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Comparison of Standard (7–14 Days) versus Extended (>14 Days) Intravenous Antibiotic Treatment for Vesicoureteral Reflux-Associated Acute Pyelonephritis in Children: A Retrospective Cohort Study

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Research Article

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Abstract

Background: The standard 7–14 day intravenous antibiotic regimen is typically adequate for treating acute pyelonephritis (APN) in children. However, for those with vesicoureteral reflux (VUR)-associated APN, the risk of recurrence is higher due to anatomical abnormalities. It remains unclear whether extending therapy beyond 14 days improves outcomes in this group.

Methods: In this retrospective observational study, children diagnosed with VUR-associated APN were categorized into two groups: standard (7–14 days) and extended (>14 days) intravenous antibiotic therapy. The primary outcomes included APN recurrence rates at 6 and 24 months. The secondary outcomes included total pyelonephritis episodes, estimated glomerular filtration rate (eGFR) changes, and severe adverse events.

Results: Among 99 children with VUR-associated APN, 45 received standard antibiotic courses, and 54 received extended antibiotic courses, with a median ageof 4 months (IQR: 2-10). The recurrence rates were 37.8% and 33.3% at 6 months (P > 0.05) and 44.4% and 40.7% at 24 months (P > 0.05) in the standard and extended course groups, respectively. Elevated WBC counts at admissionwerecorrelated with

recurrence risk, necessitating extended CAP. During follow-up, 74 pyelonephritis episodes occurred in 42 children (10 in the standard-course group and 7 in the extended-course group developed 2 or more APNs during follow-up) . No significant differences in eGFR or severe adverse events were observed.

Conclusion: In this retrospective cohort study of children with VUR-associated APN, extended IV antibiotic therapy (>14 days) did not outperform the standard 7–14 day regimen in lowering recurrence risk, total APN episodes, or adverse outcomes. With balanced baseline disease severity (reflux features, serum PCT/CRP, urinary indicators) between groups, and despite potential clinical adjustment of treatment duration by inflammatory marker normalization, our data do not support routine prolonged therapy for most patients—the standard regimen suffices for optimal outcomes, with no extra benefit from extension.

Introduction

Acute pyelonephritis (APN) is a common and potentially serious bacterial infection disease in children, affecting approximately 2% of boys and 8% of girls under six years of age. Vesicoureteral reflux (VUR), a congenital urinary tract abnormality, is a leading predisposing factor, present in 30% to 50% of children with APN episodes [1, 2]. Recurrent APN in children with VUR may lead to the development of renal scarring and reflux nephropathy, ultimately increasing the risk of chronic kidney disease and long-term renal impairment[3–7].

Optimizing the duration of intravenous (IV) antibiotic therapy is a critical component of APN management. Current international guidelines generally recommend a 7–14 day antibiotic course for

uncomplicated APN in children[8–12]. However, these guidelines predominantly target patients without structural urinary tract abnormalities. In children with VUR-associated APN, treatment duration remains controversial, and no consensus exists on whether extended courses provide superior protection against recurrence or renal sequelae.

Several retrospective studies and meta-analyses have suggested that standard-duration regimens (7–14 days) are as effective as extended courses (14–42 days) in managing uncomplicated APN[13]. Nonetheless, in clinical practice, children with VUR are often prescribed extended IV antibiotic regimens (> 14 days), largely driven by concerns regarding anatomical anomalies, more severe initial infections, and the potential for early recurrence. This empirical practice has not been systematically evaluated and may contribute to prolonged hospital stays, increased healthcare costs, and higher risks of nosocomial infections and antimicrobial resistance[14–16].

Recent efforts in pediatric infectious disease management advocate for shorter, individualized antibiotic therapies to balance efficacy with safety and resource optimization[9]. However, evidence supporting this approach in the context of VUR-associated APN is limited.

Therefore, we conducted a retrospective cohort study to evaluate whether extended IV antibiotic treatment (> 14 days) reduces recurrence or improves clinical outcomes compared to the standard 7–14 day regimen in children with VUR-associated APN. We hypothesized that standard-duration therapy would be noninferior to extended therapy in preventing recurrence and adverse outcomes, thus supporting its adequacy in most cases.

Methods

This was a single-center observational study of children diagnosed with VUR and APN, all of whom were 18 years of age or younger. This study was reviewed and approved by the local Medical Research Ethics Committee (Ethical Review (Research) No. 2024 − 270). Laboratory tests on admission included blood count, CRP, plasma creatinine, blood culture, Dimercaptosuccinic Acid Scan(DMSA), Computed Tomography Urography（CTU）, microscopic urinalysis (cell count in noncentrifuged urine), and urine culture. No personal or identifiable data were collected during the conduct of this study.

Trial population

The inclusion criteria were as follows: age ≤ 18 years, diagnostic criteria for acute pyelonephritis associated with vesicoureteral reflux in children included a diagnosis of VUR by excretory urography, the presence of clinical symptoms (including fever, kidney percussion pain), clean midstream urinalysis suggesting more than 3 urinary leukocytes per high-power field, and DMSA or CTU) scans showing infection in the kidneys, which must be confirmed by three experienced nephrologists. Exclusion criteria included patients with other urinary tract malformations that may increase the risk of acute pyelonephritis (for example, neurogenic bladder, tethered cord syndrome, etc.), surgery that may affect

urinary system function before admission, incomplete clinical data, chronic kidney disease stages 1–5 before the diagnosis of VUR, and immunodeficiency. Routine blood, urine, urine culture, and imaging examinations were performed on all children after admission.

