Objectives: Prescribing antibiotics for suspected urinary tract infection (UTI) is common practice and may lead to unnecessary antibiotic exposure. We aimed to review UTI diagnosis and management in the emergency department and to identify targets for antimicrobial stewardship.

Methods: Single-center, retrospective cohort study of children aged 12 weeks to younger than 18 years discharged from the emergency department with a diagnosis of UTI between October and December 2016. Children with genitourinary malformations were excluded. Clinical information, urine collection method, laboratory findings, and urine culture results were gathered. The sensitivity and specificity of nitrite and leukocyte esterase for UTI diagnosis were calculated. The relationship between urinalysis characteristics and confirmed UTI was examined using logistic regression.

Results: A total of 183 children with a median (interquartile range) age of 4.2 (1.1–7.3) years were included; 82.5% were female. Almost all children were discharged home on antibiotics (n = 180, 98%) for a median (interquartile range) duration of 7 (7–10) days. A total of 85 patients (46.4%) received antibiotics despite negative urine cultures leading to 525 unnecessary antibiotic days. The presence of nitrites was the strongest predictor of UTI (odds ratio = 20.22, P < 0.001) and was highly specific.

Conclusions: Current practice in managing suspected pediatric UTIs in our ED resulted in significant and unnecessary antibiotic exposure. We identified targets to reduce unnecessary antibiotic exposure including improving the diagnostic accuracy of UTIs, a process to discontinue antibiotics for negative cultures and standardizing antimicrobial duration.

Key Words: urinary tract infections, antimicrobial stewardship, urinalysis

Urinary tract infection (UTI) is a leading cause for acute care visits, and it is estimated to affect 2.6% to 7.5% of febrile children annually.2 The diagnosis of UTI is usually made presumptively based on typical symptoms and pyuria and confirmed by demonstrating significant bacterial growth from an appropriate urine sample.2 Bacterial identification and susceptibility testing usually require a turnaround time of 48 hours. The clinical diagnosis of UTI can often be challenging and requires a high index of suspicion particularly in younger children in whom typical symptoms cannot be elicited. Because UTI can progress to a potentially serious infection, clinicians often prescribe empiric antibiotics for presumed UTI awaiting confirmation by culture, especially when follow-up is uncertain (ie, emergency department [ED]). However, dipstick urinalysis generally lacks specificity and this practice may lead to unnecessary antibiotic prescribing.4 Furthermore, because of the high volume of outstanding test results, lack of continuity of care and healthcare resource constraints in acute care settings, many EDs are only able to follow up on positive test results. As part of an antimicrobial stewardship initiative, our objective was to review the practice of diagnosing and treating suspected UTIs in the ED to determine the frequency with which antibiotics are empirically prescribed for suspected UTI that is not confirmed by urine culture and to identify targets for intervention to reduce unnecessary antibiotic exposure. As secondary outcomes, we also evaluated the performance of urinalysis and urine microscopy in the identification of positive urine culture.

METHODS

We performed a single-center, retrospective cohort study at the Hospital of Sick Children (Toronto, Ontario, Canada) from October to December 2016. The Hospital for Sick Children is a quaternary care children’s hospital in downtown Toronto with annual ED volumes of approximately 75,000 patients. We included all patients 12 weeks to younger than 18 years who were discharged from the ED with the diagnosis of UTI. Patients were excluded if they (1) were younger than 12 weeks, (2) had underlying genitourinary tract abnormalities, (3) were admitted or transferred to another center, (4) were receiving antibiotics on presentation, (5) had urine testing done in an outpatient setting, (6) had urine culture results, (7) had duplicate occurrences of a diagnosis (ED visit within the same illness period).

