

Original Article



Effectiveness of Short-Course Antibiotic Treatment in Uncomplicated, Non-Bacteremic Pediatric Urinary Tract Infections: A Rapid Systematic Review

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Conflict of Interest

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

Author Contributions

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ABSTRACT

Purpose: Urinary tract infections (UTIs) pose a significant disease burden in children. This study aims to determine whether a short-course regimen is non-inferior to a standard-course regimen in children with UTIs without complication and presence of bacteremia, and to define, in the optimal way possible, the term “short-course” in this context.

Methods: We conducted a rapid systematic review of research up to April 2021 in PubMed, Embase, and Cochrane databases. We included studies that compared clinical outcomes in pediatric UTIs treated with short-course (≤ 4 days) or standard ($\geq 5-7$ days) courses.

Results: Our analysis suggests that short-course regimens have equivalent efficacy to standard-course regimens, with similar clinical cure rates and recurrence rates. All 10 studies comparing the clinical cure rates of short- and standard-course regimens reported comparable outcomes. The study evaluating renal scarring indicated no inferiority of short-course regimens compared to standard-course ones. Regarding UTI relapse, 8 out of 10 studies reported no significant difference in outcomes between short- and standard-course regimens.

Conclusions: Our results purpose that short-course UTI regimens of 6 days or less are just as effective as standard-term regimens of 7 days or more in terms of infection cure and prevention of recurrence. Considering the equivalent rates of clinical cure and relapse between short- and standard-course regimens, it could be inferred that short-course regimens might be a more optimal strategy for managing pediatric UTIs without increasing the risk of complications.

Keywords: Urinary tract infections; Children; Therapeutics; Antibiotic

INTRODUCTION

Urinary tract infections (UTIs) are a significant disease burden in children. Yet, a consensus on the optimal duration for pediatric UTI therapy remains unclear. Existing guidelines suggest that short-duration antibiotic treatment is acceptable, but the exact definition of “short-course” regimen varies among these guidelines.^{1,2)} Intuitively, clinicians may not prefer a short-duration therapy for pediatric UTI, in concern for treatment failures. Hence, it is important to address this issue to provide an updated evidence-guided practices for children with UTI.

The aim of this rapid systematic review was to determine if short-course regimen yields clinical outcomes that are not inferior to those of standard-course regimen in uncomplicated, non-bacteremic pediatric UTIs. Furthermore, we intended to use the available data to define the term “short-course” as precisely as possible for this context.

MATERIALS AND METHODS

We conducted a systematic review of research up to April 2021 in PubMed, Embase, Cochrane, and KoreaMed databases. The search was conducted using the following keywords: Urinary Tract Infections, urinary tract infection, UTI, UTIs, genitourinary tract infection, urinary infection, urine infection, urine tract infection, urologic infection, urological infection. Two investigators (Kim HH, Choe YJ) independently conducted study selection and extracted the data from articles. From eligible studies, we collected the following information: author, year, country, study design, study population, health outcome, antibiotics, age range, and prevalent causative pathogen.

We included studies that compared clinical outcomes in pediatric UTIs treated with short-course regimens or long course regimens. Studies on UTIs associated with systematic infections, including bacteremia, were excluded. For our systematic review, we used the treatment duration definitions provided by the original study investigators from the individual studies to determine treatment duration. Specifically, treatment durations of 4 days or less were considered “short-course,” while those of 5–7 days or more were classified as “standard-course.” We defined the cut-off date as above because 7–14 days is considered a standard duration of therapy in children with UTI, per standard antimicrobial stewardship practices. We excluded studies that presented cases with acute or subacute complication from UTI and patients with bacteremia. Studies that did not report standard or minimum treatment durations, only mean or median, as well as case reports, conference abstracts, and studies involving individuals over 18 were excluded.

From each study, we extracted data, including the study’s primary characteristics (first author’s name, year, study design, and country), number of clinically evaluable patients, and patient setting (outpatients/inpatients). The number of cured patients in each group was also recorded. The primary outcome of this systematic review was a clinical cure, as defined by the study investigators. Other primary outcomes of interest were: renal scarring, abnormal ultrasound, UTI relapse, and readmission within 30 days. For all analyses, patients were categorized into “short-course” and “standard-course” groups for all analyses. For each study, data on time, place, setting, and exposure risk categories were summarized.