Study Design

The antibiotic treatment protocols were jointly established by at least two attending physician and one associate chief physician. All enrolled children had urine culture specimens collected before the initiation of intravenous antibiotics—this baseline urine culture was used to confirm the pathogenic bacteria and test drug sensitivity, providing a basis for selecting targeted antibiotics. During treatment, C-reactive protein (CRP), procalcitonin (PCT), urinalysis, and urine culture were rechecked every 7 days. This monitoring frequency was tailored to the high-risk characteristics of our cohort: 81.8% of children had VUR of grade III or higher (Table 1), and 65.7% were infants aged < 6 months (median age: 4 months). For this population, infants often present with nonspecific symptoms (e.g., irritability instead of typical fever)—thus, enhanced laboratory monitoring was necessary to avoid missed detection of unresolved infection. Course extension (by 3–5 days) was only initiated when both clinical symptoms (e.g., persistent fever, flank tenderness) and laboratory indicators (sustained elevation of urine leukocytes/CRP/PCT) were present—single abnormal laboratory values without clinical correlates were not used as the basis for extension. This multi-dimensional decision-making framework was designed to minimize misjudgment caused by isolated fluctuations in inflammatory markers (e.g., transient CRP elevation due to non-infectious factors) .Notably, both groups ultimately achieved the same antibiotic discontinuation criteria before treatment cessation: complete resolution of clinical symptoms, urine white blood cell count < 3/HPF for three consecutive days, and negative urine culture. This ensures that the two groups were compared on the same "infection-cleared" basis when evaluating post-treatment outcomes (e.g., recurrence, eGFR).Eligible participants were divided into two groups according to the duration of receiving intravenous antibiotics (total duration of intravenous antibiotics during the course of the disease): a standard course group (in this course of treatment, the course of intravenous antibiotic use is ≥ 7 days and ≤ 14 days.) and an extended course group (in this course of treatment, the course of intravenous antibiotic use is greater than 14 days.) (Fig. 1). The primary study endpoints are the recurrence rates assessed at 6 and 24 months during the follow-up period, as well as the recurrence-free survival. The secondary outcomes included total urinary tract infection, estimated Glomerular Filtration Rate(eGFR) changes, and incidence of severe adverse events.

Table 1
Clinical and Demographic Characteristics of Enrolled Infants at Baseline.

Characteristic	**standard course** **N = 45**	**extended course** **N = 54**	**P**
Male sex-no(%)	24(53.3)	28(62.2)	0.22
Median age (IQR) - mo	4(3–9) 4(2,20)		0.97
First APN-no(%)	18(40.0)	27(50.0)	0.24
Ultrasound abnormal-no(%)	20(44.4)	27(50.0)	0.52
Grade of vesicoureteral reflux-no.			0.91
	4	6	
	6	2	
	12	20	
	19	23	
	4	3	
Bilateral vesicoureteral reflux-no. (%)	25(55.5)	21(38.9)	0.10
Median estimated GFR(IQR)- ml/min/1.73 m2	143.0(121.0-169.5)	143.0(121.0-172.3)	0.82
CAP treatment duration (IQR) – mo	3(1,7.5)	2.5(1,6)	0.34
PCT(IQR)-ng/ml	0.3(0.06,3.20)	0.48(0.17,3.17)	0.33
CRP(IQR)-mg/ml	21(0.43, 53.8)	41.8(7.5,76.7)	0.10
Urinalysis			
WBC* (cells/HP), median (IQR))	34(6,232.5)	75.5(18.75,311.25)	0.100
RBC (cells/HP), median (IQR)	1(0, 9)	3(0, 12.5)	0.558
Pyuria (cells/HP), median (IQR)**	0(0,0)	0(0,0.25)	0.105
Urine Leukocyte Esterase			0.374
0 (Negative)	16	16	
+- (Trace)	4	5	
+ (Low)	6	7	
++ (Moderate)	11	10	
+++ (High)	5	11	
Urine Nitrite			0.540

Characteristic	standard course N = 45	extended course N = 54	P
Negative	43	50	
Positive (+)	2	4	
Penicillins,n (%)	22(48.9)	32(59.2)	0.302
cephalosporins,n (%)	17(37.8)	26(48.1%)	0.300
combined use of antibiotics,n (%)	7(15.6)	9(16.7)	0.881
surgical evaluation,n (%)	19(42.2)	23(42.6)	0.94

Follow-up procedures

Two-year follow-up was conducted after discharge through inpatient visits, outpatient clinic visits, and remote monitoring via telephone and WeChat. The data collected included patients' baseline medical information, visit records, and the following specific outcomes: During the 24-month post-discharge follow-up period, we assessed the following outcomes: APN recurrence rate, frequency of APN recurrence, longitudinal kidney function evaluations, and incidence of serious adverse events.

Outcomes

The primary outcomes of this study were the recurrence rates assessed at the 6th and 24th months during the follow-up period, as well as the recurrence-free survival. The secondary outcomes included the total number of pyelonephritis cases, changes in the estimated glomerular filtration rate (eGFR), and incidence of serious adverse events within the same follow-up period.

Trial Definitions

The diagnosis of APN should be established by integrating clinical manifestations with laboratory tests. The diagnosis requires confirmation through DMSA or CTU, and must be agreed upon by at least two attending physicians and one director or associate director physician at our hospital. The clinical manifestations must include at least one of the following: fever, frequent urination, urinary urgency, or dysuria. However, there is marked age heterogeneity in these presentations: in infants and young children, increased crying during urination may be added to the above symptoms, while older children may present with costovertebral angle tenderness[17]. Loratory examinations include: urine collection via urinary catheter, or clean-catch midstream urine collection for children able to void voluntarily or refusing catheterization, followed by urinalysis and urine culture. Microscopic urinalysis (clean-catch midstream urine analysis showing > 3 white blood cells per high-power field [HPF]), serum C-reactive protein (CRP)

