JPPT | Single Center Retrospective Study

Evaluation of Outpatient Antibiotic Prescribing for Urinary Tract Infection in Pediatric Patients Ages 2 Months to 18 Years

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OBJECTIVE To characterize the diagnosis and management of urinary tract infection (UTI) in pediatric patients at the University of Illinois Hospital and Health Sciences System (UIH), with an emphasis on antibiotic prescribing; in addition, to characterize pediatric uropathogen patterns to help guide future empiric therapy choices.

METHODS We used a retrospective, descriptive study of pediatric patients ages 2 months to ≤18 years seen at the UIH emergency department or clinic from January 1, 2014, to August 31, 2018, with ICD-9 or ICD-10 discharge diagnosis of UTI. Data collected included presenting symptoms, urinalysis, details of antibiotic regimens, urine culture, and susceptibility results.

RESULTS Of the 207 patients included, the median age was 5.7 years (IQR, 3.2–9.4), and 183 patients (88.4%) were female. Common symptoms included dysuria (57%) and fever (37%). Empiric antibiotics were prescribed in 96.1% of cases, most commonly cefdinir (42%), cephalexin (22%), and sulfamethoxazole-trimethoprim (14%). Urine cultures were collected in 161 patients (77.8%), with 81 growing >50,000 colony-forming units bacteria. *Escherichia coli* was the most commonly isolated organism (82.1%), showing susceptibility to third-generation cephalosporins (97%), nitrofurantoin (95%), and sulfamethoxazole-trimethoprim (84%). Although 25 urine cultures showed no growth, antibiotics were discontinued in only 4 cases.

CONCLUSIONS Pediatric patients with UTI symptoms were often empirically prescribed cefdinir, possibly an unnecessarily broad choice because many *E coli* isolates were susceptible to narrower agents. Both urinalysis and urine cultures should be obtained during the diagnostic evaluation of UTI, with better follow-up of negative cultures to potentially discontinue antibiotics. This study highlights areas for improvement in the diagnosis, treatment, and antimicrobial stewardship in pediatric UTI.

ABBREVIATIONS AAP, American Academy of Pediatrics; CFU, colony forming units; ED, emergency department; MIC, minimum inhibitory concentration; UIH, University of Illinois Hospital & Health Sciences System; UTI, urinary tract infection; WBC, white blood cell

KEYWORDS antibiotics; antimicrobial stewardship; pediatric; urinary tract infection

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Introduction

Antibiotics are commonly prescribed in pediatric patients for ear, respiratory tract, and urinary tract infections (UTIs). Exposure to antibiotics can lead to adverse effects, some of which may be inappropriately diagnosed and documented as drug allergies, thereby limiting future therapeutic options.[1] Antibiotics can also alter the natural gut flora, leading to additional long-term consequences for children, including an increased risk for obesity, antibiotic resistance, and *Clostridioides difficile* infections.[1] Several studies have evaluated outpatient antibiotic prescribing in children with respiratory tract infections, but relatively few studies have evaluated prescribing for UTIs.

The annual incidence of UTI in children in the United States is 3.5%, with 8% of girls and 2% of boys affected by 7 years of age.[2,3] According to the American Academy of Pediatrics (AAP), a definitive diagnosis of UTI is made with both a urinalysis suggestive of UTI (i.e., pyuria and/or bacteriuria) and a urine culture positive for a uropathogen with at least 50,000 colony-forming units (CFUs) per milliliter from a catheter or suprapubic aspiration sample.[4] However, obtaining urine samples in children can be challenging and invasive, and contaminants can confound the diagnosis.

The most common causative organism in UTI is *Escherichia coli*, responsible for 85% to 90% of cases in children, but the preferred antimicrobial agent for UTI in children and adolescents is not well defined.[3–5] The AAP guidelines focus on patients ages 2 to 24 months, stating there are insufficient data to determine whether the recommendations apply to children older than 24 months. The recommended oral treatments, per AAP, include amoxicillin-clavulanate, cephalosporins (e.g., cephalexin, cefuroxime, cefixime), and sulfamethoxazole-trimethoprim.[4] For patients who have poor oral intake or more severe illness requiring intravenous therapy, aminoglycosides, cephalosporins (e.g., ceftriaxone, ceftazidime), or piperacillin-tazobactam are considered. The National Institute of Health and Care Excellence has very similar recommendations, which include pediatric patients up to age 16 years.[4,6] The recommended duration of therapy for UTI is also controversial. The AAP recommends 7 to 14 days, although there is literature supporting the shortened duration of 7 days because of a lack of significant differences in outcomes compared with 10- or 14-day courses.[7] The AAP states that courses less than or equal to 3 days have been associated with treatment failure; however, various international guidelines for pediatric UTI recommend 3-day courses for uncomplicated lower UTI.[4,8,9]