Patient charts were reviewed to collect data on patient demographics, clinical presentation, significant underlying co-morbidities, medical management, and urinalysis and urine culture results. Upper UTI signs and symptoms were defined as the presence of fever, costovertebral angle tenderness, or vomiting. Lower UTI symptoms included frequency, dysuria, urgency, or incontinence. Confirmed UTI was defined as pyuria and the presence of more than 50,000 CFU/mL (>50 × 10⁶ CFU/mL) of 1 or more uropathogens.5 In addition, presence of more than 50,000 CFU/mL of a uropathogen along with less than 50,000 CFU/mL of nonuropathogens was considered significant growth. Clinitek Status (Siemens Healthcare, Munich, Germany) was used to test unspun urine for point-of-care testing to measure both leukocyte esterase (LE) (sensitivity 5–15 white blood cells [WBC]/high power field) and urinary nitrite (sensitivity 13–22 umol/L). The semiquantitative results of LE were trace, small (1+), moderate (2+), and large (3+) that corresponded to 15, 75, 125, and 500 WBC/high power field, respectively. Clinically significant pyuria was determined in the Microbiology Laboratory by the presence of greater than 10⁶ WBC/L (10 WBC/mm³) by hemocytometer analysis of uncentrifuged urine. Unconfirmed UTI included patients with a negative urine culture that was defined as cultures that failed to show bacterial growth after 24 hours, had growth of less than 50,000 CFU/mL, or had significant but mixed growth of more than 1 organism
TABLE 1. Demographic Characteristics of Study Population (n = 183)

| Variable                  | n (%)                  |
|---------------------------|------------------------|
| Age, y                    |                         |
| Median (IQR)              | 4.2 (1.1–7.5)          |
| Sex                       |                         |
| Male                      | 32 (17.4)              |
| Urinary symptoms (n = 175)|                         |
| Upper                     | 99 (54.1)              |
| Lower                     | 76 (41.5)              |
| Urine collection method   |                         |
| Catheter                  | 61 (33.3)              |
| Midstream urine           | 119 (65.8)             |
| Bag                       | 2 (1.1)                |
| Not specified             | 1 (0.5)                |
| Urisnalysis (n = 180)     |                         |
| LE negative               | 10 (5.6)               |
| LE trace                  | 33 (18.3)              |
| LE positive               | 137 (76.1)             |
| Nitrite positive          | 42 (23.3)              |
| Urine culture results     |                         |
| No growth                 | 38 (20.8)              |
| Insignificant growth      | 42 (23.0)              |
| Mixed growth              | 8 (4.4)                |
| Significant growth of single organism: |          |
| Escherichia coli          | 82 (44.8)              |
| Klebsiella pneumoniae     | 6 (3.3)                |
| Proteus species           | 5 (2.7)                |
| Streptococcus pyogenes    | 1 (0.5)                |
| Methicillin-resistant Staphylococcus aureus | 1 (0.5)         |
| Antibiotic prescription for negative culture | 85 (46.4) |
| Antibiotic prescription for positive culture | 95 (51.9) |
| Total antibiotic prescriptions* | 180 (98.4) |
| Amoxicillin               | 3 (1.7)                |
| Amoxicillin/clavulanic acid | 48 (26.7)       |
| Cefixime                  | 8 (4.4)                |
| Cephalexin                | 103 (57.2)             |
| Ciprofloxacin             | 3 (1.7)                |
| Nitrofurantoin            | 3 (1.7)                |
| TMP/SMX                   | 9 (5.0)                |

*1 patient received 2 antibiotics.

TMP/SMX indicates trimethoprim/sulfamethoxazole.

Other than a typical uropathogen. In addition, a growth of an uropathogen and a nonuropathogen, both greater than 50,000 CFU/mL, was considered to result from contamination.4

Descriptive statistics were used to examine the study sample characteristics. Continuous variables were reported using the mean and standard deviation for normally distributed variables and the median and range for nonnormally distributed data. Number and percentage were reported for dichotomous outcomes. Univariable analyses were conducted using χ² or Fisher exact test for dichotomous variables. Logistic regression was used to examine the relationship between urinalysis characteristics and confirmed UTI. Subgroup analyses were conducted to determine whether the predictors were different in catheter specimens versus other specimens (midstream urine).

All estimates are presented with 95% confidence intervals. A P value <0.05 was considered statistically significant. All analyses were conducted using Stata Statistical Software release 12 (StataCorp, 2011; StataCorp LP, College Station, Tex).