concentration > 10 mg/L (normal < 4 mg/L), and serum procalcitonin (PCT) > 0.5 ng/mL (normal < 0.05 ng/mL). A positive urine culture was defined as the presence of gram-negative bacteria with a colony count ≥ 105/ml and gram-positive bacteria with a colony count ≥ 104/ml in clean midstream urine collected via urinary catheter or voiding(For infants and young children unable to use the toilet independently, urine specimens were collected via urethral catheterization; for older children who could urinate independently or whose guardians refused catheterization, "clean midstream urine" was collected —with guardians assisting in cleaning the child's perineum first, followed by collecting the specimen during urination by discarding the initial urine stream and retaining the midstream portion). During the administration of intravenous antibiotics, urinalysis and urine culture were dynamically reviewed around the 7th day of treatment based on the patient's condition. The criteria for discontinuing antibiotics were as follows: complete resolution of clinical symptoms, a urine white blood cell count of < 3/high-power field (HPF) for three consecutive days, and a negative urine culture. This criterion was specifically developed based on the high-risk characteristics of the study population, with the specific basis as follows: (1) 65.7% of the enrolled children were infants aged < 6 months (median age: 4 months). These infants often present with nonspecific symptoms (e.g., only irritability without typical fever), making it difficult to determine whether the infection has been cleared based solely on clinical manifestations; (2) 81.8% of the children had vesicoureteral reflux (VUR) of grade III or higher (Table 1). Urinary reflux in such children may lead to persistent subclinical intrarenal infection—abnormalities in a single urinary indicator or temporary relief of symptoms cannot reflect whether the pathogen has been truly eradicated. During follow-up, APN recurrence was defined as at least one post-discharge clean midstream urine sediment microscopy showing > 3 WBCs per HPF plus typical APN symptoms (e.g., frequent urination, urgency, fever); for actual assessment, cross-verification was done with paper-based diagnostic certificates retained by guardians (including primary care physicians' summary diagnosis, e.g., "APN recurrence suspected based on urinalysis and symptoms") to avoid reliance on single indicators or subjective descriptions and improve rigor. No etiological data of recurrent APN were collected during follow-up, mainly due to primary care constraints: urine culture requires ≥ 2 days of incubation (guardians often failed to collect results after specimen submission due to symptom relief and inconvenient hospital visits) and primary hospitals lack mobile app-based report uploads (paper reports are easily lost), which are common issues in primary pediatric follow-up. To address this, a multi-dimensional assessment ("urinalysis + symptoms + paper certificates") was used to minimize the impact of missing etiological data on recurrence classification accuracy. Additionally, non-first-episode APN was defined as a previous diagnosis of APN that had been treated for more than 2 weeks with symptom resolution before the current episode.

Statistical analysis

For continuous variables, the Kolmogorov-Smirnov test was used to assess normal distribution. Categorical variables are presented as counts and percentages, whereas continuous variables with a normal distribution are expressed as the mean ± standard deviations. Skewed data are reported as medians and interquartile ranges (IQRs). Categorical variables were compared via the chi-square test or

Fisher's exact test, and differences in continuous variables between the two groups were evaluated via the t-test or Mann-Whitney U test. A p-value < 0.05 was considered statistically significant. Kaplan-Meier survival curves were constructed to compare recurrence-free survival between the standard and extended treatment groups, with the log-rank test used to assess the statistical significance between the curves. Univariate and multivariate logistic regression analyses were conducted to evaluate the associations between treatment duration (standard vs. extended) and other potential predictors of APN recurrence. Statistical analysis was performed via IBM SPSS Statistics 26.0 (IBM Corporation, Armonk, NY, USA). For variables that did not satisfy the proportional hazards assumption, landmark analysis was conducted using Rstudio(R-4.3.2) to compare whether there were significant differences in the survival curves between different groups after the landmark time point.

Results

Participant characteristics

From January 2017 to December 2022, a total of 328 children were screened, and finally 99 were enrolled in the cohort: 45 (45.5%) in the standard-course antibiotic treatment group and 54 (54.5%) in the extended-course treatment group(Table 1), the two groups showed excellent comparability at baseline, including key indicators of infection and inflammation (all P > 0.05, detailed in Table 1) .

A total of 52 male children were included in this study (accounting for 52.5%), with a median age of 4 months (interquartile range: 2–8.5 months); there were 47 female children (accounting for 47.5%), with a median age of 4 months (interquartile range: 3–13 months). 77.8% of the children in the cohort were under 1 year old, among whom infants under 6 months of age accounted for as high as 65.7%. The most common clinical manifestation was fever (accounting for 81.8%).The commonly used antibiotics during treatment included semi-synthetic penicillin-class antibiotics (e.g., piperacillin, amoxicillin-clavulanic acid), accounting for 53.3%, and cephalosporins, accounting for 43.4%. Notably, the selection of all antibiotics was based on urine culture results and drug sensitivity test results. In addition, 28.83% of the patients received a combination of 2 or more antibiotics during treatment.

The median duration of antibiotic use in the 7–14 day intravenous treatment group was 12 days (interquartile range: 10–13 days), while that in the intravenous treatment group with a duration exceeding 14 days was 20.5 days (interquartile range: 17–27 days). At admission, 54.5% of the children were diagnosed with non - first - episode urinary tract infection. The proportions of females in the standard - course group and the extended - course group were 46.7% and 37.8% respectively. Among all patients, 81.8% had VUR of grade III or higher, with 77.8% in the standard - course group and 85.2% in the extended - course group.

A total of 81 children received continuous antibiotic prophylaxis (CAP). The median duration of CAP in the standard - course group was 3 months (interquartile range: 1–7.5 months), and that in the extended - course group was 2.5 months (interquartile range: 1–6 months). There was no statistically significant

difference in the duration of CAP between the two groups. After discharge, the families of 4 children refused to continue using CAP.