The lack of clear UTI treatment guidelines for older children is reflected in previous studies, which have found a wide variability in prescribing, as well as a significant proportion of antibiotics prescribed inappropriately.[10,11] Thus, the aim of the current study was to characterize antibiotic prescribing for pediatric UTI in an academic medical center, to provide guidance to our prescribers and inform future antimicrobial stewardship initiatives at our institution.

Materials and Methods

This was a retrospective review of pediatric patients treated for a UTI in the emergency department (ED) and outpatient clinic at the University of Illinois Hospital & Health Sciences System (UIH) in Chicago, Illinois, between January 1, 2014, and August 31, 2018. The primary objective was to describe the antibiotic regimens prescribed for UTI, and the secondary objectives were to characterize diagnostic workup for UTI and summarize susceptibility patterns for commonly isolated uropathogens. The AAP criteria for the definition of a UTI were used for analyzing data.

Patients ages 2 months to ≤18 years were identified by a query of the UIH ED and clinic electronic medical records for ICD-9 or ICD-10 discharge diagnosis of UTI during the specified time frame. ICD-9 codes 599.0 and 788.1, and ICD-10 codes N39, N39.0, N39.8, N39.9, and R30.0 were used for inclusion. Progress notes from the encounter were independently reviewed for accuracy of the diagnosis code for inclusion. Patients could be included more than once if the UTI encounters were separated by >2 weeks. Patients with underlying kidney or urinary tract abnormalitities, complicated UTI, pyelonephritis, or asymptomatic bacteriuria were excluded. ICD-9 codes 590.1, 590.8, and 771.82, and ICD-10 codes N10 and P39.3 were used for exclusion. Asymptomatic bacteriuria was determined by review of progress notes.

In addition to demographic data, presenting symptoms (i.e., fever, dysuria, hematuria, frequency, urgency, abdominal pain, suprapubic pain, flank pain, vomiting, feeding intolerance), urinalysis (i.e., nitrites, leukocyte esterase, white blood cells [WBCs], bacteria, epithelial cells), method of urine collection (i.e., suprapubic aspiration, catheterization, clean catch, bag specimen), details of the antibiotic regimens (i.e., drug, dose, route, frequency, duration), urine culture (i.e., CFU, organism), and susceptibility results were collected.

Data were entered and analyzed using Research Electronic Data Capture (REDCap, version 8.11.9) and Microsoft Excel 2016. Descriptive and frequentist statistics were used to analyze the data. Results are reported as median with IQR for non-parametric data or mean with standard deviation for parametric data.

Results

Of 469 encounters between August 2017, and August 2018, a total of 262 were excluded (see Supplemental Table). Among the 207 patients included, 97 (47%) were managed in the ED, 69 (33%) in urgent care, and 41 (20%) in the outpatient clinic. No patient in this dataset was included more than 1 time; each patient was a unique encounter. The median age was 5.7 years (IQR, 3.2–9.4), and 183 patients (88.4%) were female. Presenting symptoms most commonly included dysuria (57%), fever (37%), and abdominal pain (34%). Patients could have presented with more than 1 symptom.

Antibiotics were prescribed for 199 patients (96.1%) during their visit, with 2 additional patients prescribed antibiotics after their visit. Reasons for not prescribing antibiotics at the time of their visit included physician preference to call patient and send a prescription if symptoms persisted, no bacteruria, symptom management with phenazopyridine, and education for urinary hygiene. Of the empiric antibiotics prescribed, half were a third-generation cephalosporin, followed by cephalexin and sulfamethoxazole-trimethoprim (Figure 1). The most common duration of treatment was 7 to 10 days (Table 1). The empiric antibiotic regimen was revised in 15 cases, because of insurance coverage (7), patient intolerance (3), pathogen resistance (2), de-escalation (1), wrong dose (1), and lack of clinical improvement (1). Antibiotics were discontinued in 5 cases because of negative urine culture (4) and lack of clinical improvement (1).

A urinalysis was collected in 207 patients; not all samples had both macroscopic and microscopic analysis performed (Table 2). Microscopic analysis for WBC count and presence of bacteria was not done for 42.5% of urinalyses. Most urinalyses (73.4%) were negative

Figure 1. Empiric antibiotic agent (n = 199).

