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Alkaline Urine in the Emergency Department Predicts Nitrofurantoin Resistance

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□ **Abstract—Background: The *Proteeae* group (i.e., *Proteus* species, *Morganella morganii*, and *Providencia* species) frequently causes urinary tract infections (UTIs) and is generally resistant to nitrofurantoin. *Proteeae* species can produce urease, which can increase urine pH. Objective: Our aim was to determine whether higher urine pH in the emergency department is associated with nitrofurantoin resistance. Methods: A single health system database of emergency department patients aged 18 years and older who received urinalysis between April 18, 2014, and March 7, 2017, was examined using χ^2 test and multivariable regression analysis. Results: Of 67,271 urine samples analyzed, 13,456 samples grew a single bacterial species. Urine cultures growing the *Proteeae* group were associated with significantly more alkaline urine than other bacteriuria cultures (odds ratio [OR] 2.20, 95% confidence interval [CI] 2.06–2.36; $p < 0.001$). The *Proteeae* species represented 4.4% of urine samples at pH 5–7, 24.4% at pH 8–9, and 40.0% at pH 9. At urine pH 5–7, 80.4% of urine samples were sensitive to nitrofurantoin; however, this percentage decreased to 66.1% for urine pH 8–9 and 54.6% for urine pH 9. Nitrofurantoin had the highest OR (2.10, 95% CI 1.85–2.39) among cefazolin, ciprofloxacin, and trimethoprim/sulfamethoxazole for bacteriuria sensitive to those antibiotics at urine pH 5–7. At urine pH 8–9 and 9, nitrofurantoin had the lowest OR among the antibiotics: 0.48 (95% CI 0.42–0.54) and 0.31 (95% CI 0.24–0.40), respectively ($p < 0.001$ for both). Conclusions: Urine pH of 8 or higher is associated with high rates of nitrofurantoin resistance.**

□ **Keywords—cystitis; *Morganella*; *Proteeae*; *Providencia*; urinary tract infection; urine culture**

Introduction

Urinary tract infections (UTIs) affect about 150 million people around the world annually, making it one of the most common human bacterial infections (1,2). Approximately 1% of all outpatient clinic visits and about 2 million to 3 million emergency department (ED) visits are for UTIs each year (3–5).

In the absence of rapid antimicrobial sensitivity testing or recent culture and sensitivity data, emergency physicians treat UTIs with empirical antibiotic therapy until either culture and sensitivity information is available to guide therapy or clinical symptoms resolve. The Infectious Diseases Society of America, together with the Society of Academic Emergency Medicine, recommends nitrofurantoin as first-line antibiotic treatment of simple UTIs (6). Complicating the empirical use of nitrofurantoin for UTI treatment is intrinsic resistance to the antibiotic in the *Proteeae* group, which constitutes 3 genera of bacteria—*Proteus* (*Proteus mirabilis, Proteus myxofaciens*, and *Proteus vulgaris*), *Morganella* (*Morganella morganii*), and *Providencia* (*Providencia alcalifaciens, Providencia rettgeri*, and *Providencia stuartii*)—in the Enterobacteriaceae family (7–11). *Proteeae* bacteria are

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among the more common bacterial organisms causing UTIs, especially in patients with long-term indwelling bladder catheters (7–9). The *Proteeae* species produce the enzyme urease, which hydrolyzes urea into ammonia and carbon dioxide and has been proposed as the reason for their association in higher urine pH (7–9,12–15). The study objective was to determine whether higher urine pH is associated with nitrofurantoin resistance and with the growth of a *Proteeae* group bacterium in urine culture.

Methods

Study Population

A database was created of 75,000 consecutive ED patient encounters. All patients were aged 18 years and older, and the encounter occurred between April 18, 2014, and March 7, 2017, at a single health care system. All patients in the database received either ED urinalysis and urine culture or testing for gonorrhea, chlamydia, or trichomonas. Our research was a subgroup analysis of the database. The database was created by University Hospitals' information technology personnel, who pulled data from the electronic health record. Our analysis included only those patients with a documented urine pH. The study was approved by the University Hospitals and Mayo Clinic institutional review boards.

