# Antibiotic Prescribing Practices for Urinary Tract Infection in a Pediatric Emergency Department: Is This a Problem Worth Cefix-ing?

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## ABSTRACT

**Background:** Pediatric urinary tract infection (UTI) is associated with diagnostic and therapeutic challenges.

**Objective:** To determine the least-broad-spectrum oral antibiotic that would cover 80% of pathogens from lower (afebrile) and upper (febrile) UTIs in a Canadian pediatric emergency department (ED).

**Methods:** This retrospective case series involved children discharged from the ED between September 2020 and February 2021 with a diagnosis of UTI and collection of a sample for urinalysis that had growth on culture.

**Results:** Of 188 patients who met the inclusion criteria, 184 (97.9%) were discharged on antibiotics. Culture results indicated a UTI in 170 cases (92.4% of those discharged on antibiotics). The 95 urinary isolates from lower UTIs were susceptible to cephalexin ($n$ = 81, 85.3%), cefixime ($n$ = 78, 82.1%), nitrofurantoin ($n$ = 76, 80.0%), trimethoprim–sulfamethoxazole (TMP–SMX) ($n$ = 64, 67.4%), and amoxicillin ($n$ = 55, 57.9%). The 75 urinary isolates from upper UTIs were susceptible to cefixime ($n$ = 71, 94.7%), TMP–SMX ($n$ = 57, 76.0%), and amoxicillin ($n$ = 48, 64.0%). The mean prescribed duration of antibiotic therapy was 8.3 days for patients with a lower UTI and 9.1 days for those with an upper UTI (mean difference 0.80 days, 95% confidence interval 0.05–1.54).

**Conclusions:** Empiric treatment with cephalexin or nitrofurantoin would have been successful for almost all lower UTIs. More complete reporting of cephalexin minimal inhibitory concentrations might have allowed use of this drug for most upper UTIs. Although there was a trend toward shorter duration of therapy for lower versus upper UTI, lower UTIs were always treated for longer than recommended by current guidelines.


**Keywords:** pediatrics, urinary tract infection, emergency department, antimicrobial stewardship


## RÉSUMÉ

**Contexte :** L'infection des voies urinaires (IVU) pédiatrique présente des défis diagnostiques et thérapeutiques.

**Objectif :** Déterminer l'antibiotique oral à large spectre le moins élevé qui couvrirait 80 % des pathogènes des IVU inférieures (sans fièvre) et des IVU supérieures (avec fièvre) dans un service d'urgences pédiatriques canadien.

**Méthodes :** Cette série de cas rétrospective impliquait des enfants sortis du service des urgences entre septembre 2020 et février 2021 avec un diagnostic d'IVU et la collecte d'un échantillon pour une analyse d'urine avec croissance dans la culture d'urine.

**Résultats :** Parmi les 188 patients répondant aux critères d'inclusion, 184 (97,9 %) ont reçu des antibiotiques au moment du congé. Les résultats de la culture ont indiqué une IVU dans 170 cas (92,4 % des patients ayant reçu des antibiotiques au moment du congé). Les 95 isolats urinaires des IVU inférieures étaient sensibles à la céphalexine ($n$ = 81, 85,3 %), au céfixime ($n$ = 78, 82,1 %), à la nitrofurantoïne ($n$ = 76, 80,0 %), au triméthoprime-sulfaméthoxazole (TMP-SMX) ($n$ = 64, 67,4 %) et à l'amoxicilline ($n$ = 55, 57,9 %). Les 75 isolats urinaires des IVU supérieures étaient sensibles au céfixime ($n$ = 71, 94,7 %), au TMP-SMX ($n$ = 57, 76,0 %) et à l'amoxicilline ($n$ = 48, 64,0 %). La durée moyenne de prescription d'antibiotiques était de 8,3 jours pour les patients atteints d'une IVU inférieure et de 9,1 jours pour ceux atteints d'une IVU supérieure (différence moyenne 0,80 jours, IC à 95 % 0,05-1,54).

