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Original Research Article.

Is Nitrite Negativity in Urine Analysis an Indicator of Antibiotic Resistance?

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ABSTRACT

Introduction: Studies have reported a correlation between a negative nitrite on urine analysis and resistance to cephalosporin in urine cultured isolate in cases of UTI. Nitrite negativity has therefore been suggested as an aid for physicians in choosing initial empiric specific antimicrobial therapy in patients with UTI. Other studies however have shown contrary results.

Study Question: Does whether urinary nitrite test negativity identify pediatric patients with a higher likelihood of antibiotic resistance in bacterial isolates from urines sample cultures.

Method: Retrospective chart review of all pediatric patients from birth to 14 years old who received a diagnosis of UTI based on urine analysis and cultures. We analyzed urine analysis result, nitrite test result, urine culture and antibiotic sensitivity pattern and statistically looked for any correlation of nitrite negativity on urine analysis with antibiotic resistance pattern of bacterial isolates from urine cultures.

Results: No significant statistical difference found between antibiotic sensitivity rates of isolates grown from cultures of nitrite-positive & from nitrite-negative urinary specimens.

Conclusions: Physicians should choose initial antimicrobial agent based on knowledge of locally prevalent patterns of antibiotic resistance, and not on urinary nitrite test results.

Key Words: Nitrite Test, UTI, Urinary Tract Infection, Antibiotic Resistance.

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INTRODUCTION

Urinary tract infection (UTI) results from bacterial colonization of the genitourinary tract. UTIs are one of the most common infections in children, with a cumulative incidence of 3-7% in females and 1-2% in males.[1,2] UTI in children result in over 500,000 emergency department (ED) visits annually in the United States alone, corresponding to 0.7 and 7% of all physician ED visits and febrile presentations, respectively.[1,3,4]

Factors that increase the risk of contracting UTI, including being female or Caucasian and having vesicoureteral reflux (grades IV-V), bladder dysfunction, constipation, malnourishment, renal transplant, and a history of prior UTI.[5-8] An increasingly recognized risk factor is an uncircumcised phallus[9]. Other associations reported are the use of superabsorbent diapers, vitamin D supplementation, history of maternal UTI, and idiopathic hypercalciuria.[10-13]

The mainstay for treating UTI is antimicrobial. Choice of appropriate antibiotics depends on the culture and sensitivity of the cultured organisms. An association between positive urinary nitrite and UTIs was first reported in 1914.[14]

A positive nitrite test requires the presence of nitrates in the urine and specific bacteria that have the ability to convert these nitrates to nitrites. A positive nitrite is typically measured using a calorimetric dipstick. Urinary nitrite testing is a useful bedside cost-effective tool with a rapid turnaround time. The test divides patients into two distinct groups namely nitrite positive or negative.[15,16]

Weiz et al reported a correlation between a negative nitrite and urine cultured isolate resistance to cephalosporin in cases of UTI.[17] This suggested nitrite negativity on urine analysis might help physicians chose specific antimicrobial therapy. However, other studies investigating this have shown contrary results.[18-21] Furthermore, there are no local studies from Saudi Arabia assessing this relation between nitrite and antibiotic resistance in UTI cases.

The primary objective of this study was to determine whether urinary nitrite test can identify patients with a higher likelihood of antibiotic resistance in bacterial isolates from urines sample in children. Identifying such patients would potentially allow the physician to adjust antimicrobial therapy before the patient leaves the ED. The secondary objective of this study was to review the growth patterns and sensitivities of common bacteria from urine cultures of pediatric patients from our study population.

MATERIALS AND METHODS

The study was conducted in the Pediatric Emergency Department (ED) at King Khalid University Hospital. We conducted a retrospective chart review of all pediatric patients from birth to 14 years old who received a diagnosis of UTI based on urine analysis and cultures. Routine practice for suspected UTIs in our department is to perform a urine urinalysis and culture on a transurethral catheter or midstream clean catch urine specimen. The study was conducted from May 2015 to April 2017. The setting was a tertiary care urban pediatric ED in Riyadh The study was approved by the Ethics Review Board for Research Involving Human Subjects at King Saud University.

Inclusion Criteria: Any pediatric ED patient presented during the study period with a reported positive urine culture, defined as >100,000 CPF/ml by clean catch, or >1000 CPF/ml by catheterization was included in the study.

Data were collected by data extractors from patients' electronic medical records using preformatted data collection sheets. Data included age, gender, underlying conditions (VUR, neurogenic bladder), previous history of UTI, ongoing UTI prophylaxis, recent or current antimicrobial intake for any infection, symptoms presented (e.g. fever, abdominal pain, hematuria, painful micturition, urinary smell change, part of neonatal sepsis), urine sample technique (e.g. catheter, bag, suprapubic aspiration, clean catch, vesicostomy) urine analysis result, urine culture and sensitivity results, outpatient/inpatient treatment, and the antibiotics that were initiated.