Patients were considered to have a UTI diagnosis if they had one of the following ED discharge codes from the ninth revision of the *International Classification of Diseases* or 10th revision of the *International Statistical Classification of Diseases*: 595.0, 595.1, 595.9, 599.0, N30.91, N30.90, N30.80, N30.81, N30.00, N30.01, N39.0, or N30.20. Urinalysis included bacteria (0–4+), bilirubin (0–3+), blood (0–3+), squamous epithelial cells/high-power field (HPF), glucose (present or absent), ketones (0–3+; trace was recorded as 0.5 for the analysis), leukocyte esterase (0–3+), nitrite (positive or negative), urine pH (5-9), and protein (0–3+; trace recoded as 0.5) (16,17). The analysis also evaluated mean red blood cell (RBC) count (> 100 cells/HPF recoded as 101 cells/HPF), urobilinogen (0–12; < 2 recoded as 0), mean white blood cell (WBC) count (> 100 cells/HPF recoded as 101 cells/HPF), budding yeast (present or not), and sensitivity vs. intermediate sensitivity or resistance to nitrofurantoin, cefazolin, ciprofloxacin, and trimethoprim/sulfamethoxazole (TMP-SMX).

The primary outcome was the association between the different bacterial genus and groups and the urine pH, defined as the median pH value on urinalysis. Secondary outcomes included the proportion of UTIs that showed sensitivity to nitrofurantoin classified as pH levels 5–7, 8–9, and 9 and identification of demographic, clinical, and urinalysis variables associated with urine pH.

Statistical Analysis

Categorical variables were summarized as number and percentage and with χ^2 test. Continuous variables were summarized as median and interquartile range (IQR) and with Wilcoxon rank sum test. Stepwise regression analysis was performed to identify the clinical characteristics for multivariable regression models, which included age, ED disposition (admitted vs. not) and, from urinalysis, data on bilirubin, blood, glucose, ketones, leukocyte esterase, mucus, protein, RBCs, WBC clumps, WBCs, and yeast. A separate analysis was done with patients who could be treated with nitrofurantoin in the ED and included those diagnosed with a UTI and with a glomerular filtration rate (GFR) of 30 mL/min/1.73 m^2 or greater if creatinine level was checked during the ED visit. Statistical software (JMP Pro 14, SAS Institute Inc.) was used in the analyses. A p value of < 0.05 was considered statistically significant.

Results

The clinical characteristics of patients in the analysis are summarized in Table 1. In total, 67,271 urinalyses had a urine pH and 13,456 samples grew a single bacterial organism. Of urine cultures, 341 grew yeast.

The study evaluated 13,762 patients diagnosed with a UTI; 5676 urine samples grew a single bacterial species and 4107 patients were admitted to the hospital. Among the 9655 ED patients not admitted to the hospital who had a UTI, 2501 left the ED with a prescription for nitrofurantoin, 1220 with cephalexin, 2807 with ciprofloxacin, and 1888 with TMP-SMX. (Some patients received multiple antibiotics.)

The median urine pH was 6 (IQR 5–6). Of the 67,271 urinalysis samples, 60,879 (90.5%) had a pH of 5–7; 6392 (9.5%) had a pH of 8–9; and 1212 (1.8%) had a pH of 9 (Figure 1). For the 13,244 patients diagnosed with a UTI who had a GFR of 30 mL/min/1.73 m^2 or more (only if creatinine was measured in the ED), 11,706 (88.4%) had a urine pH of 5–7; 1286 (9.7%) had a urine pH of 8–9; and 252 (1.9%) had a urine pH of 9. The nonbacterial variables associated with urine pH are listed in Supplementary Table 1.

Bacteria and Urine pH

The most common bacteria on urine culture were *Escherichia* species at 52.3% (n = 7035); *Enterococcus* species, 7.1% (n = 965); and *Proteeae* group, 6.7%

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Table 1. Baseline Demographic and Triage Results for Patient Encounters Among Those with Urine pH and Urine Culture Growing a Single Bacterial Species

