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Can Urinalysis and Past Medical History of Kidney Stones Predict Urine Antibiotic Resistance?

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Introduction: Urinary tract infections (UTI) are one of the most common infections encountered in the emergency department (ED) with an estimated 2-3 million annual visits. Commonly prescribed antibiotics for UTIs have shown growing rates of resistance. Previous studies lack direction on improving UTI treatment based on the limited laboratory data available to the bedside clinician.

Methods: We sought to determine if antibiotic resistance in UTIs was related to demographics, urinalysis, and history of renal failure or kidney stones. We conducted an analysis of 892 women ≥18 years of age discharged from the ED with a UTI diagnosis. We assessed predictors of nitrofurantoin resistance, cefazolin resistance, ciprofloxacin resistance, and trimethoprim-sulfamethoxazole resistance using unadjusted and multivariable logistic regression models.

Results: Antibiotic resistance was 13.6% for nitrofurantoin, 11.9% for cefazolin, 12.8% for ciprofloxacin, and 17.1% for trimethoprim-sulfamethoxazole. In multivariable analysis, significant independent associations with an increased likelihood of resistance to nitrofurantoin were observed for less urine blood (OR [per 1 category increase of score] 0.81; P = 0.02); greater mucous (OR [per 1 category increase of score] 1.22; P = 0.02); less specific gravity urine (OR [per 1 category increase] 0.87; P = 0.04), and presence of any history of kidney stones (OR 3.24; P = 0.01). There were no significant predictors for cefazolin resistance (all P ≥0.06); age was the only significant predictor of ciprofloxacin resistance (OR per 10 year increase 1.10, P = 0.05), and lower specific gravity urine was significantly associated with an increased risk of resistance to trimethoprim-sulfamethoxazole (OR [per 1 category increase] 0.88, P = 0.04).

Conclusion: Women with any history of kidney stones may have bacteriuria resistant to nitrofurantoin, suggesting that providers might consider alternative antibiotic therapies in this scenario. [West J Emerg Med. 2022;23(5)613–617.]

Urinary tract infections (UTI) are one of the most common infections encountered in the emergency department (ED) with an estimated 2-3 million annual visits. Widespread rapid antibiotic sensitivity testing is not available during the ED clinical visit; so antibiotics may be prescribed for which the bacteriuria is resistant. Given the difficulty in predicting the proper antimicrobial sensitivity in the setting of emerging and increasingly resistant bacteria, treatment failures may occur. Commonly prescribed antibiotics for UTIs, including trimethoprim-sulfamethoxazole, fluoroquinolones, and beta-lactams, have all shown growing rates of resistance. Previous studies have attempted to elucidate general characteristics of antimicrobial resistance of bacteria but lack clear direction on improving successful UTI treatment based on the limited laboratory data available to the bedside clinician.

We sought to determine whether nitrofurantoin, cefazolin, ciprofloxacin, and trimethoprim-sulfamethoxazole resistance could be predicted based on triage and demographic data, urinalysis results, and past histories of renal failure/dialysis or kidney stones. We conducted an analysis of an existing dataset of ED patient encounters ≥18 years of age from a single healthcare system between April 18, 2014–March 7, 2017. We examined 892 women discharged from the ED with a UTI based on their discharge International Classification of Diseases (ICD) code and who had a positive urine culture (≥10,000 colony forming units per milliliter (CFU/mL) (CFU/mL bacteria in monoculture).
Women were considered pregnant if they had a pregnancy-related ICD code or a positive pregnancy test.

We assessed predictors of nitrofurantoin resistance, cefazolin resistance, ciprofloxacin resistance, and trimethoprim-sulfamethoxazole resistance using unadjusted and multivariable logistic regression models. Odds ratios (OR) and 95% confidence intervals (CI) were estimated and are interpreted as the multiplicative increase in the odds of antibiotic resistance for the given antibiotic. Multivariable models were adjusted for any variable with a \( P \)-value < 0.10 in the unadjusted analysis for the given antibiotic resistance outcome (and also had <10% missing data). \( P \)-values less than 0.05 were considered statistically significant. We performed analyses using R Statistical Software version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria).