RESULTS

Our initial search identified a total of 461 publications (**Fig. 1**), from which 9 studies met our inclusion criteria.^{3,41} These studies provided data on 26,500 clinically evaluable patients.

Table 1 illustrates the characteristics of the included studies. Five studies were conducted in the United States,^{4,6,7,9,10} with 2 more from Canada,^{9,12} one from France,⁵ and one from Sweden.³ Of the total, 2 were outpatient-based studies,^{4,8} whereas 7 were inpatient-based.^{3,5,6,8,41} One study⁵ was a prospective randomized trial, one study¹¹ was a case-

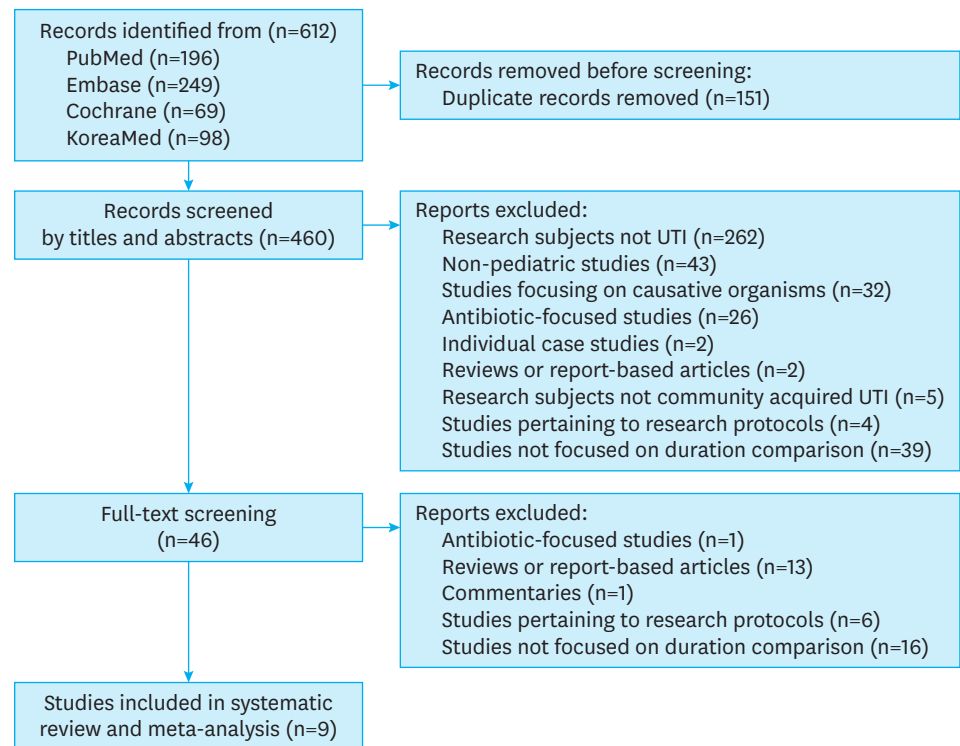


Fig. 1. Search criteria for the systematic review.
Abbreviation: UTI, urinary tract infection.

control study, and all others were retrospective cohort studies. The duration of the short-course regimens varied among the studies, with one study lasting ≤ 48 hours,¹⁰⁾ 5 under 96 hours,^{5,6,8,9,11)} and 2 under 10 days.^{3,8)} Standard-course regimens also varied, extending > 48 hours in one study,¹⁰⁾ ≥ 96 hours in 5,^{5,6,8,9,11)} and ≥ 10 days in 4.^{3,4,6,7)} Regarding the microbiological causes of UTI, *Escherichia coli* was the predominant pathogen in 7 of the studies that identified causative agents.^{3-5,7,8,10,11)} Eight studies included UTI recurrence as a clinical outcome measure, while one examined DMSA scarring,⁵⁾ 3 evaluated abnormal ultrasound results,^{5,8,9)} and 4 assessed readmissions.^{4,9,11)}

