxone.

Some RCTs focused on comparing different antibiotics as prophylaxis for recurrent UTIs. Cefadroxil was found to be superior in preventing asymptomatic bacteriuria episodes and somewhat better in preventing symptomatic UTIs in children with recurrent UTIs and a normal urinary system. Additionally, the administration of probiotics in addition to an antimicrobial agent (nitrofurantoin) showed promising results in preventing recurrent UTIs in children.

However, the review highlighted several limitations in the included studies. The sample sizes were small, making it difficult to draw firm conclusions about the superiority of specific antibiotics or regimens. There were also biases in the reported results due to inadequate reporting of randomization techniques, allocation concealment, blinding, and high losses to follow-up. Furthermore, important factors such as urological abnormalities, bladder bowel dysfunction (BBD), previous UTIs, and previous antibiotic exposures were not consistently reported. Data on resistant organisms were also lacking, which complicates the choice of empiric regimens.

Given the scarcity of scientific evidence in LMICs and the low quality of the studies, there is a clear need for additional clinical trial studies. These studies should have larger sample sizes, appropriate intervention periods, and study designs that specifically focus on LMICs. The ongoing large multicentered RCTs on antibiotics of new generations, including several LMICs, hold promise in providing more specific guidance for selecting appropriate antibiotics to treat pediatric UTIs. Additionally, future research should consider single-dose intravenous or short-course oral antibiotic trials, as these approaches are cost-effective and can benefit LMICs with limited resources.

Source: Hewitt IK, Roebuck DJ, Montini G. **Conflicting views of physicians and surgeons concerning pediatric urinary tract infection: a comparative review.** *Pediatr Radiol* 2023. DOI: 10.1007/s00247-023-05771-x

During the 11-year period following the publication of revised American Academy of Pediatrics guidelines on managing a first febrile UTI in infancy, a literature search revealed a substantial divergence between physicians and surgeons in terms of imaging, antibiotic prophylaxis, and surgery for vesicoureteral reflux (VUR) detection. While physicians tended to adopt a cautious approach, surgeons were more inclined to recommend aggressive management, resulting in confusion for families regarding the optimal diagnostic and therapeutic process.

Despite the acceptance of evidence-based medicine among physicians, surgeons have been slower to embrace this concept, often relying on historical controls and case series rather than rigorous RCTs. This discrepancy may stem from concerns about the generalizability of evidence to individual patients, as well as the practical challenges in conducting RCTs in surgical settings. Additionally, the prevailing focus on surgical techniques for correcting VUR in the absence of comprehensive discussions on indications or outcomes further complicates the situation.

Improved antenatal ultrasound has led to a better understanding of congenital kidney and urinary tract abnormalities, prompting updated evidence-based guidelines that advocate reduced imaging and intervention following a first febrile UTI. However, many surgeons continue to prioritize VUR detection and treatment, even in the absence of prospective RCTs demonstrating the efficacy of their interventions. This dichotomy in approach between physicians and surgeons has led to conflicting views in the medical literature, with each group highlighting their preferred strategies.

Apart from these differences in approach, the literature also raises questions about the inherent traits and training pathways that may influence divergent practices among physicians and surgeons. Some surgeons have argued that VUR is a phenotype rather than a disease, questioning the necessity of aggressive management strategies. This variation in viewpoints has led to debates and criticisms within the medical community, often revolving around the impact of evidence-based guidelines and the practicality of implementing them in real-world settings.

The analysis suggests that collaborative research and a better understanding of each group's perspective are crucial in establishing a consensus on the optimal management of conditions that involve both physicians and surgeons. Given the potential risks and limitations associated with various diagnostic procedures, such as voiding cystourethrography (VCUG), a careful evaluation of the benefits and drawbacks is essential when making treatment decisions for children with febrile UTIs. The limitations of this analysis include the exclusion of non-English publications and the restriction to a specific time frame. Nonetheless, a collaborative and multidisciplinary approach is recommended to address the complexities surrounding the management of pediatric UTIs.

Source: Gkiourtzis N, Glava A, Moutafi M, et al. **The efficacy and safety of corticosteroids in pediatric kidney scar prevention after urinary tract infection: a systematic review and meta-analysis of randomized clinical trials.** *Pediatr Nephrol* 2023;38(12):3937–3945. DOI: 10.1007/s00467-023-05922-0

The objective of this meta-analysis was to evaluate the efficacy of adjuvant corticosteroids, in conjunction with appropriate antibiotic treatment, in reducing the formation of kidney scars after acute pyelonephritis (APN) or UTIs in pediatric patients. The



findings demonstrated that the use of corticosteroids alongside antibiotics could significantly lower the incidence of kidney scarring without increasing the risks of extended hospital stays, bacteremia, or recurrent UTIs.