**Conclusions :** Un traitement empirique avec la céphalexine ou la nitrofurantoïne aurait été efficace pour la grande majorité des infections urinaires inférieures. Un rapport plus complet des concentrations minimales inhibitrices de la céphalexine aurait peut-être permis d'utiliser ce médicament pour la plupart des infections urinaires supérieures. Bien qu'il y ait eu une tendance vers une durée de traitement plus courte pour les infections urinaires inférieures par rapport aux infections urinaires supérieures, les infections urinaires inférieures étaient toujours traitées plus longtemps que ce qui est recommandé par les lignes directrices actuelles.


**Mots-clés :** pédiatrie, infection des voies urinaires, service des urgences, gestion des antimicrobiens

## INTRODUCTION

Urinary tract infection (UTI) is one of the most common infections seen in the pediatric emergency department (ED). Diagnosis is challenging, as symptoms cannot be elicited in preverbal children, urine is commonly contaminated with bowel flora upon collection, and urinalysis lacks diagnostic accuracy.[1] Almost all children with a UTI have 1 or more of the following signs: positive test result for nitrites, positive test result for leukocyte esterase, and presence of white blood cells or bacteria on microscopy. The specificity of these tests ranges from 78% for leukocyte esterase to 98% for nitrites.[2]

Empiric antimicrobial selection should be guided by local susceptibility patterns. The current guideline of the Canadian Paediatric Society (CPS) states that "Currently, cefixime is a good choice in most areas."[3] However, there is increasing recognition of the need for antimicrobial stewardship to prevent development of resistance, and cefixime may have a broader spectrum of activity than currently required.

The main objective of this study was to determine whether cefixime is still the optimal choice for pediatric UTI or whether less-broad-spectrum antibiotics could be used for empiric outpatient treatment of UTIs in a Canadian pediatric ED.

## METHODS

### Study Design and Participants

A retrospective case series was performed at the Alberta Children's Hospital, where patients up to 17 years of age are seen. There is currently no guideline for management of UTIs at this hospital. The study was based on a sample of convenience. Patient visits to the ED from September 1, 2020, through February 28, 2021, were included if UTI was listed as a potential diagnosis, urinalysis and urine culture had been performed, and any growth was reported from the culture. Patients were excluded if they had been referred to the Ambulatory Parenteral Therapy Clinic for IV antibiotics or if they had been admitted.

The following data were collected (by J.K.) from electronic charts: demographic characteristics, results of urinalysis and culture, antibiotic prescribed, time to reporting of susceptibilities, any documented follow-up, and return visits to the ED within 14 days. It was assumed that pathogens other than *Staphylococcus aureus* or coagulase-negative staphylococci that were susceptible to cephalexin were also susceptible to cefixime. Approximately 10% of the charts ($n$ = 20) were reviewed by a second investigator (T.T.) to confirm accuracy in the interpretation of follow-up documentation and intervention coding.

This study was approved by the Health Research Ethics Board at the University of Alberta. Parental consent was waived, and the STROBE guidelines[4] were followed.

### Definitions

A positive urinalysis result was defined as any of the following: positive for leukocyte esterase (at any level) or nitrites, leukocyte count above 5 white blood cells per high-power field, or bacteria present on microscopy. A positive result on urine culture was defined as $10^7$ colony-forming units per litre (CFU/L) or above for a midstream urine sample or an in–out catheter specimen, or any growth from a suprapubic aspirate specimen. Lower colony counts were considered to represent negative culture results. Cultures with mixed growth were excluded unless the urinalysis results were abnormal and the colony count for all organisms met the definition of a positive urine culture result. Upper UTI (pyelonephritis) was defined by temperature of 38°C or above in the ED and/or documentation of fever at home. Afebrile cases were assumed to be lower UTI (cystitis).

### Objectives

The primary objective of the study was to determine the least-broad-spectrum antibiotic that would have covered an arbitrarily chosen minimum 80% of cases with positive urine culture results for patients with upper and lower UTIs. Coverage of 100% of isolates would be ideal but would likely require empiric parenteral antibiotics. The reason for considering upper and lower UTIs separately was that for some antibiotics (specifically cephalexin and nitrofurantoin), even if the minimal inhibitory concentration (MIC) is low, it is not clear that concentration in the renal parenchyma will be adequate to cure upper UTI; there appear to be no published studies on use of these antibiotics for upper UTI.