Table 2 displays the primary outcomes from the studies in the systematic review. All 10 studies comparing clinical cure rates between short- and standard-course regimens indicated comparable efficacy. The study focused on renal scarring demonstrated the non-inferiority of short-course regimens compared to standard-course. Regarding UTI relapse, 8 of 10 studies reported no significant difference in outcomes between short- and standard-course therapies.^{3-5,7,11)} In specific, clinical cure rates were comparable between short vs. standard courses as follows: Afolabi et al.⁴⁾ (96% vs. 94%), Brady et al.⁶⁾ (98.4% vs. 97.8%), Fox et al.⁷⁾ (88.1% vs. 90.6%), Lessard et al.⁸⁾ (91% vs. 89%), Lewis-de los Angeles et al.⁹⁾ (95.9% vs. 95.0%), Marsh et al.¹⁰⁾ (96.4% vs. 93.0%) (**Table 2**). Bouissou et al.⁵⁾ evaluated renal scarring (13% vs. 17%; short vs. standard courses, repeatedly), abnormal ultrasound (18% vs. 23%), UTI relapse (5.4% vs. 6.3%), which were all comparable between the 2 groups. Readmission within 30 days were evaluated in Afolabi et al.⁴⁾ (4.0% vs. 5.9%; short vs. standard courses, repeatedly), Brady et al.⁶⁾ (1.6% vs. 2.25%), Lewis-de los Angeles et al.⁹⁾ (4.1% vs. 5.0%), and Marsh et al.¹⁰⁾ (3.6% vs. 7.0%), which were all comparable between the 2 groups. In particular, standard IV antibiotics has increased the odds of readmission due to IV-line associated complications.^{4,6,10)}

Table 1. Characteristics and outcome measures of the studies included in the systematic review

Ref. No.	First author, Year	No. of pts	Country	Setting	Age	Type of UTI	Causative agents	Short course regimen	Standard course regimen	Clinical evaluation
3)	Abrahamsson, 2002	300	Sweden	Inpatient (retrospective)	<16 yr	Acute cystitis, uncomplicated UTI	<i>Escherichia coli</i> , <i>Proteus</i> (boys)	5 days in 210 (70%) nitrofurantoin or trimethoprim (PO)	7 days in 60 (20%) and 10 days in 24 (8%) patients (PO)	Urinalysis, CRP
4)	Afolabi, 2020	7,698	US	Ambulatory practice settings (retrospective)	2–17 yr	APN or acute cystitis, uncomplicated UTI	<i>E. coli</i>	3–5 days (PO/IV)	7 days, 10 days, 14 days (PO/IV)	Relapse, reinfection, recurrence (relapse/reinfection), progressing infection
5)	Bouissou, 2008	548	France	Inpatient (prospective RCT)	3 mon to 16 yr	First APN episode	<i>E. coli</i> , <i>Proteus mirabilis</i> , or <i>Klebsiella</i> spp.	3 days (PO/IV)	8 days (PO/IV)	Ultrasound results, renal scarring, VUR
6)	Brady, 2010	12,333	US	Inpatient (retrospective)	<6 mon	Primary UTI	NE	≤3 days (PO/IV)	4–14 days (PO/IV)	Treatment failure
7)	Fox, 2020	791	US	Inpatient and outpatient (retrospective)	6 mon to 18 yr	Pyelonephritis (urine culture positive)	<i>E. coli</i> , <i>Klebsiella</i> spp., <i>Proteus mirabilis</i>	<10 days (PO/IV)	≥10 days (PO/IV)	Treatment failure
8)	Lessard, 2020	108	Canada	Inpatient (retrospective)	≤60 days	Pyelonephritis	<i>E. coli</i> , <i>Enterobacter aerogenes</i> , <i>Enterococcus faecalis</i>	≤4 days (PO)	≥5 days (PO/IV)	Recurrence, VUR, ultrasound results, initial urinalysis, gender
9)	Lewis-de los Angeles, 2017	3,973	US	Inpatient (retrospective)	≤60 day	Diagnosed UTI	NE	≤4 days (PO)	≥5 days (PO/IV)	UTI readmission, all-cause readmission, adjusted OR for UTI Readmissions, adjusted OR for all-cause readmissions
10)	Marsh, 2020	112	US	Inpatient (retrospective)	≤28 days	Diagnosed UTI	<i>E. coli</i> , <i>Enterococcus</i> pp., <i>Klebsiella pneumoniae</i> , other enteric Gram-negative bacilli, group B <i>Streptococcus</i> , <i>S. aureus</i> , CoNS	≤4 days (IV)	>5 day (IV)	Organisms, blood culture result, CSF WBC count, renal ultrasound result, VCUG result, additional indication for hospitalization, readmission
11)	McMullen, 2014	522	Canada	Inpatient (case-control)	<6 mon	UTI by ICD-10 code confirmed by positive urine culture	<i>E. coli</i> , an organism other than <i>E. coli</i>	<96 hr (PO/IV)	≥96 hr (PO/IV)	Culture results, antibiotic resistance, imaging results, NICU or PICU admission