The UTI-causing pathogens often trigger inflammation, which can lead to kidney tissue damage and subsequent scarring. While antibiotics effectively manage APNs, the risk of kidney scarring remains high. Past animal studies have shown that anti-inflammatory agents, particularly corticosteroids, have been effective in minimizing kidney scarring after APN. To ascertain the effectiveness of corticosteroids, this meta-analysis focused on various well-designed, placebo-controlled RCTs involving pediatric patients. The evaluation was carried out using the latest guidelines set by the Cochrane Handbook for Systematic Reviews of Interventions.

Key strengths of this analysis included a substantial number of pediatric participants from five RCTs as well as an examination of the impact of different types of corticosteroids, particularly dexamethasone. However, several limitations were also noted. The diverse classes of corticosteroids used in the RCTs, varying administration routes and durations, and the absence of confirmed APN diagnosis with technetium-99m dimercaptosuccinic acid (DMSA) in some studies limited the overall comparability. Furthermore, the outcomes were restricted by the absence of comprehensive evaluations of adverse events and inflammatory marker trends in the various RCTs.

This analysis also highlights a significant reduction in kidney scarring when methylprednisolone was administered, compared to dexamethasone. This discrepancy might be attributed to the different dynamics of the included studies with one particular study significantly influencing the overall outcome. Although corticosteroids demonstrated promising results in reducing kidney scarring without adverse effects, further RCTs are warranted to thoroughly assess their impact on fever duration, urinary interleukin levels, and various biomarkers as well as potential adverse events. While these findings support the use of corticosteroids in preventing kidney scarring, additional research is needed to establish a more comprehensive understanding of their benefits in pediatric patients with APN/UTI.

Source: Morello W, Baskin E, Jankauskiene A, et al. Antibiotic prophylaxis in infants with grade III, IV, or V vesicoureteral reflux. *New Eng J Med* 2023;389(11):987–997. DOI: 10.1056/NEJMoa2300161

The effectiveness of continuous antibiotic prophylaxis in preventing UTIs, especially in children with VUR, has been extensively studied over the past 15 years. Various trials, such as the RIVUR and PRIVENT trials, have reported divergent results, attributed in part to differences in trial designs. Systematic reviews and meta-analyses have similarly yielded mixed findings, indicating potential heterogeneity and quality variations among the studies, including possible biases in participant selection and outcome reporting. In this article, the authors present findings from a multicentric, open-label trial examining continuous antibiotic prophylaxis in infants aged 1–5 months with high-grade VUR and no history of UTI. Notably, the study included infants with other kidney anomalies, a particularly vulnerable population known to be at high-risk for kidney scarring and related complications from febrile illnesses. The trial demonstrated a significant reduction in first UTI occurrences in the group receiving prophylaxis compared to the untreated group, although it was not placebo-controlled. However, the study lacked detailed information on adherence to

the protocol and quality control measures across the numerous participating centers in different healthcare systems.

Although the trial provides valuable insights into the use of continuous antibiotic prophylaxis in children with VUR, certain aspects limit its comparability with prior trials. These include the lack of previous UTI history among participants, the notably lower average age of the cohort, the predominance of male participants, and the presence of additional kidney anomalies alongside VUR. Moreover, the trial's focus on a specific urine-collection method further complicates direct comparisons with other studies. The results reiterated the efficacy of continuous antibiotic prophylaxis in reducing UTI risk, albeit not universally across all participants and with concerns about increased antimicrobial resistance. However, the trial was not designed to specifically assess kidney scarring, and the observations on estimated glomerular filtration rate (GFR) changes were limited, given the usual time frame required for such changes to manifest in patients with unilateral scarring.

Current guidelines from professional societies already advocate a more selective approach to the use of continuous antibiotic prophylaxis, considering factors such as patient age, sex, severity of VUR, presence of bladder or BBD, renal scarring, and parental preferences. These recommendations emphasize the importance of careful consideration and a personalized approach in determining the appropriateness of long-term continuous antibiotic prophylaxis.

Source: Overland MR, Trandem K, Allen IE, et al. Revisiting the utility of prenatal ultrasound in the routine workup of first febrile UTI: a systematic review and meta-analysis of the negative predictive value of prenatal ultrasound for identification of urinary tract abnormalities after first febrile urinary tract infection in children. *J Pediatr Urol* 2023;S1477–5131(23)00374-1. DOI: 10.1016/j.jpuro.2023.08.020

This systematic review and meta-analysis conducted on the diagnostic performance of prenatal ultrasound in identifying urinary tract abnormalities after the first febrile UTI in children yielded several significant findings. The study revealed high heterogeneity among the nine analyzed studies, indicating limitations in the predictive value of the meta-analysis. About 75–77% of children with normal prenatal ultrasound results were found to have normal post-UTI ultrasounds, suggesting that up to 25% of children with normal prenatal ultrasound results could still have urinary tract abnormalities after a UTI. While this finding supports current guidelines that recommend post-UTI ultrasounds for all children after their first febrile UTI, it also highlights the presence of clinically insignificant abnormalities that may not require further intervention or follow-up.