RESULTS

During the study period, 293 patients were discharged from the ED with the diagnosis of UTI. This represented 1.5% of total ED visits during the study period. Of the study population, 110 were included; 26 were admitted, 25 urine culture results were not available (either not ordered [n = 10] or done elsewhere [n = 15]), 23 had underlying genitourinary tract abnormalities, 2 were on UTI prophylaxis, 6 were transferred to another institution, 3 were duplicate, 6 were younger than 12 weeks, 7 had conditional antibiotic prescription, and 12 had urine cultures done on therapeutic antibiotics. A total of 183 patients were included in the analysis. Subjects were mainly females (82.5%) with a median (interquartile range [IQR]) age of 4.2 (1.1–7.5) years (Table 1). Most specimens were collected by midstream urine (n = 119, 65.8%) and catheterization (n = 61, 33.3%). Upper UTI signs and symptoms were noted in 99 patients (54.1%), whereas lower UTI symptoms were documented in 76 patients (41.5%).

Almost all patients were discharged home on antibiotics (n = 180, 98.4%). The most common antibiotic prescribed was cephalexin (n = 103, 57.2%), followed by amoxicillin-clavulanic acid (n = 48, 26.7%). The median (IQR) duration of antibiotics was 7 (7–10) days. Most antibiotic choices and duration were compatible with local UTI guidelines based on the susceptibility pattern. Eighty-nine patients had a negative urine culture (38 no growth, 42 insignificant growth, 8 mixed growth). Of those, 85 patients (46.4%) received antibiotics despite negative urine cultures and none of these patients received a call to stop the antibiotic.

Urine LE on point-of-care testing was associated with the presence of pyuria on microscopy; the odds of microscopic pyuria increased as the LE result increased from trace to 3+ (P < 0.001). The sensitivity and specificity of UTI and nitrite positivity are summarized in Table 2. The predictive abilities of combinations of urinalysis results are summarized in Tables 3–5. The presence of nitrites was the strongest predictor of UTI (odds ratio [OR] = 20.22, 95% confidence interval [CI] = 5.95–68.71, P < 0.001) (Table 6). On subgroup analysis of urine samples collected by catheter, the presence of nitrites was 100% predictive of UTI in catheter specimens and had an OR of 11.51 (95% CI = 5.95–22.06, P < 0.001) for other

TABLE 2. Test Performance for LE and Nitrite Detection

| Test          | Sensitivity, % | Specificity, % | PPV, % | NPV, % |
|---------------|---------------|----------------|--------|--------|
| All specimens |               |                |        |        |
| LE*           | 83.0          | 32.6           | 57.4   | 63.6   |
| Nitrite       | 43.6          | 97.7           | 95.3   | 61.3   |
| Catheter specimens |         |                |        |        |
| LE*           | 86.0          | 41.2           | 78.7   | 53.8   |
| Nitrite       | 51.2          | 100            | 100    | 44.7   |
| Noncatheter specimens |       |                |        |        |
| LE*           | 82.0          | 31.4           | 46.1   | 71.0   |
| Nitrite       | 36.0          | 95.7           | 85.7   | 67.7   |

*Positive result considered to be ≥ +1.

NPV indicates negative predictive value; PPV, positive predictive value.
samples. It remained significant after adjusting for LE result (OR = 28.96, 95% CI = 7.78–107.84, \( P < 0.001 \)). An LE result of 2+ (OR = 4.07, 95% CI = 0.88–18.87, \( P = 0.073 \)) or 3+ (OR = 3.35, 95% CI = 0.81–13.90, \( P = 0.096 \)) were predictors of UTI in all specimens but did not reach statistical significance. However, on subgroup analysis, an LE result of 2+ was only a significant predictor of UTI in catheter specimens, which predicted UTI perfectly.

**DISCUSSION**

Urinary tract infection is responsible for a significant number of acute care visits and antibiotic prescriptions in children. We observed that approximately 50% of patient with presumed UTI based on either symptoms or dipstick urinalysis have a negative urine culture. This highlights a limitation of the specificity of clinical assessment and rapid urinalysis testing in the acute care setting\(^2\) and leads to considerable unnecessary antibiotic exposure. However, on subgroup analysis, an LE result of 2+ was only a significant predictor of UTI in catheter specimens, which predicted UTI perfectly.