Characteristic	Data (N = 67,271)
Age, y, median (IQR)	47 (27-72)
Sex, n (%)	
Male	16,364 (24.3)
Female	50,907 (75.7)
Race (n = 66,949), n (%)	
Black/African American	36,870 (55.1)
White	29,007 (43.3)
Asian	306 (0.5)
Other	766 (1.1)
Timing of ED visit, median (IQR) (scale, 0–24 h)	14 (10-18)
Documented primary care physician, n (%)	
Yes	25,267 (37.6)
No	42,004 (62.4)
ED triage pain score, median (IQR) (scale 0–10) (n = 24,142)	0 (0-6)
ESI, median (IQR) (n = 64,849)	3 (3–3)
Arrival to ED (n = 66,566), n (%)	
EMS or police	19,513 (29.3)
Other mode	47,053 (70.7)
No. of times in data set, median (IQR)	2 (1-3)
Diagnosed with a UTI, n (%)	13,762 (20.5)
Urine sample source (n = 42,185), n (%)	
Clean catch	31,009 (73.5)
Condom catheter	12 (< 0.1)
Cystoscopy	3 (< 0.1)
Bladder catheter not known to be new	6742 (16.0)
Ileal conduit/ileostomy, n (%)	20 (< 0.1)
Nephrostomy, n (%)	150 (0.4)
Straight catheter or new bladder catheter, n (%)	3872 (9.2)
Suprapubic catheter, n (%)	292 (0.7)
Urostomy, n (%)	85 (0.2)
Urine pH, median (IQR)	6 (5-7)
Outpatient prescription, n (%)	
Nitrofurantoin	4839 (7.2)
Cephalexin	2542 (3.8)
Ciprofloxacin	8180 (12.2)
TMP-SMX	4001 (5.9)

ED = emergency department; EMS = emergency medical service; ESI = emergency severity index; IQR = interquartile range; TMP-SMX = trimethoprim/sulfamethoxazole; UTI = urinary tract infection.

(n = 906) (Table 2). The median urine pH for the *Proteeae* group was 7 compared with 6 for *Escherichia* species, *Klebsiella* species, *Enterococcus* species, *Streptococcus* species, *Staphylococcus* species, *Pseudomonas* species, and all other bacteria in the database combined. On multivariable regression analysis, the urine pH for each bacterial genus or group was compared with the urine pH for all other bacteria not in that genus or group. Only the *Proteeae* group (odds ratio [OR] 2.20, 95% confidence interval [CI] 2.06–2.36; $p < 0.001$) and *Staphylococcus* species (OR 1.14, 95% CI 1.03–1.27; $p = 0.01$) were significantly associated with more alkaline urine. On

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Table 2. Association of Bacteriuria with Urine pH

Bacterium	Urine pH				
	Median (IQR)	Adjusted OR (95% CI)*	Adjusted *p* value*	Adjusted estimate (SE)†	Adjusted *p* value†
Proteeae group species (n = 906)	7 (6-8)	2.20 (2.06-2.36)	< 0.001	0.478 (0.017)	< 0.001
Escherichia species (n = 7035)	6 (5-6)	0.79 (0.76-0.83)	< 0.001	−0.103 (0.009)	< 0.001
Klebsiella species (n = 1677)	6 (5-6)	0.89 (0.84-0.94)	< 0.001	−0.053 (0.013)	< 0.001
Enterococcus species (n = 965)	6 (5-7)	0.96 (0.90-1.03)	0.30	−0.015 (0.017)	0.39
Pseudomonas species (n = 420)	6 (5-7)	1.08 (0.98-1.20)	0.12	0.044 (0.025)	0.07
Staphylococcus species (n = 400)	6 (6-7)	1.14 (1.03-1.27)	0.01	0.061 (0.025)	0.02
Streptococcus species (n = 212)	6 (6-7)	1.03 (0.89-1.20)	0.67	0.022 (0.036)	0.54
None of the above species (n = 1841)	6 (5-6)	0.97 (0.92-1.03)	0.30	−0.012 (0.013)	0.33

CI = confidence interval; IQR = interquartile range; OR = odds ratio; SE = standard error.

* Dependent variable was the bacterial group, compared with all positive urine cultures not part of that bacterial group in the multivariable regression model.

† Urine pH is the dependent variable in the multivariable regression model, with each bacterial group analyzed separately.