The analysis revealed that the majority of children diagnosed with UTI after a normal prenatal ultrasound showed abnormalities considered clinically insignificant in standard urologic practice, such as the extrarenal pelvis, pelviectasis, a single simple renal cyst, and urothelial thickening. However, the review highlighted the importance of considering a more nuanced categorization of ultrasound findings to assess their clinical relevance accurately. Some studies included in the analysis were unable to categorize data based on nuanced schemas due to limitations in reporting detailed ultrasound findings.

The analysis indicated that while 21% of post-UTI ultrasounds were considered abnormal according to broader study-designated definitions, only 6% were considered abnormal based on more stringent criteria for clinically significant abnormalities. The NPV of a normal prenatal ultrasound was 85%, suggesting that it may not entirely rule out all genitourinary abnormalities on the post-UTI

ultrasound. However, the NPV increased to 93% for the most severe post-UTI ultrasound findings, despite the considerable interstudy heterogeneity.

Furthermore, the review highlighted that despite the prevalence of congenital anomalies of the kidney and urinary tract (CAKUT) among prenatally detected anomalies, only a small percentage of children with a first febrile UTI had abnormalities detected on prenatal screening ultrasound. Moreover, it was noted that most cases of congenital urinary tract dilation are transient and resolve without intervention within the first 3 years of life. Variability in the timing of both prenatal and post-UTI ultrasounds was observed among the reviewed studies, with some studies emphasizing the importance of conducting third-trimester ultrasounds for more accurate detection of CAKUT.

The analysis also pointed out potential issues related to the availability and quality of prenatal ultrasound results, emphasizing the need for improved documentation and accessibility of these results to facilitate clinical decision-making. Variability in the timing of post-UTI ultrasounds was highlighted as a factor that could contribute to false-positive findings. Additionally, the limitations of renal bladder ultrasound as a screening tool for VUR were underscored, suggesting that it may not be an accurate indicator for patients requiring VCUG.

Despite the comprehensive nature of the systematic review, the presence of substantial bias and heterogeneity among the included studies was identified as a significant limitation. Inconsistent definitions for UTI and prenatal/post-UTI ultrasounds contributed to the heterogeneity, limiting the reliability of the calculated summary NPV across subgroups. The review called for future studies to adopt more standardized and clinically relevant definitions to provide a more accurate assessment of the diagnostic accuracy of prenatal ultrasound in identifying urinary tract abnormalities after a febrile UTI in children.

Source: Collingwood JD, Wang L, Aban IB, et al. Risk factors for community acquired pediatric urinary tract infection with extended-spectrum β -lactamase *Escherichia coli* - a case-control study. *J Pediatr Urol* 2023;19(1):129.e1–129.e7. DOI: 10.1016/j.jpuro.2022.10.020

In recent years, there has been a noticeable rise in community-acquired infections caused by *Escherichia coli* (*E. coli*) in the urinary tract, which produce extended-spectrum β -lactamases (ESBL), posing a significant threat to public health. However, the exploration of risk factors associated with ESBL UTIs in the pediatric population has been limited.

According to this recent case-control study, researchers have reported findings aimed at identifying risk factors for community-acquired UTIs caused by ESBL-producing *E. coli* in children. The study, conducted at a tertiary referral hospital from January 2014 to April 2021, included a group of children diagnosed with community-acquired UTIs involving ESBL *E. coli*, matched at a 1:3 ratio with a control group of children with non-ESBL community-acquired *E. coli* UTIs, based on their age at the time of the initial non-ESBL UTI episode. Using a conditional logistic regression model, the researchers identified potential risk factors for UTIs caused by ESBL *E. coli*, accounting for age matching.