All extracted data were transcribed into a secure computerized Microsoft Excel sheet on a secure computer database for subsequent appropriate statistical analysis using SPSS version 23.0 (SPSS Inc., IBM, Armonk, New York, USA). Results were presented as the mean and standard deviation for continuous variables and as the number and percentage of the total for categorical variables. A test of association was done using the Pearson correlation test. A chi-square test was done to determine significant differences among categorical groups. P value <0.05 was considered statistically significant.

Table 1: General demographic characteristics of 578 patients

Demographic profile	n	%
Gender		
Male	154	26.6
Female	424	73.4
With underlying conditions		
VUR	62	10.7
Neurogenic bladder	48	8.3
Posterior urethra valve	21	3.6
Others	159	27.5
Had previous UTI	229	39.6
Had prophylaxis	154	26.6
Recent / current antibiotic	257	44.5
Presenting symptoms		
Urine smell	58	10.0
Fever	255	44.1
Abdominal pain	146	25.3
Hematuria	49	8.5
Dysuria	94	16.3
Sepsis screening	7	1.2
Others	78	13.5
Nitrite positive	225	38.9

Table 2: Nitrite positivity for the variables tested

		Nitrite (+) n=225	Nitrite (-) n=353	P values
VUR	**Yes**	15 (6.7%)	47 (13.3%)	0.011*
	No	210 (93.3%)	306 (86.7%)	
Neurogenic bladder	**Yes**	18 (8.0%)	30 (8.5%)	0.825
	No	207 (92.0%)	323 (91.5%)	
Posterior urethra valve	**Yes**	7 (3.1%)	14 (4.0%)	0.588
	No	218 (96.9%)	339 (96.0%)	
Previous UTI	**Yes**	140 (62.2%)	208(59.1%)	0.453
	No	85 (37.8%)	144 (40.9%)	
Prophylaxis	**Yes**	67 (29.8%)	87 (24.6%)	0.180
	No	158 (70.2%)	265 (75.4%)	
ESBL (for 482 samples only)	**Yes**	48 (25.8%)	79 (26.7%)	0.830
	No	138 (74.2%)	217 (73.3%)	

* - statistically significant (chi-square test)

Table 3: Differences in mean age (in months) and laboratory values between nitrate positive and negative samples

	Nitrate (+)	Nitrate (-)	P values
Age, in months	4.66 ± 3.87	4.95 ± 3.98	0.396
RBC	76.47 ± 472.13	63.26 ± 306.86	0.684
WBC	576.0 ± 1771.6	403.89 ± 1178.59	0.161
pH	5.71 ± 1.78	5.85 ± 1.77	0.346
Epithelial cells	3.00 ± 1.42	2.82 ± 1.35	0.114

Table 4: Pearson correlation test for variables associated with nitrite positivity

Variables	Correlation coefficient	P values
Age	-0.036	0.388
Gender	0.064	0.126
Antibiotics use before UA	0.024	0.559
VUR	-0.105	0.011*
Neurogenic bladder	-0.009	0.825
Posterior urethra valve	-0.023	0.589
Previous UTI	0.031	0.454
Prophylaxis	-0.056	0.181
Recent / current antibiotics	0.052	0.216
Sample type	0.058	0.163
Leukocyte esterase	0.081	0.052
RBC	0.017	0.681
WBC	0.088	0.034*
pH	-0.055	0.190
Epithelial cells	0.065	0.119
Susceptibility	-0.012	0.619
Antibiotic resistance	0.041	0.327

* = statistically significant

Table 5: Nitrite Negativity correlation with individual antibiotics

Antibiotics	Total n (%)	Nitrite positive n (%)	Nitrite negative n (%)	Correlation Coefficient (r) and p value	Chi-square p value
Amoxicillin –Clavulanic acid					
Sensitive	476	191 (84.9)	285 (80.7)	-0.053	0.201
Resistant	102	34 (15.1)	68 (19.3)	(0.219)	
Cefazolin					
Sensitive	449	170 (75.6)	279 (79.0)	0.041	0.327
Resistant	129	55 (24.4)	74 (21.0)	(0.357)	
Nitorfurantoin					
Sensitive	514	199 (88.8)	315 (90.3)	-0.023	0.586
Resistant	59	25 (11.2)	34 (9.7)	(0.673)	
Trimethoprim- Sulfamethoxazole					
Sensitive	411	156 (69.6)	255 (72.9)	-0.035	0.405
Resistant	163	68 (30.4)	95 (27.1)	(0.448)	