Primary outcome

During the two-year follow-up period, pyelonephritis recurred in 42.4% of the patients. Most pyelonephritis recurrences occurred within 6 months of discharge, with 34 participants experiencing recurrences during this period, and no new cases of APN recurrence were identified in the participants during the last six months of follow-up. The recurrence rates were 37.8%(standard-course)and 33.3% (extended-course) at 6 months and 44.4% (standard-course) and 40.7%(extended-course) at 24 months in the standard and extended course groups, respectively, with no significant difference in the recurrence rate or relapse-free time between the groups (Fig. 2).

All the baseline data were checked via Cox regression models to verify their possible associations with the outcome. After univariate logistic regression, the duration of continuous antibiotic prophylaxis (CAP), routine white blood cell count, platelet count, and hemoglobin level were found to be important predictors. After multivariate adjustment, a longer duration of CAP treatment (OR 1.072, 95% CI 1.024–1.122) and higher routine white blood cell counts at admission (OR 1.076, 95% CI 1.027–1.129) were associated with APN recurrence. However, after multifactorial correction, there was still no significant difference between standard and longer courses of antibiotics and the recurrence of APNs (OR 0.848, 95% CI: 0.463–1.554).

Subgroup analysis was again performed for the enrolled children who used intravenous antibiotics. In the subgroup analysis of the treatment effect in all four combinations of participant sex and grade of vesicoureteral reflux, there was still no significant difference between the comparison groups in male and female children with different reflux grades.

When children under 2 years of age were divided into high-grade and low-grade groups for comparison of recurrence-free surviableval, there was no statistically significant difference between the two groups.

Secondary Outcomes

Total pyelonephritis

During the 24-month follow-up period, the recurrence of APN in the standard-course group and the extended-course group was as follows: a total of 53 APN events were recorded at the 6-month mark (29 in the standard group and 24 in the extended-course group), and recurrent APN (≥ 2 episodes) occurred in 6 children in each group. By 24 months, there were cumulatively 74 APN events (48 in the standard group and 30 in the extended-course group), with 10 and 7 children experiencing recurrent APN, respectively. There was no significant difference between the groups (P = 0.224). The results of the multivariate analysis indicated that prolonged intravenous antibiotic courses did not significantly reduce the risk of recurrent APN.

Estimated GFR

During the follow-up period, the renal function and eGFR of the children were regularly monitored, and no abnormalities in eGFR were observed in any of the patients. The following conditions were considered indicative of eGFR abnormalities: in the neonatal period, < 10 ml/min/1.73m² at birth for preterm infants, < 30 ml/min/1.73m² after corrected gestational age of 40 weeks, < 20 ml/min/1.73m² within 1 week of birth for term infants, and < 40 ml/min/1.73m² at 1 month of age; in infancy (1 month–1 year), < 60 ml/min/1.73m² at 1–6 months and < 70 ml/min/1.73m² at 6–12 months (using the Filler formula); in early childhood (1–3 years), < 80 ml/min/1.73m²; in preschool age (3–6 years), < 90 ml/min/1.73m²; in school age (6–12 years), < 95 ml/min/1.73m²; and in adolescence (13–18 years), < 100 ml/min/1.73m² for males and < 95 ml/min/1.73m² for females. (Schwartz Formula used for children aged > 1 year: $GFR = \mathrm{k} \times \frac{\mathrm{Height(cm)}}{\mathrm{Serum\ Creatinine(}\mu\ \mathrm{mol/L)}}$,for children aged 1 to 12 years, the constant k = 0.45,for those aged 13 years and older k = 0.55; Filler Formula used for children aged ≤ 1 year: $GFR = 0.33 \times \frac{\mathrm{Height(cm)}}{\mathrm{Serum\ Creatinine(}\mu\ \mathrm{mol/L)}}$).

Serious adverse events

No treatment-related adverse events, including infectious complications (drug-resistant bacterial infections and sepsis), renal-related adverse outcomes (e.g, acute or chronic renal impairment), or drug-related adverse reactions (e.g, antibiotic-induced gastrointestinal symptoms, allergic reactions) were observed during the follow-up period. In addition, no other system-related adverse events (e.g, hematologic abnormalities, or neurological symptoms) were identified.

Because of regional differences in China (with no widespread religious or cultural traditions requiring routine circumcision), Chinese children were not routinely circumcised in our study population—only two children underwent circumcision. It is important to note that this characteristic is specific to our Chinese cohort, as many other Asian countries have routine circumcision practices driven by religious backgrounds. Thus, our results may not be suitable for generalization to older children or populations with different circumcision practices (e.g., regions with routine religious circumcision).

Discussion

This study demonstrates that prolonging intravenous antibiotic therapy beyond 14 days offers no clinical advantage over the standard 7–14 day regimen in preventing acute pyelonephritis (APN) recurrence in children with vesicoureteral reflux (VUR), at both 6- and 24-month follow-ups. Tentatively, these results indicate that the 7–14-day duration of intravenous antibiotic treatment may be similarly effective in controlling infections in children with VUR-associated APN, rather than definitively suggesting it "does not affect efficacy." Given the preliminary nature of this finding, it may support the consideration of 7–14-day antibiotic regimens in pediatric patients with VUR-associated APN, with the aim of minimizing unnecessary drug exposure, reducing the risk of adverse reactions, and alleviating treatment-related burdens in clinical practice, but further validation with larger cohorts is warranted.

Our study population primarily consists of young infants (with a median age of 4 months), who have a high recurrence rate of pyelonephritis (53% had a history of previous infections) and normal kidney function. A key difference from previous studies is that our research specifically focuses on the impact of intravenous antibiotic treatment duration in the population of children with vesicoureteral reflux (VUR), rather than solely evaluating the effects of continuous antibiotic prophylaxis (CAP). This research focus still helps fill a potential gap in the existing literature.