The secondary objective was to determine how often the duration of therapy fit with CPS guidelines, which recommend 7 to 10 days for upper UTI and 2 to 4 days for older children (not further defined) with lower UTI.[3] A Cochrane review[5] and guidelines from the UK National Institute for Health and Care Excellence[6] support the shorter duration for lower UTI in children as young as 3 months of age.

Data analysis was limited to descriptive statistics.

## RESULTS

Charts were reviewed for 232 patients seen during the study period, of whom 44 (19%) were excluded because they had been admitted ($n$ = 20) or referred ($n$ = 24) to the Ambulatory Parenteral Therapy Clinic. The remaining 188 patients (86.7% female; median age 5.0 [interquartile range 1.6–9.4] years) met the inclusion criteria (Table 1). Forty-one (21.8%) of the 188 patients had a history of UTI. Urinalysis results were positive in 183 (97.3%) of the cases. Eighty-three (44.1%) of the patients had fever at home or in the ED.

Empiric antibiotics were started in the ED for 184 (97.8%) of the 188 patients, specifically cefixime ($n$ = 156, 84.8%),

with 5 of these patients also receiving 1 dose of ceftriaxone in the ED; amoxicillin–clavulanate ($n$ = 8, 4.3%); nitrofurantoin ($n$ = 7, 3.8%); trimethoprim–sulfamethoxazole (TMP–SMX; $n$ = 6, 3.3%); amoxicillin ($n$ = 4, 2.2%); ciprofloxacin ($n$ = 2, 1.1%); and cephalexin ($n$ = 1, 0.5%). Urine culture results met the study definition of "positive" for 170 patients (92.4% of the 184 with initiation of antibiotics), of whom 95 (55.9%) had lower UTIs. Organisms and susceptibilities (which were reported a mean of 2.01 [standard deviation 0.56] days after the ED visit) are shown in Table 2. The 95 urinary isolates from lower UTIs were susceptible to cephalexin ($n$ = 81, 85.3%, cefixime ($n$ = 78, 82.1%), nitrofurantoin ($n$ = 76, 80.0%), TMP–SMX ($n$ = 64, 67.4%), and amoxicillin ($n$ = 55, 57.9%). The 75 urinary isolates from upper UTIs were susceptible to cefixime ($n$ = 71, 94.7%), TMP–SMX ($n$ = 57, 76.0%), and amoxicillin ($n$ = 48, 64.0%). Of the 156 isolates treated with cefixime, 153 (98.1%) were susceptible to one or both of cephalexin and nitrofurantoin.

**TABLE 1. Characteristics of 188 Children Discharged from an Emergency Department with a Diagnosis of Urinary Tract Infection**

| Characteristic | No. (%) of Patients[a] ($n$ = 188) |
|---|---|
| Sex, female | 163 (86.7) |
| Age | |
| Median (IQR) | 5.0 (1.6–9.4) years |
| 2 months to 3 years | 78 (41.5) |
| 4–12 years | 83 (44.1) |
| 13–18 years | 27 (14.4) |
| Febrile[b] | 83 (44.1) |
| Comorbidities/history | |
| History of UTI | 41 (21.8) |
| Structural kidney/bladder abnormalities[c] | 11 (5.9) |
| Immunosuppression | 0 |
| Other[d] | 14 (7.4) |
| Antibiotic use within 7 days before the ED visit | 9 (4.8) |
| Trimethoprim–sulfamethoxazole | 2 |
| Trimethoprim | 1 |
| Nitrofurantoin | 4 |
| Cephalexin | 1 |
| Cefixime | 1 |
| Urine collection method | |
| Midstream | 126 (67.0) |
| In-out catheter | 62 (33.0) |
| Positive urinalysis result[e] | 183 (97.3) |
| Positive result on urine culture[f] | 170 (90.4) |

CFU = colony-forming unit, ED = emergency department, IQR = interquartile range, UTI = urinary tract infection.
[a]Except where indicated otherwise.
[b]Defined as temperature ≥ 38.0°C and/or clinician documentation of fever or parent reported fever at home before ED visit.
[c]Vesicoureteral reflux, bladder diverticulum, duplex ureter, hydronephrosis, pyeloplasty/stent, neurogenic bladder.
[d]Viral meningitis, asthma, herpes simplex virus, COVID-19, epilepsy, meningomyelocele, renal stone, depression, constipation.
[e]A urinalysis result was considered positive if at least 1 of the following was true: leukocyte esterase or nitrite was detected, urine white blood cell count was > 5 cells per high-power field, or bacteria was present on microscopy.
[f]Positive result on urine culture was defined as ≥ $10^7$ CFU/L for clean-catch midstream urine, ≥ $10^7$ CFU/L for an in–out catheter specimen, and any growth from a suprapubic aspirate specimen.