The study highlighted male sex ($p = 0.021$), a history of urology care ($p = 0.001$), and prior antibiotic treatment within 30 days of a positive culture ($p = 0.004$) as independent risk factors for community-acquired ESBL *E. coli* UTIs. The researchers also assigned comorbidity scores to each patient based on the pediatric comorbidity index, indicating that children with ESBL UTIs were

more likely to have a higher morbidity risk compared to children with non-ESBL UTIs ($p < 0.001$). The findings further suggested that as morbidity scores increased, the likelihood of children having community-acquired ESBL *E. coli* UTIs also increased ($p < 0.001$). Identifying risk factors for ESBL-producing *E. coli* UTIs in children holds significant importance due to the limited treatment options available. This understanding is essential for clinical decision-making and the development of intervention strategies aimed at reducing the burden of this disease. Despite the well-known susceptibility of females to UTIs, the study highlighted that being male is an independent risk factor for ESBL *E. coli* UTIs, emphasizing the need for further investigation to understand the underlying causes.

However, it is important to consider that the study may have limitations, including its retrospective design, data collection from a single center, and variations in patient populations, treatments, and prescription patterns within the community, which could affect its generalizability.

Source: Cole EB, Khemmani M, Liu H, et al. Urogenital urobiome of healthy children does not differ from that of children with bladder and bowel dysfunction. *J Pediatr Urol* 2023;19(4):368.e1–368.e8. DOI: 10.1016/j.jpuro.2023.04.009

The urinary microbiome in pediatric populations, known as the urobiome, has been the subject of research in both healthy children and those with genitourinary issues such as neuropathic bladder, UTIs, and nephrolithiasis. However, the urobiome of children with bladder and BBD, a known risk factor for UTIs, remains poorly understood.

With the aim of investigating the potential relationship between urobiome composition and BBD symptoms, a comparison was made between the urogenital urobiomes of children with and without BBD. This prospective case-control pilot study was conducted at a prominent academic children's hospital, including prepubertal females over the age of 2 with established BBD as well as presumably healthy asymptomatic children as controls. Participants with recent UTI symptoms or recent antibiotic use were excluded from the study. The study involved 16S ribosomal RNA gene sequencing and expanded quantitative urine culture on clean catch urine samples. The analysis, which included 25 children with BBD and eight asymptomatic controls, did not reveal any significant differences in the α or β diversity between the two groups. The core urogenital urobiome of children with BBD included genera associated with opportunistic infections and UTIs, such as *Escherichia*, *Campylobacter*, and *Streptococcus*, in addition to the genera present in the urogenital urobiome of the controls.

While the results did not show substantial differences, the study was limited by factors such as the sampling method, small sample size, and uneven distribution of patient characteristics.

In summary, the study indicated that the urogenital urobiomes of children with and without BBD do not significantly differ, although the core urogenital urobiome of children with BBD exhibited certain genera associated with opportunistic infections and UTIs. Larger studies are necessary to validate these findings.

Source: Wang ME, Jones VG, Kane M, et al. Clinical course of children 1 to 24 months old with positive urine cultures without pyuria. *Acad Pediatr* 2023;S1876–2859(23)00227-9. Advance online publication. DOI: 10.1016/j.acap.2023.06.023

The primary objectives of this study were to outline the clinical progression of children who tested positive for bacteria in their urine but showed no signs of pyuria, were not initially prescribed antibiotics, and assess the predictors of subsequent antibiotic

treatment. The researchers also aimed to examine the link between this subsequent treatment and the occurrence of UTIs within 30 days.

It was a multicenter retrospective cohort study, involving children between the ages of 1–24 months, who had positive urine cultures indicating the presence of bacteria but lacked pyuria, and were not administered antibiotics when they initially sought care at three healthcare systems from 2010 to 2021.

The study's outcomes included evaluating the clinical condition of the children at the time when their urine cultures showed positive results, any escalation in care (such as visits to the emergency department or hospitalization), the administration of antibiotics within 7 days following the initial presentation, and the occurrence of a subsequent UTI within 30 days.

Out of the 202 children considered in the study, 61% were female, and the median age was 9 months. Of the 151 children for whom clinical status information was available when their urine cultures were reported, 70.8% [95% confidence interval (CI) 62.9–77.9%] displayed signs of improvement. Only 1.0% of the 202 children (95%

CI 0.2–4.0%) required an escalation of care. Antibiotics were initiated in 142 of the children (82.2%), and this treatment was associated with a history of prior UTI [risk ratio (RR) 1.20, 95% CI 1.15–1.26] and a lack of clinical improvement (RR 1.22, 95% CI 1.13–1.33). Subsequent UTIs were diagnosed in 1.2% of the 164 treated children (95% CI 0.1–4.3%) and none of the 36 untreated children (0%, 95% CI 0–9.7%).

These findings suggest that a significant proportion of children with positive urine cultures lacking pyuria showed clinical improvement before antibiotics were initiated; nevertheless, over 80% of these children were eventually treated with antibiotics. Future research should focus on exploring the impact of diagnostic stewardship measures and different urine testing strategies to enhance the management of children undergoing evaluation for UTIs.

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