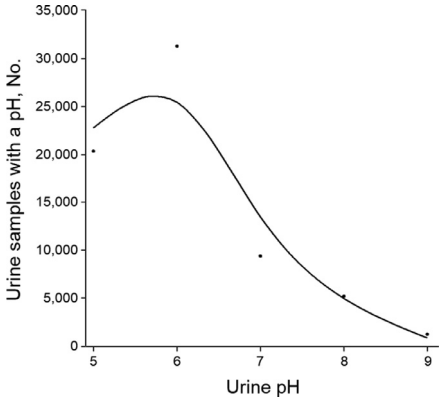

Figure 1. Urine samples at each pH.

multivariable regression analysis when urine pH was the dependent variable, only the *Proteeae* group ($p < 0.001$) and *Staphylococcus* species ($p = 0.02$) were significantly associated with more alkaline urine. The *Proteeae* group grew in 906 urine cultures, of which 729 (80.5%) were *P. mirabilis* and 15 were reported as a *Proteus* species. The clinical and laboratory variables associated with a urine culture growing a species of the *Proteeae* group are listed in Supplementary Table 2.

The most common bacteriuria present with urine pH > 7.0 (n = 1509) involved *Escherichia* species (36.4%, n = 550), the *Proteeae* group (24.6%, n = 371), *Klebsiella* species (10.3%; n = 155), *Enterococcus* species (7.0%, n = 105), *Pseudomonas* species (4.0%, n = 61), *Staphylococcus* species (3.1%, n = 47), *Streptococcus* species (1.7%, n = 25), and other bacteria (12.9%, n = 195). The most common bacteriuria present with urine pH > 8.0 (n = 366) involved the *Proteeae* group (40.2%, n = 147), *Escherichia* species (27.6%, n = 101), *Klebsiella* species (6.8%, n = 25), *Enterococcus* species (6.3%, n = 23), *Pseudomonas* species (4.4%, n = 16), *Staphylococcus* species (2.2%, n = 8), *Streptococcus* species (1.9%, n = 7), and other bacteria (10.7%, n = 39).

Proteeae Group

Among the urine cultures that grew bacteria of the *Proteeae* group, 535 (59.1%) had a urine pH of 5–7; 371 (40.9%) had urine pH of 8–9; and 147 (16.2%) had urine pH of 9. Among urine samples growing a single bacterial species, the *Proteeae* group represented 535 of 12,275 (4.4%) for those with urine pH of 5–7; 371 of 1522 (24.4%) for those with urine pH of 8–9; and 147 of 368 (39.9%) for those with urine pH of 9.

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Table 3. Association Between Urine pH and Urine Culture Showing Sensitivity to the Antibiotic

Antibiotic*	Urine pH, n (%); OR (95% CI)			*p* value for differences among pH 5–7, 8, and 9
	5–7	8	9	
Nitrofurantoin (n = 11,406)	8195 (80.4); 2.10 (1.85–2.39)	655 (69.5); 0.58 (0.50–0.69)	149 (54.6); 0.31 (0.24–0.40)	< 0.001
Cefazolin (n = 10,555)	7623 (80.8); 1.15 (0.99–1.33)	683 (78.5); 0.87 (0.73–1.03)	200 (78.7); 0.89 (0.66–1.21)	0.19
Ciprofloxacin (n = 12,508)	8218 (73.7); 1.27 (1.12–1.43)	745 (70.4); 0.86 (0.75–0.99)	193 (63.5); 0.63 (0.50–0.80)	< 0.001
TMP-SMX (n = 11,186)	7740 (77.5); 1.16 (1.01–1.34)	708 (76.1); 0.93 (0.80–1.09)	188 (70.2); 0.69 (0.53–0.90)	0.01

CI = confidence interval; OR = odds ratio; TMP-SMX = trimethoprim/sulfamethoxazole.
* Overall sensitivity: 78.9% for nitrofurantoin, 80.6% for cefazolin, 73.2% for ciprofloxacin, 77.2% for TMP-SMX. The median (interquartile range) urine pH was the same for the 4 antibiotics, at 6 (5–6). Significant differences were observed in the median urine pH for nitrofurantoin ($p < 0.001$) and ciprofloxacin ($p = 0.02$), but not for cefazolin ($p = 0.72$) or TMP-SMX ($p = 0.40$).