The mean prescribed duration of antibiotics was 8.3 days for the 95 patients with a lower UTI and 9.1 days for the 75 patients with an upper UTI, for a mean difference of 0.80 days (95% confidence interval [CI] 0.05–1.54 days). For patients with a lower UTI, the duration of therapy was specified in the chart for 74 of the 95 cases: 5 days ($n$ = 3), 7 days ($n$ = 47), 10 days ($n$ = 20), or 14 days ($n$ = 4), with no patients having the recommended duration of 2–4 days. For patients with an upper UTI, the duration of therapy was specified in the chart for 62 of the 75 cases: 7 days ($n$ = 24), 10 days ($n$ = 33), and 14 days ($n$ = 5).

Follow-up was documented for all but 2 patients. Antibiotic interventions at follow-up included changing antibiotics because of resistance of the empiric choice ($n$ = 7), narrowing empiric treatment to an alternative antibiotic ($n$ = 3), and initiating an antibiotic (for 2 of the 4 patients not initially treated). Antibiotics were not discontinued for any of the 14 children with negative culture results. There were a total of 13 visits to the ED within 14 days, of which 9 were related to the initial UTI: worsening of UTI symptoms ($n$ = 4, none of whom had an isolate resistant to the prescribed antibiotic); difficulties in administering oral cefixime ($n$ = 2); and adverse effects of antibiotics, specifically 1 case each of diarrhea (patient receiving cefixime), rash (patient receiving TMP–SMX), and fussiness with poor feeding (patient receiving cefixime). None of these patients required admission to hospital.

Agreement between the 2 investigators who reviewed the charts was 100%.

## DISCUSSION

More than 80% of urinary isolates were susceptible to cefixime, nitrofurantoin, cephalexin, and amoxicillin–clavulanate. Cefixime was by far the most frequently prescribed antibiotic for UTIs in this study. Although almost all patients could have been changed to a narrower-spectrum antibiotic once susceptibilities were available, this happened in only 3 cases. Changing therapy after ED discharge is a logistical challenge and is costly to parents, which highlights the importance of ensuring optimal initial empiric prescribing. Only 14 (7.6%) of the 184 patients who were started on antibiotics did not have a UTI, compared with 46% in another recent Canadian study,[8] which suggests that clinicians in our organization rarely prescribed antibiotics if the urinalysis results were negative.

Nitrofurantoin is not recommended for upper UTI because renal penetration is poor, but this drug should be considered for lower UTI given that almost all isolates were susceptible. However, nitrofurantoin requires 4 times daily administration except for adolescents, who can take the macrocrystal/monohydrate capsule twice daily.

Cephalexin is another empiric antibiotic that is appropriate for lower UTIs, given it covered almost all isolates. Rates of susceptibility to cephalexin have increased in recent years after the Clinical and Laboratory Standards Institute's introduction of urinary cefazolin-surrogate testing in 2014 (after the CPS guideline[3] was written), which corrected errors in reporting of cephalexin resistance that had resulted from cephalothin-surrogate testing.[7] However, the MIC breakpoint for cephalexin reported in our laboratory is based on the treatment of lower UTI. In the absence of reporting of breakpoints for upper UTI, cephalexin should be reserved for lower UTI. Traditional 4 times daily dosing is a barrier to compliance, but the product monograph states that twice-daily dosing can be used for children with lower UTI.[9]