A summary of patient characteristics is shown in Table 1. Median age was 49 years, and 53.3% of the patients were White. Antibiotic resistance was 13.6% for nitrofurantoin, 11.9% for cefazolin, 12.8% for ciprofloxacin, and 17.1% for trimethoprim-sulfamethoxazole. An evaluation of predictors of resistance to nitrofurantoin is provided in Table 2. In multivariable analysis (adjusting for urine blood, mucous, white blood cell clumps, and a history of kidney stones), significant independent associations with resistance to nitrofurantoin were observed for urine blood

Table 1. Summary of patients characteristics in 892 women analyzed.

| Variable                                           | N   | Median (minimum, maximum) or No. (%) of patients |
|----------------------------------------------------|-----|-------------------------------------------------|
| Age (years)                                        | 892 | 49 (18, 103)                                    |
| Race                                               | 889 |                                                 |
| White                                              | 474 | (53.3%)                                         |
| Black                                              | 405 | (45.6%)                                         |
| Other                                              | 10  | (1.1%)                                          |
| Marital status                                     | 890 |                                                 |
| Single                                             | 423 | (47.5%)                                         |
| Married                                            | 259 | (29.1%)                                         |
| Other                                              | 208 | (23.4%)                                         |
| Primary care doctor                                | 892 | 378 (42.4%)                                     |
| Emergency severity index                           | 869 |                                                 |
| 1                                                   | 1   | (0.1%)                                          |
| 2                                                   | 34  | (3.9%)                                          |
| 3                                                   | 568 | (65.4%)                                         |
| 4                                                   | 262 | (30.1%)                                         |
| 5                                                   | 4   | (0.5%)                                          |
| Urine specimen source                              | 698 |                                                 |
| Clean catheter/voided urine                        | 631 | (90.4%)                                         |
| Straight catheter or urine from new bladder catheter| 41  | (5.9%)                                          |
| Bladder catheter not known to be new               | 25  | (3.6%)                                          |
| Suprapubic catheter                                | 1   | (0.1%)                                          |
| Amorphous crystals urine (positive)                | 885 | 62 (7.0%)                                       |
| Bacteria urine score                               | 886 |                                                 |
| 0                                                   | 117 | (13.2%)                                         |
| 1                                                   | 255 | (28.8%)                                         |
| 2                                                   | 159 | (17.9%)                                         |
| 3                                                   | 151 | (17.0%)                                         |
| 4                                                   | 204 | (23.0%)                                         |
| Bilirubin urine score                              | 885 |                                                 |
| 0                                                   | 852 | (96.3%)                                         |
| 1                                                   | 11  | (1.2%)                                          |
| 2                                                   | 17  | (1.9%)                                          |
| 3                                                   | 5   | (0.6%)                                          |
| Variable                                | N   | Median (minimum, maximum) or No. (%) of patients |
|-----------------------------------------|-----|-------------------------------------------------|
| Blood urine score                       | 880 |                                                 |
| 0                                       |     | 256 (29.1%)                                     |
| 1                                       |     | 189 (21.5%)                                     |
| 2                                       |     | 154 (17.5%)                                     |
| 3                                       |     | 281 (31.9%)                                     |
| Glucose urine (positive)                | 886 | 63 (7.1%)                                       |
| Ketones urine (positive)                | 885 | 115 (13.0%)                                     |
| Leukocyte esterase urine score          | 873 |                                                 |
| 0                                       |     | 76 (8.7%)                                        |
| 1                                       |     | 144 (16.5%)                                     |
| 2                                       |     | 104 (11.9%)                                     |
| 3                                       |     | 549 (62.9%)                                     |
| Mucous urine score                      | 885 |                                                 |
| 0                                       |     | 634 (71.6%)                                     |
| 1                                       |     | 133 (15.0%)                                     |
| 2                                       |     | 43 (4.9%)                                        |
| 3                                       |     | 39 (4.4%)                                        |
| 4                                       |     | 36 (4.1%)                                        |
| Nitrite urine (positive)                | 885 | 328 (37.1%)                                     |
| Urine pH                                | 887 | 6 (5.9)                                          |
| Protein urine (positive)                | 887 | 557 (62.8%)                                     |
| Red blood cells                         | 882 | 11 (0, 100)                                      |
| Specific gravity urine                  | 887 |                                                 |
| 1.000 to 1.004                          |     | 31 (3.5%)                                        |
| 1.005 to 1.009                          |     | 227 (25.6%)                                     |
| 1.010 to 1.014                          |     | 187 (21.1%)                                     |
| 1.015 to 1.019                          |     | 162 (18.3%)                                     |
| 1.020 to 1.024                          |     | 128 (14.4%)                                     |
| 1.025 to 1.029                          |     | 96 (10.8%)                                       |
| 1.030 to 1.034                          |     | 48 (5.4%)                                        |
| ≥ 1.035                                 |     | 8 (0.9%)                                         |
| Trichomonas urine (positive)            | 885 | 4 (0.5%)                                         |
| Urobilinogen urine (≥2)                 | 887 | 173 (19.5%)                                     |
| White blood cell clumps urine (present) | 882 | 205 (23.2%)                                     |
| White blood cells                       | 877 | 36 (0, 100)                                      |
| Yeast in urine (positive)               | 885 | 20 (2.3%)                                        |
| Pregnant                                | 892 | 12 (1.3%)                                        |
| History of renal failure or dialysis    | 892 | 21 (2.4%)                                        |
| History of kidney stones                | 892 | 28 (3.1%)                                        |
| Resistance to cefazolin                 | 831 | 99 (11.9%)                                       |
| Resistance to ciprofloxacin             | 892 | 114 (12.8%)                                     |
| Resistance to nitrofurantoin            | 853 | 116 (13.6%)                                     |
| Resistance to trimethoprim-sulfamethoxazole | 859 | 147 (17.1%)                                     |
Table 2. Evaluation of predictors of resistance to nitrofurantoin.