Abbreviations: pts, patients; UTI, urinary tract infection; NE, not evaluated; PO, per oral; IV, intravenous; CRP, C-reactive protein; APN, acute pyelonephritis; RCT, randomized controlled trial; VUR, vesicoureteral; OR, odds ratio; CoNS, coagulase-negative staphylococci; CSF, cerebrospinal fluid; WBC, white blood cell; VCUG, voiding cystourethrogram; ICD-10, International Classification of Diseases, 10th Revision; NICU, neonatal intensive care unit; PICU, paediatric intensive care unit.

DISCUSSION

The appropriate duration for antibiotic therapy in pediatric UTI is yet to be conclusively determined. Our research has focused on comparing the clinical outcomes of short and standard-course regimens, which is in line with previous meta-analysis on UTI treatment duration in children published in 1996.¹²⁾ Our findings indicate that a shorter duration of antimicrobial treatment may be used in selected patient group without complication and

Table 2. Primary outcomes of the studies included in the systematic review

Ref. No.	First author, Year	Clinical cure		Renal scarring		Abnormal ultrasound		UTI relapse		Readmission within 30 day	
		Short course	Standard course	Short course	Standard course	Short course	Standard course	Short course	Standard course	Short course	Standard course
3)	Abrahamsson, 2002	296/300 (96)		NE	NE	NE	NE	4/300 (2)		NE	NE
4)	Afolabi, 2020	1,504/1,567 (96)	5,767/6,131 (94)	NE	NE	NE	NE	42/1,567 (2.7)	269/6,131 (4.4)	63/1,567 (4)	364/6,131 (5.9)
5)	Bouissou, 2008	NE	NE	26/205 (13)	31/178 (17)	36/205 (18)	41/178 (23)	15/277 (5.4)	17/271 (6.3)	NE	NE
6)	Brady, 2010	NE (98.4)	NE (97.8)	NE	NE	NE	NE	NE	NE	NE (1.6)	NE (2.2)
7)	Fox, 2020	260/295 (88.1)	445/491 (90.6)	NE	NE	NE	NE	35/297 (11.8)	46/494 (9.3)	NE	NE
8)	Lessard, 2020	49/54 (91)	48 (89)	NE	NE	37/53 (28.3)	36/53 (37.7)	5/54 (9)	6/54 (11)	NE	NE
9)	Lewis-de los Angeles, 2017	2,627/2,739 (95.9)	1,172/1,234 (95.0)	NE	NE	NE	NE	42/2,739 (1.5)	19/1,234 (1.5)	112/2,739 (4.1)	62/1,234 (5.0)
10)	Marsh, 2020	53/55 (96.4)	53/57 (93)	NE	NE	NE	NE	1/55 (1.8)	0/57 (0)	2/55 (3.6)	4/57 (7.0)
11)	McMullen, 2014	NE	NE	NE	NE	29/48 (60)	48/60 (80)	NE	NE	NE	NE

Values are presented as number/total number (%).

Abbreviations: UTI, urinary tract infection; NE, not evaluated.

bacteremia. Studies varied in terms of their primary outcome of interests, however, in terms of clinical cure, renal scarring, abnormal ultrasound, UTI relapse, and readmission within 30 days, most studies with identifiable dataset were found to show noninferior outcomes in shorter treatment group. A recently reported randomized trial showed that pediatric patients with short-course therapy had higher treatment failure rates than children assigned to standard-course therapy, contrary to our result.¹³⁾ Despite the differences, the short-course therapy still had low relapse rate, therefore authors suggested that it be considered in selected patients with clinical improvement after the initial antibiotic therapy. Given the comparability of clinical cure and recurrence rates between short- and standard-course treatments, an antibiotic regimen of less 5–7 days could serve as an effective approach for managing pediatric UTI, without increasing the risk of complications.