Several studies in adult and pediatric populations have reported that shorter antibiotic courses can be effective in treating complicated pyelonephritis. For example, a study on complicated APN (involving adult patients with immunocompromise or multidrug-resistant infections) showed that prolonging antibiotic treatment provided no benefit, but since the study did not include pediatric patients, the applicability of its conclusions in children requires further validation[18]. In a study of 791 children with pyelonephritis, Miriam T et al. reported no differences in outcomes between short-term (median 8 days) and long-term (median 11 days) antibiotic use, although their cohort did not specifically focus on children under 6 months of age[19]. Another study on infants under 3 months of age also suggested that short antibiotic courses (≤ 3 days) did not increase readmission rates for pyelonephritis, with 16.9% of participants having VUR[20]. Our findings are consistent with these studies, but unlike these studies, our children were all children with combined VUR (and excluding the possibility of other urinary tract malformations), and our study revealed that such patients do not require long-term antibiotic therapy during hospitalization.

In our study, Cox regression model analysis showed that prolonged use of CAP was associated with UTI recurrence. This finding diverges from that of the large RIVUR trial[21], which demonstrated a significant reduction in pyelonephritis recurrence among VUR patients receiving CAP with trimethoprim-sulfamethoxazole [21]. This also contrasts with a single-center cohort study conducted by Fudan University—a key domestic study focusing on vesicoureteral reflux (VUR) and continuous antibiotic prophylaxis (CAP)—in which 256 children with grade I–V VUR received standardized CAP[22]. This study reported a breakthrough urinary tract infection (UTI) recurrence rate of 31.64%, which was significantly lower than the overall acute pyelonephritis (APN) recurrence rate of 42.4% in our study. This discrepancy underscores the critical role of CAP implementation in modulating recurrence risk. Notably, key differences in cohort characteristics between the two studies may contribute to this divergence: (1) Cohort Risk Characteristics: The RIVUR trial cohort had a median age of 12 months and a lower proportion of high-grade reflux cases (only 8.3% had grade IV or higher VUR). Further multivariate analysis in the Fudan study confirmed that younger age at the initial diagnosis of urinary tract infection (UTI) (≤ 12 months, hazard ratio [HR]: 4.629; 95% confidence interval [CI]: 1.302–16.462), bilateral VUR (HR: 2.078; 95% CI: 1.084–4.022), and bladder and bowel dysfunction (BBD) (HR: 3.194; 95% CI: 1.243–8.206) were independent risk factors for recurrence. In contrast, our cohort had a higher baseline risk: 65.7% of children were < 6 months old (below the high-risk threshold in the Fudan study), and 49.9% had grade IV–V VUR.(2) Standardization of CAP: Both the RIVUR trial and the Fudan study implemented long-term, standardized continuous antibiotic prophylaxis (CAP). The median duration of CAP was inferred to

be 6–12 months in the Fudan study (based on its low recurrence rate) and 2 years in the high-risk subgroup of the RIVUR trial. In sharp contrast, the CAP duration in our study was significantly shorter (median 3 months in the standard course group and 2.5 months in the extended course group)—far below the minimum 6-month duration recommended by guidelines for high-grade VUR and the standardized duration used in the Fudan study.

Furthermore, other studies that have confirmed the efficacy of CAP in reducing pyelonephritis recurrence (even in high-grade reflux cases) have uniformly reported prolonged CAP durations[23], such as standard 2-year treatment periods[24–29] —in stark contrast to our study, where CAP use was substantially shorter (median 3 months), potentially insufficient to exert a sustained preventive effect. Compounding this, our study was conducted in a real-world clinical setting, where CAP adherence varied significantly due to practical factors[30] including inconsistent family follow-up, parental concerns about long-term medication safety, and accidental missed doses—challenges that may have led to suboptimal drug concentrations, failed infection prevention, or even increased bacterial resistance, further influencing our results.

A strength of this study is the use of an extended 24-month follow-up period, which allows for the capture of both short-term and long-term outcomes. Although most recurrences of acute pyelonephritis (APN) occurred within the first 6 months after discharge, vesicoureteral reflux (VUR) is a chronic condition, and the risk of APN may persist over the long term. In addition, the baseline reflux grades were balanced between the two groups, reducing their potential confounding effect on follow-up outcomes—which is consistent with previous studies concluding that "higher reflux grades are associated with a higher recurrence risk" but does not alter the comparison results between the two groups in this study. However, due to the limited number of cases, we cannot rule out the possibility that unmeasured confounding factors may have affected the results.

Notably, our monitoring and course-adjustment protocol, while more intensive than the standard of care for uncomplicated APN, was a pragmatic choice for our high-risk cohort (high-grade VUR, young infants). However, our key finding—no significant difference in recurrence rates or adverse outcomes between the extended and standard course groups ($P > 0.05$)—indirectly validates the limitations of over-reliance on this protocol to prolong therapy. Even with enhanced monitoring to detect subclinical inflammation, extending courses beyond 14 days did not provide additional clinical benefit, which further reinforces that the standard 7–14-day regimen is sufficient for most children with VUR-associated APN.

We acknowledge that routine UA/UC monitoring may not be necessary for all pediatric APN patients. For low-grade VUR or older children with typical clinical responses to antibiotics, less frequent monitoring (e.g., based on symptom resolution alone) may be appropriate—a point that could be explored in future prospective studies to optimize resource utilization.

Strengths and Limitations

A primary strength of this study is its unique focus on the duration of antibiotic treatment for acute pyelonephritis (APNs) in children with vesicoureteral reflux (VUR), which addresses a gap in guidance for treating this complex condition. Our findings may be particularly applicable to young, uncircumcised children under two years of age with VUR grades I to V.

However, several limitations must be considered. This was a retrospective, single-center study with a relatively small sample size. While we collected a range of clinical data, other potentially influential variables[31–33], such as bowel and bladder dysfunction (BBD)[4, 34], prenatal ultrasound findings, antibiotic resistance were not included. Additionally, the low circumcision rate among Chinese males in our study may limit the generalizability of our results to populations with higher circumcision rates, as uncircumcised male infants have a greater risk of pyelonephritis due to preputial colonization[35].