**TABLE 2. Susceptibility of Isolates from Urine Cultures of Children Seen in a Pediatric Emergency Department[a]**

| Isolate and Variable | Amoxicillin–ampicillin | Amoxicillin–clavulanate | Cephalexin | Gentamicin | Nitrofurantoin | Trimethoprim–sulfamethoxazole | Ceftriaxone | Cefixime | Cefazolin[b] | Ciprofloxacin | Tobramycin | Carbapenems[b,c] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Escherichia coli* (*n* = 135)[c,d] | | | | | | | | | | | | |
| No. of patients/cultures | 135 | 135 | 135 | 135 | 135 | 135 | 9[e] | 3[e] | 10[e] | 3[e] | 5[e] | 1[e] |
| Susceptible | 63% | 7% | 97% | 97% | 99% | 78% | 100% | 67% | 0% | 100% | 20% | 100% |
| Resistant | 37% | 8% | 3% | 3% | 1% | 22% | 0% | 33% | 100% | 0% | 0% | 0% |
| Intermediate resistance | 0% | 5% | 0% | 0% | 0% | 0% | 0% | 0% | 0% | 0% | 80% | 0% |
| *Proteus mirabilis* (*n* = 8) | | | | | | | | | | | | |
| No. of patients/cultures | 8 | – | 8 | 8 | 8 | 8 | 1 | – | 1 | – | – | – |
| Susceptible | 100% | – | 100% | 100% | 12% | 100% | 100% | – | 0% | – | – | – |
| Resistant | 0% | – | 0% | 0% | 88% | 0% | 0% | – | 100% | – | – | – |
| Intermediate resistance | 0% | – | 0% | 0% | 0% | 0% | 0% | – | – | – | – | – |
| *Klebsiella pneumoniae* (*n* = 7)[d] | | | | | | | | | | | | |
| No. of patients/cultures | 6 | 6 | 6 | 6 | 6 | 5 | – | – | – | 3 | – | – |
| Susceptible | 0% | 100% | 100% | 100% | 17% | 100% | – | – | – | 100% | – | – |
| Resistant | 100% | 0% | 0% | 0% | 0% | 0% | – | – | – | 0% | – | – |
| Intermediate resistance | 0% | 0% | 0% | 0% | 83% | 0% | – | – | – | 0% | – | – |
| *Citrobacter* sp. (*n* = 3) | | | | | | | | | | | | |
| No. of patients/cultures | 3 | 3 | 3 | 3 | 3 | 3 | – | – | 2 | – | – | – |
| Susceptible | 0% | 33% | 33% | 100% | 67% | 100% | – | – | 0% | – | – | – |
| Resistant | 100% | 67% | 67% | 0% | 33% | 0% | – | – | 100% | – | – | – |
| Intermediate resistance | 0% | 0% | 0% | 0% | 0% | 0% | – | – | 0% | – | – | – |
| *Enterococcus faecalis* (*n* = 6)[d] | | | | | | | | | | | | |
| No. of patients/cultures | 6 | – | – | – | 6 | – | – | – | – | – | – | – |
| Susceptible | 100% | – | – | – | 100% | – | – | – | – | – | – | – |
| Resistant | 0% | – | – | – | 0% | – | – | – | – | – | – | – |
| Intermediate resistance | 0% | – | – | – | 0% | – | – | – | – | – | – | – |

CFU = colony-forming unit, MIC = minimum inhibitory concentration, UTI = urinary tract infection.

[a]Two patients had 2 organisms each. In addition, the table includes results for 3 patients who did not meet the study definition of a positive urine culture result. Other organisms: *Klebsiella oxytoca* (*n* = 2), *Staphylococcus aureus* (*n* = 1), coagulase-negative *Staphylococcus* (*n* = 5), *Streptococcus agalactiae* (*n* = 4), *Aerococcus urinae* (*n* = 1), *Enterococcus faecium* (ampicillin sensitive) (*n* = 1), *Staphylococcus saprophyticus* (*n* = 2).

[b]Six of the 10 *E. coli* cultures with cefazolin resistance had concurrent cephalexin susceptibility. Cefazolin is used as a surrogate for cephalexin and when used specifically for lower UTI has a higher MIC breakpoint (≤ 16 µg/mL) than when it is used for any infection other than lower UTI (for which MIC breakpoint is ≤ 2 µg/mL).[7] Therefore, in cases where the bacteria is reported as resistant to cefazolin but susceptible to cephalexin, cephalexin can be used for lower UTIs, but there is uncertainty as to whether cefazolin or cephalexin should be used for upper UTIs.