RESULTS

A total of 578 patients were included in the study, 154 (26.7%) males and 424 (73.4%) females. The mean age was 4.84 ± 3.94 months (range: 4 days – 16 years). The most commonly identified underlying condition was VUR (n=62, 10.7%). There were 229 patients (39.6%) with a previous history of UTI. One hundred fifty-four patients (26.6%) were on prophylaxis and 257 (44.5%) had recent/current antibiotics. The most common symptom was fever (n=225, 44.1%). Most sample were clean catch midstream urine (n=236, 40.8%). Four hundred twenty-one samples showed some kind of antimicrobial resistance (n=72.8%). There were 225 patients (38.9%) who were nitrite positive. (Table 1)

Table 2 shows nitrite positivity for the variables tested. There were no significant differences in the frequencies of nitrite positivity and negativity for presence of neurogenic bladder, presence of posterior urethra valve, previous history of UTI, antibiotic prophylaxis, or ESBL on urine culture isolate.

There were no significant differences in the mean age, RBC count, WBC count, pH, or number of epithelial cells between patients who were nitrite positive and negative (Table 3).

Table 4 shows the correlations between nitrate positivity and the tested variables. Nitrite positivity was significantly negatively associated with VUR (r=-0.105, P=0.011) and high WBC count (r=0.088, P=0.034), the clinical significance of which was not clear to the authors. No other variables tested were significantly correlated with nitrite positivity. Table 5 shows that there was also no observed statistical significant difference in proportion of patients who had a nitrite negative or nitrite positive urine analysis and antibiotic resistance in their urinary culture isolates when calculated individually for Amoxicillin+Clavulinic acid, Cefazolin, Nitrofurantoin, and Sulphamethoxazole + Trimethoprim.

DISCUSSION

Urinary culture and antibiotic sensitivity is the proven gold standard investigation for the diagnosing of UTI and choosing of appropriate antimicrobial agent for treatment of individual patients. Unfortunately, the culture results are not available immediately to the ED physician. It is also well known that uropathogens that can reduce nitrates to nitrites yield a positive nitrite test result. Examples of such pathogens include *E. coli*, Klebsiella, and Proteus.

Some investigators[17] had earlier suggested that a negative urine nitrite test is a possible indicator that a microorganism is resistant to the first and third generation of cephalosporins. This observation however was not consistently corroborated by the few other small sample sized studies in medical literature. Our study was therefore conducted to further explore whether the initial UA and specifically urine nitrite results could serve as a guide for physicians in choosing the most appropriate empirical antibiotic regimen for their patients with UTI.

In our patients, bacterial resistant to Ampicillin, reached a resistance rate of almost 50% consistent with reported resistance rates from other studies. It may be reasonable, based on this resistance data, to avoid the use of Ampicillin alone as first-line therapy for outpatient UTIs in our patient population. First generation cephalosporin was mostly acceptable as a first-line empirical therapy, with a Cefazolin resistance rate of 22.6%. Nitrofurantoin (resistance rate of 11%) and Cefixime (resistance rate 10%) were also very effective among other oral antibiotics. The low resistance percentages of cefixime in our study support its common use as effective first-line therapy for managing febrile, nontoxic infants, and children older than 3 months with a first-time UTI.

Weiz et al[17] based on their study had earlier suggested that a negative urine nitrite test is a possible indicator that a microorganism is resistant to the first and third generation of Cephalosporins. Our study however found no detectable statistically significant difference in resistance rates to TMP-SMX, Nitrofurantoin, Amox-Clavulinic acid and Cefixime between nitrite positive and nitrate negative groups. We therefore infer that negative nitrite results is not a valid parameter for ED physicians for empirical adjustment of antimicrobial therapy in patients with UTI. This is in line with some other studies.

Grant et al[20] had concluded from their research that detection of urine nitrites should not influence the use of first-generation cephalosporins for urinary tract infections in a mixed population of adult and pediatric patient. Larson et al[21] similarly reported no significant difference between the rates of TMP-SMX resistance in nitrite negative and positive groups. Mahyar et al[19] extended their study to a larger variety of antibiotics including gentamycin, amikacin, nalidixic acid, ampicillin, and nitrofurantoin, in addition to first and third-generation cephalosporin. They also found no correlation between antibiotic resistance and nitrite negativity or positivity on urine analysis.

Our study is likely generally applicable to other pediatric centers. Our study population demographic is similar patient clientele of most tertiary care centers. Reported rates of resistance to antibiotics like TMP-SMX, amoxicillin, first and third-generation cephalosporins are comparable to those observed by us .[10,16]

CONCLUSIONS

Our data indicates that there is no significant statistical difference between the antibiotic sensitivity rates of isolates grown from cultures of nitrite-positive urinary specimens and those from nitrite-negative specimens. We therefore conclude that physicians should choose initial antimicrobial agent based on knowledge of locally prevalent patterns of antibiotic resistance, and not on urinary nitrite test results.

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