**TABLE 3. Results of Urinalysis and Culture Positivity (All Specimens, \( n = 179^* \))**

| LE     | n  | Culture Positivity | Pyuria | Pyuria and + Culture | Number Treated |
|--------|----|--------------------|--------|----------------------|----------------|
| Nitrite positive |    |                    |        |                      |                |
| Negative | 2  | 1 (50%)            | 1      | 1 (100%)             | 2              |
| Trace   | 8  | 7 (88%)            | 6      | 5 (83%)              | 8              |
| 1+      | 14 | 14 (100%)          | 12     | 12 (100%)            | 14             |
| 2+      | 5  | 5 (100%)           | 5      | 5 (100%)             | 5              |
| 3+      | 13 | 12 (92%)           | 13     | 12 (92%)             | 13             |
| Nitrite negative |   |                    |        |                      |                |
| Negative | 8  | 3 (38%)            | 2      | 1 (50%)              | 7              |
| Trace   | 25 | 3 (15%)            | 8      | 2 (25%)              | 24             |
| 1+      | 54 | 16 (31%)           | 35     | 15 (44%)             | 53             |
| 2+      | 21 | 14 (67%)           | 17     | 13 (76%)             | 21             |
| 3+      | 29 | 17 (59%)           | 27     | 16 (59%)             | 29             |

*Urinalysis not available in 3 specimens and exact LE results not available in 1 patient.

**TABLE 4. Results of Urinalysis and Culture Positivity (Catheter Specimens, \( n = 60 \))**

| LE     | n  | Culture Positivity | Pyuria | Pyuria and + Culture | Number Treated |
|--------|----|--------------------|--------|----------------------|----------------|
| Nitrite positive |    |                    |        |                      |                |
| Negative | 0  | .                  | .      | .                    | .              |
| Trace   | 3  | 3 (100%)           | 2      | 2 (100%)             | 3              |
| 1+      | 8  | 8 (100%)           | 7      | 7 (100%)             | 8              |
| 2+      | 4  | 4 (100%)           | 4      | 4 (100%)             | 4              |
| 3+      | 7  | 7 (100%)           | 7      | 7 (100%)             | 7              |
| Nitrite negative |   |                    |        |                      |                |
| Negative | 2  | 1 (50%)*           | 0      | 0                    | 2              |
| Trace   | 8  | 2 (25%)            | 3      | 1 (33%)              | 8              |
| 1+      | 12 | 5 (42%)            | 10     | 5 (50%)              | 12             |
| 2+      | 6  | 6 (100%)           | 5      | 5 (100%)             | 6              |
| 3+      | 10 | 7 (70%)            | 10     | 7 (70%)              | 10             |

*Culture positive in 20-month-old woman.
Almost half (46.4%) of the patients who received antibiotic therapy for presumed UTI had a negative urine culture. Watson et al. observed a similar finding where 49% of patients with presumed UTI had negative urine cultures. The practice of treating all patients empirically, although it may prevent a serious complication of UTI, is associated with high and unnecessary antibiotic prescribing, which leads to low value care and increased costs to the healthcare system. Equally importantly, this practice can cause antimicrobial-related adverse reactions and promotes the development and selection of antimicrobial resistance. Several antimicrobial stewardship approaches have been used in different infection syndromes including pneumonia and skin infections. Garraffo et al. showed that in the pediatric population, antibiotic exposure in the 12 months preceding a UTI diagnosis is associated with increased risk of bacterial resistance, especially with amoxicillin, Cotrimoxazole, first-, and third-generation cephalosporin. However, the pattern of resistance was dependent on the type of antibiotic that the patients were exposed to. Duration of antibiotic exposure is also associated with increased risk of the development of antimicrobial resistance. However, the effect of a brief course of antibiotics (ie, until culture is reported negative) on antimicrobial resistance is not known. Without appropriate follow-up of urine result, labeling a child with a diagnosis of a UTI can lead to recurrent urine testing with all future febrile illnesses.

Several antimicrobial stewardship approaches have been used in different infection syndromes including pneumonia and skin infections. Recently, Saha et al. implemented a standard antibiotic discontinuation protocol with negative urine culture. This practice increased the antibiotic discontinuation rate from 4% to 84% avoiding 3,429 antibiotic days for 29 months. In our study, the lack of such a protocol resulted in 525 unnecessary antibiotic days. Another potential area of antimicrobial stewardship is standardizing antibiotic prescription duration. In our study, 41.0% (n = 75) of prescription were for durations of 10 days or longer despite recent guidelines recommending 7 to 10 days of antibiotic therapy for UTI. We also found that adolescents with cystitis were generally given longer course of antibiotics (mean = 8.8 days) than the recommended duration in our local protocol.