Conclusions

This study demonstrated that extending intravenous antibiotic therapy beyond 14 days in children with VUR-associated APN did not reduce 6-month and 24-month recurrence rates, total pyelonephritis episodes, or risks of adverse outcomes (e.g., antibiotic resistance, renal impairment, or drug-related events) compared with the standard 7–14day regimen. Both strategies showed equivalent efficacy in terms of infection control and safety profiles, indicating that prolonged therapy confers no additional clinical benefit. Notably, baseline disease severity (assessed by reflux characteristics, serum PCT/CRP, urinary indicators) was balanced between groups (reducing initial clinical difference-related confounding); while clinical practice may adjust treatment duration by symptom/inflammatory marker normalization, our data do not support routine prolonged therapy for most patients. These findings reinforce the adequacy of the standard 7–14 day course for most children with VUR-associated APN, supporting its adoption to mitigate the risks of overtreatment and healthcare burden.

Abbreviations

APN
acute pyelonephritis
VUR
vesicoureteral reflux
VCUG
voiding cystourethrography
DMSA
dimercaptosuccinic acid renal scan
CTU
computed tomography urography
IV
intravenous.

Declarations

Data availability statement

The datasets supporting the conclusions of this article are included within the article (and its supplementary files).

Conflict of interest statement

None declared.

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Ethical Approval

All children enrolled in this study obtained consent to participate from their legal guardians, and written informed consent forms were signed.

The authors did not use generative AI or AI-assisted technologies in the development of this manuscript.

Clinical trial number

Not applicable.

Author Contributions:

Dr Zhang had full access to all of the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: All authors.

Acquisition, analysis, or interpretation of data: Huimin Chen.

Drafting of the manuscript: Huimin Chen.

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References

1. Naseri M, Tafazoli N, Tafazoli N. Prevalence of Vesicoureteral Reflux in Children with Urinary Tract Infection. Saudi journal of kidney diseases and transplantation: an official publication of the Saudi

Center for Organ Transplantation. Saudi Arabia. 2022;33:S111–20. http://doi.org/10.4103/1319-2442.384183.

2. Tullus K. Vesicoureteric reflux in children. Lancet (London England). 2015;385:371–9. http://doi.org/10.1016/s0140-6736(14)60383-4.
3. Najafi F, Sarokhani D, Hasanpour Dehkordi. A.The prevalence of kidney scarring due to urinary tract infection in Iranian children: a systematic review and meta-analysis. J Pediatr Urol. 2019;15:300–08. http://doi.org/10.1016/j.jpurol.2019.05.011.
4. Keren R, Shaikh N, Pohl H. Risk Factors for Recurrent Urinary Tract Infection and Renal Scarring. Pediatrics. 2015;136:e13–21. http://doi.org/10.1542/peds.2015-0409.
5. Vitko D, McQuaid JW, Gheinani AH. Urinary Tract Infections in Children with Vesicoureteral Reflux Are Accompanied by Alterations in Urinary Microbiota and Metabolome Profiles. Eur Urol. 2022;81:151–54. http://doi.org/10.1016/j.eururo.2021.08.022.
6. Mattoo TK, Chesney RW, Greenfield SP. Renal Scarring in the Randomized Intervention for Children with Vesicoureteral Reflux (RIVUR) Trial. Clin J Am Soc Nephrology: CJASN. 2016;11:54–61. http://doi.org/10.2215/cjn.05210515.
7. Garin EH, Olavarria F, Garcia Nieto V. Clinical significance of primary vesicoureteral reflux and urinary antibiotic prophylaxis after acute pyelonephritis: a multicenter, randomized, controlled study. Pediatrics. 2006;117:626–32. http://doi.org/10.1542/peds.2005-1362.
8. Tekgül S, Riedmiller H. Hoebeke P.EAU guidelines on vesicoureteral reflux in children. Eur Urol. 2012;62:534–42. http://doi.org/10.1016/j.eururo.2012.05.059.
9. Peters CA, Skoog SJ, Arant BS. Jr.Summary of the AUA Guideline on Management of Primary Vesicoureteral Reflux in Children. J Urol. 2010;184:1134–44. http://doi.org/10.1016/j.juro.2010.05.065.
10. Hari P, Meena J, Kumar M. Evidence-based clinical practice guideline for management of urinary tract infection and primary vesicoureteric reflux. Pediatr Nephrol. 2024;39:1639–68. http://doi.org/10.1007/s00467-023-06173-9.
11. Roberts KB. Urinary tract infection: clinical practice guideline for the diagnosis and management of the initial UTI in febrile infants and children 2 to 24 months. Pediatrics. 2011;128:595–610. http://doi.org/10.1542/peds.2011-1330.
12. Alsaywid BS, Alyami FA, Alqarni N, Neel KF, Almaddah TO, et al. Urinary tract infection in children: A narrative review of clinical practice guidelines. Urol annals. 2023;15:113–32. http://doi.org/10.4103/ua.ua_147_22.
13. Eliakim-Raz N, Yahav D, Paul M, Leibovici L. Duration of antibiotic treatment for acute pyelonephritis and septic urinary tract infection– 7 days or less versus longer treatment: systematic review and meta-analysis of randomized controlled trials. J Antimicrob Chemother. 2013;68:2183–91. http://doi.org/10.1093/jac/dkt177.
14. Wu TH, Huang FL, Fu LS. Treatment of recurrent complicated urinary tract infections in children with vesicoureteral reflux. Journal of microbiology, immunology, and infection = Wei mian yu gan ran za