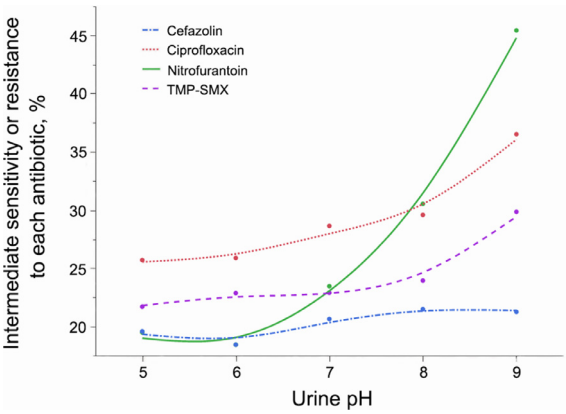

Figure 2. Association between urine pH and the frequency with which the culture shows intermediate sensitivity or resistance to each antibiotic. TMP-SMX = trimethoprim/sulfamethoxazole.

Antibiotic Resistance

Among urine cultures, 8999 (78.9%) of 11,406 cultures were sensitive to nitrofurantoin; 8506 (80.6%) of 10,555 were sensitive to cephazolin; 9156 (73.2%) of 12,508 were sensitive to ciprofloxacin; and 8636 (77.2%) of 11,186 were sensitive to TMP-SMX. The relationship between urine pH and intermediate sensitivity and resistance to antibiotics is shown in Figure 2.

Urine samples with pH 5–7 were significantly more likely to be sensitive to nitrofurantoin, ciprofloxacin, and TMP-SMX than pH 8 or 9 ($p \leq 0.01$) (Table 3). Among the *Proteeae* group, 578 (92.2%) of 627 cultures were reported as intermediate sensitivity or resistance to nitrofurantoin. Among those diagnosed with a UTI and who had a GFR < 30 mL/min/1.73 m^2 (if serum creatinine was checked in the ED), nitrofurantoin had the highest OR for a report of sensitivity at urine pH 5–7 (OR 2.01, 95% CI 1.59–2.52), but the lowest OR among the antibiotics at pH 8–9 and pH 9 (OR 0.50, 95% CI 0.40–0.63 and 0.44, 95% CI 0.28–0.68) (Supplementary Table 3). Of 1216 urine samples, 804 (66.1%) were known to show sensitivity to nitrofurantoin at urine pH 8–9. The OR (95% CI) of nitrofurantoin sensitivity was 0.48 (95% CI 0.42–0.54) ($p < 0.001$ when comparing pH 8–9 with pH 5–7).

Antibiotics Prescribed for UTI

Statistically significant differences were observed in the numbers of patients with a UTI, urine pH 5–7, and a prescription for an antibiotic for which urine culture and sensitivity data showed intermediate sensitivity or resistance for that antibiotic were 105 (16.3%) of 645 patients for nitrofurantoin, 49 (13.5%) of 362 for cefazolin, 195 (17.7%) of 1104 for ciprofloxacin, and 117 (15.6%) of 571 for TMP-SMX ($p = 0.04$). In addition, there were significant differences in the numbers of patients with a UTI, a urine pH of 8–9, and a prescription for an antibiotic for which urine culture and sensitivity data showed intermediate sensitivity or resistance: 14 (25.9%) of 54 patients for nitrofurantoin, 6 (11.3%) of 53 for cefazolin, 32 (26.4%) of 121 for ciprofloxacin, and 7 (11.5%) of 61 for TMP-SMX ($p = 0.02$).

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Discussion

In this study, we observed that among adults presenting to an ED, a higher urine pH was associated with both resistance to nitrofurantoin and increased risk of urine culture growing a *Proteeae* group bacterium that had intrinsic resistance to nitrofurantoin. Alkaline urine occurred less frequently, and patients with urine pH of 8–9 or 9 represented only 9.5% and 1.8%, respectively.

The antibacterial effect of nitrofurantoin is known to depend on urine pH and is optimal at a pH between 5.4 and 7; it is least effective at pH 8 or higher (18–23). Tubular reabsorption of nitrofurantoin is enhanced by a low pH and is independent of urine flow (18,19,24,25). With our institutional culture and sensitivity data showing unacceptably high levels of nitrofurantoin resistance at a high urine pH, this indicates that nitrofurantoin should be avoided for patients with a UTI and a urine pH of 8 or higher. Our data are suggestive that perhaps cefazolin or TMP-SMX could be considered antibiotic alternatives for patients with UTI and urine pH of 8 or higher.