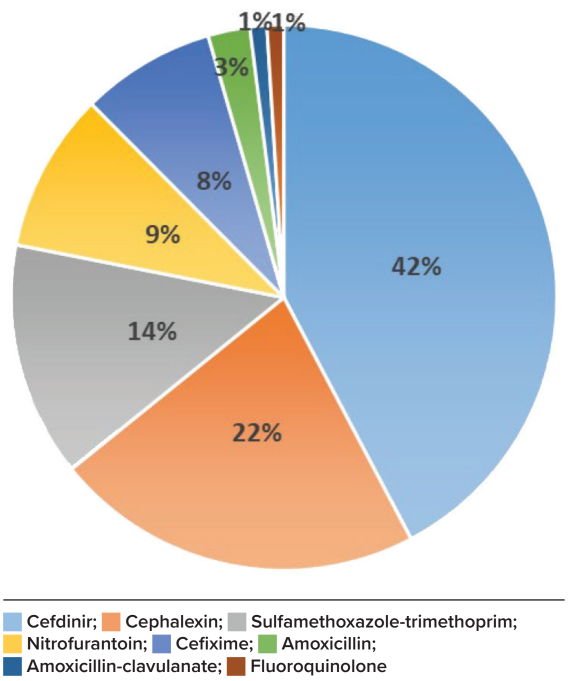

Table 1. Duration of Therapy (n = 201)

Days	n (%)
3–5	52 (25.9)
7–10	144 (71.6)
14	5 (2.5)

Table 2. Urinalysis Results (n = 207)

	n (%)
Macroscopic	
Nitrites	
Negative	152 (73.4)
Positive	53 (25.6)
Not done	2 (1)
Leukocyte esterase	
Negative	14 (6.8)
Trace	21 (10.1)
Small	36 (17.4)
Moderate	40 (19.3)
Large	94 (45.4)
Not done	2 (1)
Microscopic	
WBC	
<5 cells/hpf	8 (3.9)
≥5 cells/hpf	111 (53.6)
Not done	88 (42.5)
Bacteria	
None	15 (7.2)
Rare	40 (19.3)
Few	20 (9.7)
Moderate	14 (6.8)
Many	31 (15)
Not done	88 (42.5)

hpf, high-power field; WBC, white blood cell

for nitrites. Presence of leukocyte esterase, pyuria, and extent of bacteruria were variable. Urine cultures were collected in 161 patients (77.8%). The method of urine collection was either a voided sample (91.3%) or a catheterized sample (8.6%). Voided samples include clean-catch and bagged specimens because the electronic health record did not differentiate. No samples were collected by suprapubic aspiration.

Of the 161 urine cultures collected, 80 (49.7%) resulted with <50,000 CFU bacteria, and 25 (15.5%) resulted in no growth. The urine cultures with ≥50,000 CFU bacteria most commonly showed *E coli* or *Proteus mirabilis*, regardless of the method of urine collection (Figure 2). Other isolates included *Enterococcus* species, alpha-hemolytic *Streptococcus*, *Staphylococcus saprophyticus*, coagulase-negative *Staphylococcus*, and *Citrobacter* species. For the 75 *E coli* isolates, 97% were susceptible to third-generation cephalosporins, 95% were susceptible to nitrofurantoin, and 84% were susceptible to sulfamethoxazole-trimethoprim (Table 3). Cefazolin results were reported for 27 *E coli* isolates and showed 67% susceptibility based on the microbiology lab breakpoint of minimum inhibitory concentration (MIC) ≤2 mg/L (Table 4).

Discussion

Urinary tract infection is a common reason for antibiotic exposure in pediatric patients, but inconsistency in recommendations for management contributes to variability in clinical practice, which should be a focus for antimicrobial stewardship. We aimed to characterize current prescribing practices for pediatric UTIs to identify opportunities for improvement, which are categorized below. Our results demonstrated empiric prescribing of broad-spectrum agents and an incomplete diagnostic evaluation for UTI in most patients, which may have limited the clinician's ability to narrow or discontinue empiric therapy when appropriate.