zhi 2016;49: 717 – 22 http://doi.org/10.1016/j.jmii.2014.08.024

15. Isac R, Doros G, Stolojanu CA, Steflea RM, Stroescu RF, et al. General Characteristics and Current State of Antibiotic Resistance in Pediatric Urinary Tract Infection-A Single Center Experience. Antibiot (Basel Switzerland). 2024;13. http://doi.org/10.3390/antibiotics13080684.
16. Isac R, Basaca DG, Olariu IC, Stroescu RF, Ardelean AM, et al. Antibiotic Resistance Patterns of Uropathogens Causing Urinary Tract Infections in Children with Congenital Anomalies of Kidney and Urinary Tract. Child (Basel Switzerland). 2021;8. http://doi.org/10.3390/children8070585.
17. Boon HA, Van den Bruel A, Struyf T, Gillemot A, Bullens D, Verbakel JY. Clinical Features for the Diagnosis of Pediatric Urinary Tract Infections: Systematic Review and Meta-Analysis. Annals of family medicine 2021;19: 437 – 46 http://doi.org/10.1370/afm.2684
18. Klausner HA, Brown P, Peterson JA. trial of levofloxacin 750 mg once daily for 5 days versus ciprofloxacin 400 mg and/or 500 mg twice daily for 10 days in the treatment of acute pyelonephritis. Current medical research and opinion 2007;23: 2637-45 http://doi.org/10.1185/030079907x233340
19. Fox MT, Amoah J, Hsu AJ, Herzke CA, Gerber JS, Tamma PD. Comparative Effectiveness of Antibiotic Treatment Duration in Children With Pyelonephritis. JAMA Netw open. 2020;3:e203951. http://doi.org/10.1001/jamanetworkopen.2020.3951.
20. Zu'bi F, Pokarowski M, Al-Kutbi R, Science M, Vallipuram J, et al. A Comparison of Short Versus Long Course Intravenous Antibiotics When Treating Urinary Tract Infection in Infants < 60 Days of Age. Clin Pediatr. 2023;62:1201–08. http://doi.org/10.1177/00099228231154364.
21. Hoberman A, Greenfield SP, Mattoo TK. Antimicrobial prophylaxis for children with vesicoureteral reflux. N Engl J Med. 2014;370:2367–76. http://doi.org/10.1056/NEJMoa1401811.
22. Su D, Shen Q, Zhai Y, Chen J, Rao J, et al. Risk factors for breakthrough urinary tract infection in children with vesicoureteral reflux receiving continuous antibiotic prophylaxis. Translational Pediatr. 2022;11:1–9. http://doi.org/10.21037/tp-21-398.
23. Brandström P, Jodal U, Sillén U, Hansson S. The Swedish reflux trial: review of a randomized, controlled trial in children with dilating vesicoureteral reflux. J Pediatr Urol. 2011;7:594–600. http://doi.org/10.1016/j.jpurol.2011.05.006.
24. Brandström P, Esbjörner E, Herthelius M. The Swedish reflux trial in children: III. Urinary tract infection pattern. J Urol. 2010;184:286–91. http://doi.org/10.1016/j.juro.2010.01.061.
25. Morello W, Baskin E, Jankauskiene A. Antibiotic Prophylaxis in Infants with Grade III, IV, or V Vesicoureteral Reflux. N Engl J Med. 2023;389:987–97. http://doi.org/10.1056/NEJMoa2300161.
26. Puri P, Friedmacher F, Farrugia MK. Primary vesicoureteral reflux. Nature reviews. Disease primers. 2024;10:75. http://doi.org/10.1038/s41572-024-00560-8.
27. Wang HH, Gbadegesin RA, Foreman JW. Efficacy of antibiotic prophylaxis in children with vesicoureteral reflux: systematic review and meta-analysis. J Urol. 2015;193:963–9. http://doi.org/10.1016/j.juro.2014.08.112.
28. Williams G, Craig JC. Long-term antibiotics for preventing recurrent urinary tract infection in children. The Cochrane database of systematic reviews 2019;4: Cd001534

http://doi.org/10.1002/14651858.CD001534.pub4

29. Pérez-Gaxiola G. Antibiotic prophylaxis reduced symptomatic urinary tract infection in children with vesicoureteral reflux, but not scarring. Archives of disease in childhood. Educ Pract Ed. 2015;100:52. http://doi.org/10.1136/archdischild-2014-307056.
30. Hensle TW, Hyun G, Grogg AL. Part 2: Examining pediatric vesicoureteral reflux: a real-world evaluation of treatment patterns and outcomes. Curr Med Res Opin. 2007;23(Suppl 4):S7–13. http://doi.org/10.1185/030079907x226221.
31. Arlen AM, Leong T, Wu CQ. Predicting Breakthrough Urinary Tract Infection: Comparative Analysis of Vesicoureteral Reflux Index, Reflux Grade and Ureteral Diameter Ratio. J Urol. 2020;204:572–77. http://doi.org/10.1097/ju.0000000000001035.
32. Bertsimas D, Li M, Estrada CS. Children with Vesicoureteral Reflux Who are Most Likely to Benefit from Antibiotic Prophylaxis: Application of Machine Learning to RIVUR. J Urol. 2021;205:1170–79. http://doi.org/10.1097/ju.0000000000001445.
33. Hum SW, Shaikh N. Risk Factors for Delayed Antimicrobial Treatment in Febrile Children with Urinary Tract Infections. J Pediatr. 2019;205:126–29. http://doi.org/10.1016/j.jpeds.2018.09.029.
34. Gnech M, t Hoen L, Zachou A. Update and Summary of the European Association of Urology/European Society of Paediatric Urology Paediatric Guidelines on Vesicoureteral Reflux in Children. Eur Urol. 2024;85:433–42. http://doi.org/10.1016/j.eururo.2023.12.005.
35. Yang SS, Tsai JD, Kanematsu A. Asian guidelines for urinary tract infection in children. J Infect chemotherapy: official J Japan Soc Chemother. 2021;27:1543–54. http://doi.org/10.1016/j.jiac.2021.07.014.