The 1988 macrodantin (nitrofurantoin) product information recommended avoiding use of the drug when a patient has creatinine clearance (CrCl) < 40 mL/min (18). However, in 2003, that threshold was changed to 60 mL/min. Nevertheless, use of nitrofurantoin at CrCl down to 40 mL/min appears safe and effective (18). The American Geriatrics Society's 2015 Beers Criteria Update Expert Panel revised their recommendations to avoid nitrofurantoin for patients with CrCl < 30 mL/min (26,27). Studies have found that nitrofurantoin may not be as effective in treating UTIs of persons with GFR of 30 to 50 mL/min/1.73 m^2, and these patients may have greater drug adverse effects (28,29).

The demographic and clinical variables associated with changes in urine pH are incompletely characterized. In our cohort, Black and African American patients had significantly lower urine pH values than patients who were not Black or African American. Yet, previous reports have cited that Black women had higher urine pH values than White women (30). It also has been reported previously that urine pH did not correlate with such urinary symptoms as dysuria, frequency, or urgency and did not differ between those with and those without serious bacteriuria (31). Urine pH may be lowest in summer months and highest in winter, although we did not account for seasonal variability in our database (32). Diurnal variation may also occur in urine pH, with a higher urine pH reported in the morning and a lower pH in the evening (33–35). However, on multivariable regression, we did not observe that the hour of the ED visit was significantly associated with urine pH.

Diet, genetics, and sex may affect urine pH (36–40). In our study, we did not observe differences in urine pH between men and women, and our study did not account for diet or genetics. Low urine pH has previously been associated with higher body mass index (BMI); metabolic syndrome, including central obesity, dysglycemia and diabetes, nonalcoholic fatty liver, chronic kidney disease, older age, metabolic acidosis, hypertension, and dyslipidemia (41–62). Increased insulin resistance from diabetes and metabolic syndrome can lead to a decreased ratio of ammonium to net acid excretion (41,63). The net urinary acid excretion indicates decreased renal function (64). Our results showed that a higher GFR was associated with higher urine pH on multivariable regression analysis. Too few patients in the database had a reported BMI to include that variable in our analyses. In our regression analysis, advancing age and glucosuria were associated with lower urine pH. Medications such as loop diuretics, mineralocorticoids, and cranberry extract lower urine pH, but our database did not include information on nonantibiotic medications (60,65,66).

Drug clearance and accumulation in the urine are related to GFR, renal blood flow, ability of the kidney to reabsorb or secrete the drug, urine pH, and urine flow (67). Urine pH also affects the antimicrobial efficacy of some antibiotics (23,68–71). TMP-SMX, ertapenem, and nitrofurantoin are most effective at a lower urine pH, ciprofloxacin and gentamycin are more effective at a higher urine pH, and cefotaxime is not affected by urine pH (69,70,72–74). TMP-SMX is excreted largely unchanged in the urine and is most effective at urine pH 5–7 (68). The renal clearance and excretion rate of sulfamethoxazole depend on urine flow, and drug metabolism is indirectly associated with urine pH and flow (75). Renal excretion of sulfamethoxazole is increased with a higher urine pH (75).

Limitations

A urine pH dipstick test is not as accurate as a 24-h urine pH (76,77). Recommendations for avoiding nitrofurantoin use for uncomplicated UTIs are based on CrCl, which slightly overestimates GFR and was used in our analysis. This analysis did not exclude patients with contraindications for nitrofurantoin use, including pyelonephritis and prostatitis. Not all patients receiving a urinalysis or diagnosed with a UTI received a urine culture. The method of how the urine was obtained was documented infrequently, so that variable was not included in our multivariable regression analysis. Our database did not include all clinical variables known to affect urine pH. Documentation of many urine samples did not identify how the samples were collected, and *Proteus* species have been responsible for a substantial number of UTIs in patients with indwelling bladder catheters (14). Other bacteria in bacteriuria have been shown to produce