| Variable | N     | Unadjusted analysis | Multivariable analysis |
|----------|-------|---------------------|-----------------------|
|          |       | OR (95% CI)         | P-value    | OR (95% CI)         | P-value    |
| Age (10 year increase) | 853  | 1.03 (0.95, 1.12)   | 0.47       | 1.05 (0.95, 1.15)   | 0.34       |
| Race (non-White) | 850  | 1.24 (0.84, 1.84)   | 0.28       | 1.16 (0.77, 1.75)   | 0.49       |
| Marital status | 851  | Overall test of difference: P=0.49 |       | Overall test of difference: P=0.43 |       |
| Single | 1.00 (reference) | N/A |       | 1.00 (reference) | N/A |       |
| Married | 0.90 (0.55, 1.43) | 0.65 |       | 0.96 (0.58, 1.56) | 0.87 |       |
| Other | 1.23 (0.76, 1.97) | 0.38 |       | 1.34 (0.81, 2.19) | 0.25 |       |
| Primary care doctor | 853  | 1.01 (0.68, 1.50)   | 0.94       | 1.02 (0.68, 1.53)   | 0.91       |
| Emergency severity index (1 unit increase) | 830  | 0.86 (0.59, 1.23)   | 0.41       | 0.94 (0.65, 1.36)   | 0.74       |
| Urine specimen source (non-clean catch/void urine) | 670  | 1.42 (0.68, 2.74)   | 0.32       | 1.31 (0.62, 2.58)   | 0.45       |
| Amorphous crystals urine (positive) | 846  | 1.56 (0.75, 3.00)   | 0.21       | 1.53 (0.72, 3.03)   | 0.24       |
| Bacteria urine score (1 category increase) | 847  | 0.99 (0.86, 1.14)   | 0.85       | 0.97 (0.84, 1.12)   | 0.66       |
| Bilirubin urine score (1 category increase) | 846  | 0.76 (0.34, 1.33)   | 0.42       | 0.74 (0.32, 1.30)   | 0.37       |
| Blood urine score (1 category increase) | 842  | 0.82 (0.69, 0.96)   | 0.02       | 0.81 (0.69, 0.96)   | 0.02       |
| Glucose urine (positive) | 848  | 1.12 (0.50, 2.24)   | 0.72       | 1.12 (0.50, 2.27)   | 0.77       |
| Ketones urine (positive) | 846  | 0.68 (0.33, 1.25)   | 0.24       | 0.60 (0.29, 1.12)   | 0.13       |
| Leukocyte esterase urine score (1 category increase) | 836  | 0.98 (0.81, 1.19)   | 0.81       | 1.10 (0.90, 1.36)   | 0.37       |
| Mucous urine score (1 category increase) | 846  | 1.22 (1.03, 1.44)   | 0.02       | 1.22 (1.03, 1.43)   | 0.02       |
| Nitrite urine (positive) | 846  | 0.73 (0.47, 1.10)   | 0.13       | 0.68 (0.44, 1.04)   | 0.08       |
| Urine pH (1 unit increase) | 848  | 1.07 (0.86, 1.32)   | 0.53       | 1.08 (0.87, 1.34)   | 0.46       |
| Protein urine (positive) | 848  | 0.79 (0.53, 1.19)   | 0.26       | 0.99 (0.64, 1.55)   | 0.98       |
| Red blood cells (10 unit increase) | 843  | 0.96 (0.91, 1.02)   | 0.23       | 1.01 (0.94, 1.09)   | 0.76       |
| Specific gravity urine (1 category increase) | 848  | 0.93 (0.82, 1.05)   | 0.26       | 0.87 (0.76, 0.99)   | 0.04       |
| Urobilinogen (ug) | 848  | 0.95 (0.56, 1.53)   | 0.83       | 0.82 (0.48, 1.35)   | 0.45       |
| White blood cell clumps urine (present) | 843  | 0.64 (0.38, 1.05)   | 0.09       | 0.69 (0.40, 1.13)   | 0.15       |
| White blood cells (10 unit increase) | 838  | 0.99 (0.94, 1.04)   | 0.69       | 1.02 (0.96, 1.08)   | 0.56       |
| Yeast in urine (positive) | 846  | 1.11 (0.26, 3.38)   | 0.87       | 1.12 (0.25, 3.52)   | 0.87       |
| Pregnant | 853  | 0.63 (0.03, 3.35)   | 0.66       | 0.58 (0.03, 3.18)   | 0.61       |
| History of renal failure or dialysis | 853  | 0.70 (0.11, 2.47)   | 0.64       | 0.73 (0.11, 2.60)   | 0.67       |
| History of kidney stones | 853  | 2.72 (1.03, 6.46)   | 0.03       | 3.24 (1.21, 7.90)   | 0.01       |