Figures

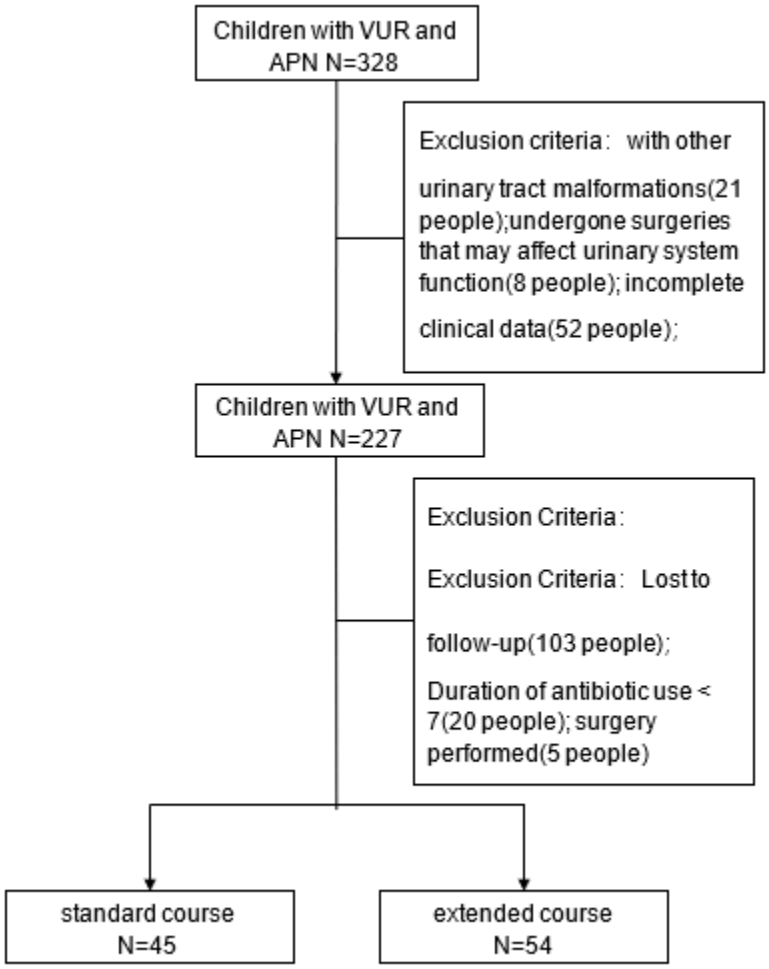


Figure 1

Flow diagram of patient selection and grouping in the retrospective cohort study.

Abbreviations: APN, acute pyelonephritis; VUR, vesicoureteral reflux; VCUG, voiding cystourethrography; DMSA, dimercaptosuccinic acid renal scan; CTU, computed tomography urography; IV, intravenous.

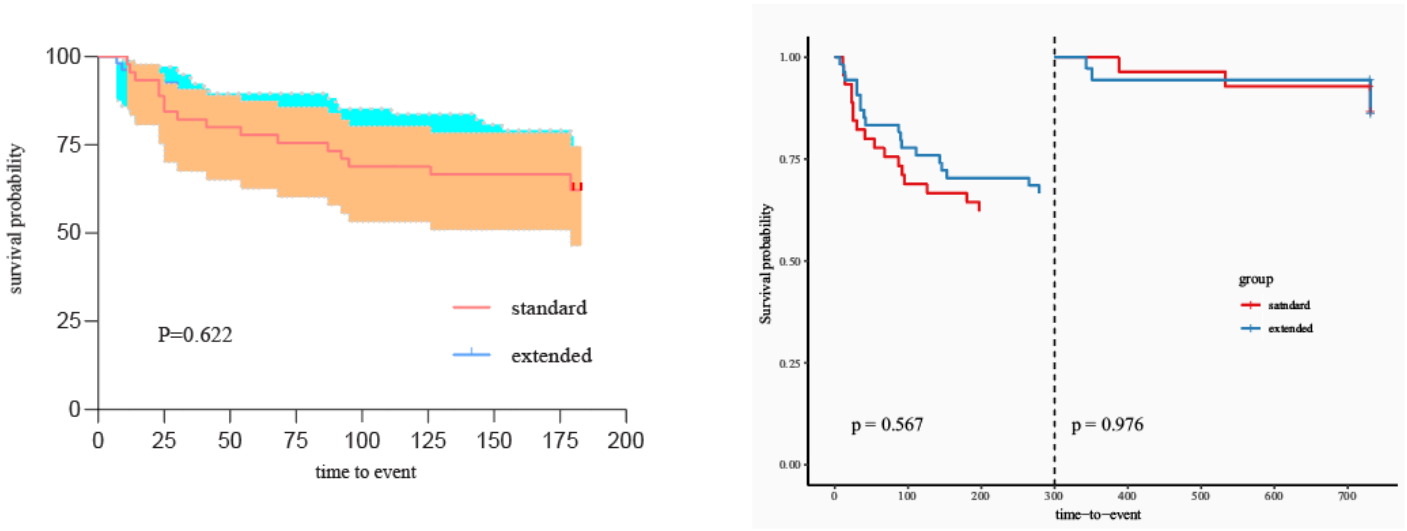


Figure 2

Kaplan–Meier curves of acute pyelonephritis (APN)–free survival in children with VUR-associated APN treated with standard versus extended intravenous antibiotic therapy. The shaded areas represent 95% pointwise confidence intervals. Confidence intervals were not adjusted for multiplicity and should not be used to infer definitive treatment effects.

a. Acute pyelonephritis (APN)–free Survival during the 6-month follow-up period.

b. Acute pyelonephritis (APN)–free Survival during the 24-month follow-up period.

Supplementary Files

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