In concordance with the existing guidelines,^{1,2)} our findings advocate the use of short-course antibiotic therapy for pediatric UTIs. These guidelines propose a specific treatment duration but provide less precise recommendations on parameters that are not well-defined. The American Academy of Pediatrics prescribes a minimum of 7 days of treatment from initiation, with patients remaining afebrile for 48–72 hours and presenting no signs of UTI-related clinical instability before treatment cessation.²⁾ The European Association of Urology/ European Society for Pediatric Urology advises continued parenteral antibiotic therapy until the child is afebrile, followed by 7–14 days of oral antibiotics.¹⁾ Nonetheless, multiple clinical studies, including those in our systematic review, define specific durations for both short- and standard-course treatments. Future clinical trials should consider these additional parameters, which can assist in the revision and precise definition of clinical considerations in the guidelines. Overall, short-course therapy seems to be an appropriate option for selected pediatric UTI cases, requiring individual case assessment by clinicians before discontinuation of antibiotics.

Our study carries certain limitations. Inaccessible unpublished data or investigative reports were not included in our analysis or review. Furthermore, the studies included in our analysis did not provide information about treatment-related adverse events, significant factors when determining therapy duration. In specific, occurrence of renal scarring may have more association with early initiation of antibiotics and genitourinary tract abnormality, rather than the duration of antibiotics; hence affecting the interpretation of our study. Lastly, the recent advent of oral antibiotic's role has not been evaluated in the current study. Oral

antibiotics are becoming a recommended treatment option in children with both cystitis and pyelonephritis, reflected in multiple guidelines, therefore should be investigated in the future research.¹⁴⁾ Despite these limitations, the collected studies emphasize the benefits of short-duration antibiotic regimens in select pediatric UTI cases.

Defining the optimal duration of antibiotic therapy in pediatric populations is critical to mitigate antimicrobial resistance, minimize toxicity, and reduce healthcare costs. Current evidence suggests that in pediatric UTI cases, an antibiotic regimen lasting 6 days or less is as effective as standarder treatments. Accordingly, shorter antibiotic therapy should be considered standard care in select pediatric cases. Future rigorously designed RCTs should include evaluations of clinical improvement, employ consistent definitions for short- and standard-course treatments, and focus on comparing outcomes between different treatment durations of the same antibiotic.

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요약

목적: 소아에서 요로감염은 높은 질병부담을 갖는다. 본 연구의 목적은 합병증이 없고 균혈증이 없는 소아 요로감염에서 단기 항생제 요법이 기존의 표준치료 방법과 비교해 비열등한지 평가하고자 한다.

방법: PubMed, Embase 및 Cochrane 데이터베이스에서 2021년 4월까지 출간된 연구에 대한 신속 체계적 문헌고찰 (Rapid Systematic Review)을 시행했다. 비교군으로는 소아 요로감염 환자를 대상으로 단기 항생제 치료(≤4일)를 한 군과 표준 항생제 치료(≥5-7일)를 한 군 간의 임상결과를 비교한 연구를 선정하였다.

결과: 신속 체계적 문헌고찰 결과, 단기 치료 방법은 표준 치료 방법에 비해 비열등한 치료 효과를 가지며, 임상 완치율 및 재발률이 유사한 것으로 측정되었다. 단기 치료와 표준 치료 방법의 임상적 치료율을 비교한 10개의 연구 모두 유사한 결과를 보고하였다. 신장 합병증을 평가를 한 연구는 단기 치료 방법이 표준 치료 방법과 비교해 비열등하지 않음을 보여주었다. 요로감염 재발에 대해서는 10개 중 8개의 연구에서 단기 치료와 표준 치료 방법 간 결과에 유의미한 차이가 없다고 보고하였다.

결론: 본 연구를 통해 결과는 균혈증이 없는 소아 요로감염 환자에서 단기 치료 방법이 표준 치료 방법에 준하는 효과성을 나타냈다. 본 연구결과를 바탕으로 일부 선택된 환자에 대한 치료 의사결정 시 참고할 수 있을 것이다.