ORs are interpreted as the multiplicative increase in the odds of resistance to nitrofurantoin for each increase given in parenthesis (continuous variables) or presence of the given characteristic (categorical variables). Multivariable models were adjusted for all variables with a p-value <0.10 in unadjusted analysis (blood urine score, mucous urine score, WBC clumps urine, and history of kidney stones). The “Overall test of difference” that is provided for marital status tests whether there is any difference in resistance to nitrofurantoin between the three marital status categories. OR, odds ratio; CI, confidence interval.

(OR 0.81; P = 0.016); mucous (OR 1.22; P = 0.019); specific gravity urine (OR 0.87; P = 0.044), and any history of kidney stones (OR 3.24; P = 0.013).

Associations of antibiotic resistance for cefazolin, ciprofloxacin, and trimethoprim-sulfamethoxazole are shown in Supplements 1-3. In multivariable analysis, there were no significant predictors for cefazolin resistance (all P ≥0.056); age was the only significant predictor of ciprofloxacin resistance (OR 1.10, P = 0.048), and specific gravity urine was significantly associated with resistance to trimethoprim-sulfamethoxazole (OR 0.88, P = 0.035). For patients resistant to nitrofurantoin, we estimated the proportion who were resistant to our other antibiotics and found that antibiotic resistance was lowest for trimethoprim-sulfamethoxazole (9.6%, 11/115), then ciprofloxacin (14.7%, 17/116), and finally cefazolin (22.6%, 26/115).

One of the risk factors for nitrofurantoin resistance in our study based on multivariable analysis was a history of kidney stones (OR 3.24). Our findings support previous studies finding a higher likelihood of resistant pathogens in patients with a history...
of nephrolithiasis. The Proteae group of bacteria (Proteus, Morganella morganii, and Providencia) are known to produce urease and are associated with kidney stones. The Proteae group has inherent resistance to nitrofurantoin, which could explain our findings although our study did not examine which bacteria were growing in patients’ culture or determine whether kidney stones were diagnosed during the current encounter. The clinical significance of our findings remains unclear, but 29.2% (7/24) of women with any history of kidney stones had bacteriuria resistant to nitrofurantoin compared to 13.1% (109/829) for those women without stones. Age ≥65 years was associated with ciprofloxacin resistance, which is consistent with the findings of our study.

The results of this study suggest female UTI patients with any history of kidney stones may have increased rates of treatment failure with nitrofurantoin. Furthermore, in our analysis, antibiotic resistance was lowest with trimethoprim-sulfamethoxazole in those cases of observed nitrofurantoin resistance.

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