Diagnostic Evaluation Including Appropriate Urine Collection Method and Microscopic Urinalysis. Urinalysis and urine culture are important diagnostic tools that can be challenging to obtain in the pediatric population depending on the age and capabilities of the patient. In this analysis, we found that only 8.6% of patients had urine collected by catheterization, whereas the remaining patients had a bagged or voided sample. When stratified by age, only 35% of patients ages ≤2 years and 11% of patients ages >2 to 5 years had urine collected by catheterization, resulting in contaminated or difficult to

Figure 2. Urine culture results for ≥50,000 colony-forming units (CFUs; n = 81). *Void includes clean-catch and bagged urine samples.

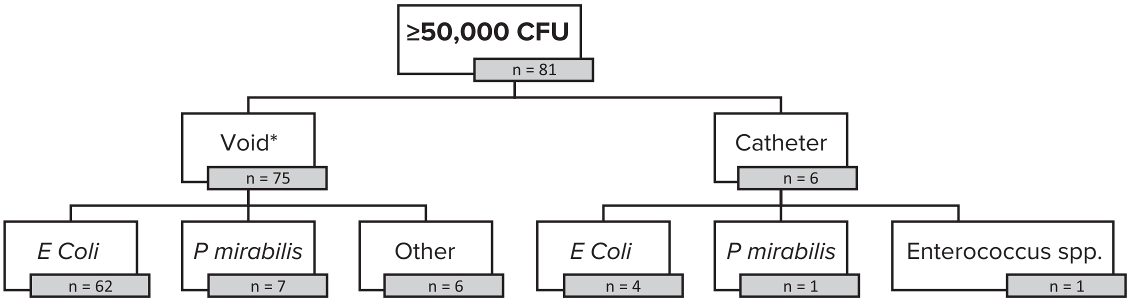

Table 3. Antibiotic Susceptibility Results for all *Escherichia coli* Isolates* (n = 75)

Antibiotic	Susceptible, %	Intermediate, %	Resistant, %
Amikacin	100	—	—
Ampicillin	52	1	47
Ampicillin-sulbactam	59	12	29
Cefazolin	See Table 4		
Cefepime	97	—	3
Ceftazidime	97	—	3
Ceftriaxone	97	—	—
Gentamicin	96	1	3
Imipenem	100	—	—
Levofloxacin	92	—	8
Nitrofurantoin	95	5	—
Piperacillin-tazobactam	95	1	4
Tobramycin	97	3	—
Sulfamethoxazole-trimethoprim	84	—	16

* Includes all *E coli* resulted in urine culture regardless of colony-forming units.

interpret urinalysis and urine culture results. Of note, the presence of squamous cells to assess for contamination was not collected. The AAP UTI guidelines for patients ages 2 to 24 months provide a strong recommendation to obtain urine through catheterization or suprapubic aspiration because a reliable diagnosis of UTI cannot be made with a culture from urine collected in a bag.[4] These results highlight an area for education in both the ED and clinic settings for providers to use and document the appropriate method of urine collection in order to confirm the diagnosis.

Nearly all patients in this study had a urinalysis obtained, but 88 samples (42.5%) were missing the microscopic analysis to assess for WBC and bacteria. A urine dipstick may have been the only test completed, which is often done as a point-of-care test at the bedside for faster macroscopic results, but it does not include microscopic analysis. In comparison, urine samples collected and sent to the microbiology lab usually include both the macroscopic and microscopic components. In patients in whom UTI is suspected, urine WBC and bacteria results are necessary for accurate diagnosis of UTI.

Narrower Empiric Therapy and Creation of Institution Pediatric-Specific Antibiogram. The most commonly prescribed antibiotic was a third-generation cephalosporin (cefdnir more than cefixime). This may be unnecessarily broad given the susceptibility results of *E coli* at this institution. We can speculate several reasons for this trend, including, at the time of this study, that the microbiology lab did not routinely report cefazolin susceptibilities, and therefore these data were not included in the antibiogram. Cefazolin susceptibilities could still be

Table 4. Cefazolin Susceptibility Results for *Escherichia coli* Isolates (n = 27)

Result	n (%)
Susceptible	18 (67)
Intermediate	0
Resistant	9 (33)
MIC 8	1
MIC 16	3
MIC ≥64	5

MIC, minimum inhibitory concentration

provided by request. Given the MIC of isolates reported for cefazolin in this study (Table 4), we can see that the susceptibility of *E coli* to cefazolin is close to 80% (22 isolates) when applying the urine-specific breakpoint of ≤16 mcg/mL.[12] Additionally, because UIH children's hospital is within the adult hospital, the antibiogram includes results from adult and pediatric isolates and is largely driven by adult resistance patterns, which may underestimate the susceptibility of other narrow-spectrum antibiotics that may be considered. For example, the susceptibility of *E coli* to sulfamethoxazole-trimethoprim is 68% per the UIH antibiogram, but our study shows that isolates in pediatric patients are likely more susceptible (84%). Creating a pediatric-specific antibiogram is a meaningful antimicrobial stewardship intervention; however, we currently lack the necessary number of positive isolates to do so at our institution.