[c]One isolate had extended-spectrum β-lactamase (ESBL) resistance.

[d]Two cultures had 2 organisms with more than $10^7$ CFU/L: *E. coli* and *E. faecalis* in combination; *E. coli* and *K. pneumoniae* in combination.

[e]Only reported according to local microbiology lab algorithm based on resistance or clinician request.

Other centres have reported the use of cephalexin rather than cefixime for empiric therapy of both upper and lower UTIs. In a study conducted in Seattle, Washington, use of cephalexin for uncomplicated UTIs treated in the ED and for inpatients increased from 19% to 80% once a guideline was introduced.[10] In a similar Kaiser Permanente study limited to outpatients, use of cephalexin increased from 29% to 53% with introduction of a guideline.[11] A study conducted in Toronto, Ontario, showed that 57% of patients seen in the ED were discharged on cephalexin.[8] None of these studies reported outcome data, but an abstract from a Philadelphia, Pennsylvania, study reported treatment failure in only 13% (95% CI 10%–15%) of 761 children treated with cephalexin versus 19% (95% CI 16%–21%) of 1010 treated with TMP–SMX and 36% (95% CI 31%–41%) of 363 treated with amoxicillin.[12] None of these 4 studies excluded children with upper UTI, and the Toronto study noted that the majority of patients had upper UTIs.[8]

Almost all isolates were susceptible to amoxicillin–clavulanate. However, this option has a broader spectrum of activity and costs more than cefixime or cephalexin, and many clinicians consider it more likely to cause diarrhea.

Adult guidelines caution that β-lactams have lower efficacy and are associated with more adverse events than other classes of antibiotics when used to treat UTI,[13] but this does not seem to be a concern in children: almost all of the patients in our study were treated with a β-lactam, with only 4 (2.4%) of 170 re-presenting with persistent symptoms.

For every child, the prescribed duration was longer than the 2- to 4-day course recommended for lower UTI,[3] but for most the prescribed duration fell within the recommended 7- to 10-day course for upper UTI. However, evidence is emerging that 7 days is sufficient for upper UTI.[14] As for lower UTI, traditional dogma is that the duration of β-lactam therapy should be longer than for other antibiotics,[7] but the previously mentioned Kaiser Permanente study successfully used a 3-day course of cephalexin.[11] In a recent trial, children with upper or lower UTI with clinical improvement on day 5 were randomly assigned to stop therapy or continue another 5 days of treatment.[15] Cure rate was inferior among the children with fever who stopped therapy after 5 days, but was still 96% (versus 99%), indicating that even in children with upper UTIs, 5 days of therapy may be sufficient if there is clinical improvement at the end of treatment.

This study had all the inherent limitations of a retrospective chart review. The definitions of UTI are not consistent across the pediatric literature. Our methodology did not allow us to determine factors that might have led to longer courses of antibiotic therapy, nor could we analyze the results of follow-up appointments outside the ED. Data on duration of antibiotic therapy were missing for some patients. In addition, the prescribed duration of antibiotics may have differed from the actual duration. Practice changes occurred in ED settings during the COVID-19 pandemic, which may have affected the results. Our results will not be applicable in all jurisdictions, given that antimicrobial susceptibilities vary. Cephalexin breakpoints have not been established for rare pathogens such as *Citrobacter*.

## CONCLUSION

Less-broad-spectrum antibiotics and shorter duration of antibiotic therapy could be used for UTIs in this pediatric ED, and these conclusions could probably be applied in many other Canadian EDs. Consideration should be given to recommending cephalexin and nitrofurantoin as appropriate empiric antibiotics for children with suspected lower UTI except in cases with previous resistant urinary isolates. The main priority for future studies should be to determine the efficacy of cephalexin for upper UTIs. Clinicians should be encouraged to order therapy of shorter duration, in particular in cases of lower UTI.

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**Competing interests:** For activities unrelated to the study reported here, Cora Constantinescu has received honoraria from the Federation of Canadian Women in Medicine, GSK, Merck, and Pfizer. Joan Robinson serves as Chair of the Data Safety and Monitoring Board for a University of Alberta group A *Streptococcus* vaccine and as Divisional Director for Pediatric Infectious Disease at the University of Alberta. No other competing interests were declared.

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