This single-center study is limited by its retrospective nature. Details of patients’ clinical data may not have been well documented. Some patients with UTI may have been missed because they were discharged with an alternative diagnosis (eg, fever without focus) without a urinalysis or urine culture. Furthermore, not all urine specimens sent for urinalysis are sent for culture. However, these patient populations were not the focus of our stewardship initiative. In addition, some patients were instructed to follow-up with their primary physician. Whether this practice led to a change in antibiotic management is not known. However, it is unlikely given that there is no process for the primary (community) physician to obtain the culture results in a timely and reliable fashion.

This study highlights the finding that in our institution, the current practice in managing pediatric UTI often results in significant and unnecessary antibiotic use. This knowledge supports the development of antimicrobial stewardship interventions aimed at improving antibiotic prescription practices in the ED to reduce unwanted antibiotic-associated adverse events and to decrease costs to the healthcare system. We identified potential strategies to

### TABLE 5. Results of Urinalysis and Culture Positive (Noncatheter Specimens, n = 119)

| LE | n | Culture Positivity | Pyuria | Pyuria and + Culture | Number Treated |
|----|---|-------------------|--------|---------------------|----------------|
| Nitrate positive  |    |                   |        |                     |                |
| Neg | 2 | 1 (50%)           | 1      | 1 (100%)            | 2              |
| Trace | 5 | 4 (80%)           | 4      | 3 (75%)             | 5              |
| 1+  | 6 | 6 (100%)          | 5      | 5 (100%)            | 6              |
| 2+  | 1 | 1 (100%)          | 1      | 1 (100%)            | 1              |
| 3+  | 6 | 5 (83%)           | 6      | 5 (83%)             | 6              |
| Nitrate negative  |    |                   |        |                     |                |
| Neg | 6 | 2 (33%)           | 2      | 1 (50%)             | 5              |
| Trace | 17| 1 (6%)            | 5      | 1 (20%)             | 16             |
| 1+  | 42| 11 (26%)          | 25     | 10 (40%)            | 41             |
| 2+  | 15| 8 (47%)           | 12     | 8 (62%)             | 15             |
| 3+  | 19| 10 (53%)          | 17     | 9 (53%)             | 19             |

### TABLE 6. Predictors of UTI (Univariable Analysis)

| Variable | OR (95% CI) | P       | Catheter Only, OR (95% CI) | P       | Other, OR (95% CI) | P       |
|----------|-------------|---------|----------------------------|---------|--------------------|---------|
| Nitrite positive | 20.22 (5.95–68.71) | <0.001 | NA*                        | 11.51 (3.15–42.06) | <0.001 |
| LE       |             |         | REF                        |         | REF                |         |
| Trace    | 0.65 (0.15–2.83) | 0.568   | 0.83 (0.04–16.99)          | 0.906   | 0.49 (0.09–2.81)   | 0.423   |
| 1+       | 1.18 (0.31–4.58) | 0.806   | 1.86 (0.10–34.44)          | 0.678   | 0.91 (0.19–4.30)   | 0.909   |
| 2+       | 4.07 (0.88–18.87) | 0.073   | NA*                        | 2.15 (0.38–12.20) | 0.390   |
| 3+       | 3.35 (0.81–13.90) | 0.096   | 4.67 (0.22–97.50)          | 0.321   | 2.5 (0.49–12.89)   | 0.273   |
| Pyuria   | 8.12 (3.73–17.67) | <0.001 | 5.46 (1.43–20.88)          | 0.013   | 9.46 (3.37–26.60)  | <0.001   |

*Unable to estimate—predicts success perfectly.
NA indicates non-applicable; neg, negative; REF, reference.
reduce unnecessary antibiotic exposure by improving the diagnostic accuracy of UTIs, discontinuing antibiotics for negative cultures, and standardizing antimicrobial duration.

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