Reassess and Tailor Antibiotic Therapy. Choosing narrower empiric antibiotics and de-escalating or discontinuing antibiotics when appropriate are important antimicrobial stewardship strategies, particularly in pediatric patients to avoid unnecessary exposure to antibiotics during childhood. In this study, nearly half (49.7%) of the 161 urine cultures showed <50,000 CFU of bacteria, including 25 (15.5%) with no growth, thus not meeting the AAP guideline definition. Despite this, antibiotics were discontinued in only 4 cases because of a negative culture. This may be a result of a lack of resources to follow up on negative urine cultures and discontinue antibiotics. Although the prescribing practices were not stratified by site of encounter, the current practice in our ED is to follow up on positive urine cultures to assess whether the empiric antibiotic prescribed is appropriate given the resulting susceptibility results. Usually this involves changing antibiotic therapy if the organism is not covered, but it rarely includes de-escalation to a narrower antibiotic, which only occurred in 1 case in this study. There is currently no formal procedure for negative cultures. Possible barriers to de-escalation could be the need for patients to fill another prescription, which may include another copay and visit to the pharmacy. Additionally, the ED provider staffing at the time of culture results may not feel comfortable de-escalating or shortening therapy for a patient without personally performing an exam, especially if the patient is improving on the current regimen. The duration of therapy was most commonly 7 to 10 days, and shorter or longer durations of therapy did not appear to be driven by the age of the patient (e.g., 3- to 5-day courses were prescribed to patients ranging in age from <1 to 18 years). Given that pyelonephritis was excluded, 14-day treatments may also be unnecessarily long for uncomplicated UTI.

Overall, our results are similar to those of Lee et al,[13] which showed narrower-spectrum empiric antibiotics like cephalexin may be more appropriate in pediatric patients, and that antibiotics are seldom discontinued in children with negative urine cultures.[13] Our findings of nearly half (49.7%) of our pediatric patients being prescribed antibiotics despite not meeting UTI diagnostic criteria is consistent with the results from Alghounaim et al,[14] in which 46.4% of patients received antibiotics despite negative urine cultures.[14] Our study showed multiple areas for improvement in the management of pediatric UTI at this institution, including using a more appropriate urine collection method, ordering a urinalysis, choosing narrower empiric antibiotic regimens, routinely reporting cefazolin susceptibility using urine-specific breakpoints, and following up with negative urine cultures. These aspects could be protocolized in an empiric treatment guideline for our institution and reassessed in the future to evaluate the change in prescribing practices.

Study Limitations. The retrospective nature of the study introduced several limitations that affected data collection and analysis. The documentation in the electronic health record did not consistently include the data requested, or the details of the data were insufficient for analysis. For example, both bagged urine samples and clean-catch voided samples are reported as "voided," which may have resulted in overestimation or underestimation of the appropriateness of the urine collection used in different ages of patients. Additionally, important microscopic urinalysis data (WBC and bacteria count) were missing because of the urinalysis type (bedside dipstick versus formal laboratory sample) performed. Other pertinent data unavailable in the medical record included compliance with the prescribed regimen, admissions or visits at outside institutions, or changes to the antibiotic regimen by outside providers. Because of the retrospective design, some data that were collected could not provide significant insight into prescribing practices that could lead to antimicrobial stewardship interventions. Although allergy data were collected, their effect on antibiotic choice could not be determined via chart review because prescribers did not document the reason for empiric antibiotic choices.

Conclusion

The AAP guidelines for UTI provide evidence and recommendations for the management of infants and young children, whereas the median age of the patients in this study was about 6 years. These results add to the existing literature by attempting to characterize the management of UTI in older pediatric patients. This study also emphasizes the importance of antimicrobial stewardship activities, including ensuring appropriate diagnosis of UTI with microscopic urinalysis and urine culture, choosing narrower-spectrum antibiotic therapy, and discontinuing empiric therapy when appropriate.

Article Information

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Ethical Approval and Informed Consent. The study was approved with Waivers of Child Assent and Parental Permission, and Waiver of Authorization under Expedited criterion by the University of Illinois at Chicago Institutional Review Board.

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