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urease, including *Klebsiella pneumoniae* and *Staphylococcus aureus*, which could affect our hypothesis that alkaline urine is associated with nitrofurantoin resistance (12). However, in vitro studies have shown that *K. pneumoniae* and *S. aureus* have much less urease activity than the *Proteeae* species (12). Clinical microbiology laboratories typically consider bacteriuria sensitive, intermediately sensitive, or resistant to antibiotics on the basis of minimal inhibitor concentration (MIC) and time-kill curves in Mueller Hinton broth (21). However, the MICs both underestimate and overestimate the local effects of antibiotics, including TMP-SMX and ciprofloxacin (21). Clinical efficacy of an antibiotic may not correlate with the reported in vitro MICs. University Hospitals' microbiology laboratory did not measure MICs to cephalexin for bacteriuria. Therefore, the MICs for cefazolin, another first-generation cephalosporin, were used as a proxy, and the results may not be equivalent.

Conclusions

Although a urine pH of 8 or higher is less common than more acidic urine, it is significantly associated with higher odds of both having bacteria with nitrofurantoin resistance and growing a *Proteeae* group bacterium in culture. Additional studies will be helpful to confirm our findings and to examine the clinical outcomes of patients with alkaline UTIs treated with nitrofurantoin. However, the combination of the known pharmacokinetics of nitrofurantoin that show less effectiveness at higher urine pH and our results of unacceptably high rates of nitrofurantoin resistance among bacteriuria with high urine pH is suggestive that an antibiotic other than nitrofurantoin should be considered when treating uncomplicated cystitis with urine pH $\geq$ 8.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jemermed.2021.10.022.

References

1. Flores-Mireles AL, Walker JN, Caparon M, Hultgren SJ. Urinary tract infections: epidemiology, mechanisms of infection and treatment options. Nat Rev Microbiol 2015;13:269–84.
2. Stamm WE, Norrby SR. Urinary tract infections: disease panorama and challenges. J Infect Dis 2001;183(Suppl 1):S1–4.
3. Foxman B. The epidemiology of urinary tract infection. Nat Rev Urol 2010;7:653–60.
4. Foxman B. Urinary tract infection syndromes: occurrence, recurrence, bacteriology, risk factors, and disease burden. Infect Dis Clin North Am 2014;28:1–13.
5. Schappert SM, Rechtsteiner EA. Ambulatory medical care utilization estimates for 2007. Vital Health Stat 2011;13:1–38.
6. Gupta K, Hooton TM, Naber KG, et al. International Clinical Practice Guidelines for the Treatment of Acute Uncomplicated Cystitis and Pyelonephritis in Women: A 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. Clin Infect Dis 2011;52:e103–20.
7. Liu H, Zhu J, Hu Q, Rao X. *Morganella morganii*, a non-negligent opportunistic pathogen. Int J Infect Dis 2016;50:10–17.
8. Bush LM, Vazquez-Pertejo MT.*Proteeae* infections. Accessed November 19, 2020. Available at: https://www.merckmanuals.com/professional/infectious-diseases/gram-negative-bacilli/Proteeae-infections
9. O'Hara CM, Brenner FW, Miller JM. Classification, identification, and clinical significance of Proteus, Providencia, and Morganella. Clin Microbiol Rev 2000;13:534–46.
10. Huttner A, Verhaegh EM, Harbarth S, Muller AE, Theuretzbacher U, Mouton JW. nitrofurantoin revisited: a systematic review and meta-analysis of controlled trials. J Antimicrob Chemother 2015;70:2456–64.
11. McOsker CC, Fitzpatrick PM. Nitrofurantoin: mechanism of action and implications for resistance development in common uropathogens. J Antimicrob Chemother 1994;33(suppl A):23–30.
12. Broomfield RJ, Morgan SD, Khan A, Stickler DJ. Crystalline bacterial biofilm formation on urinary catheters by urease-producing urinary tract pathogens: a simple method of control. J Med Microbiol 2009;58:1367–75.
13. Sheele JM, Vallabhaneni M. Should nitrofurantoin be used to treat alkaline urinary tract infection? Emerg Med 2018;50:142–4.
14. Coker C, Poore CA, Li X, Mobley HL. Pathogenesis of *Proteus mirabilis* urinary tract infection. Microbes Infect 2000;2:1497–505.
15. Armbruster CE, Mobley HL. Merging mythology and morphology: the multifaceted lifestyle of *Proteus mirabilis*. Nat Rev Microbiol 2012;10:743–54.
16. . International Classification of Diseases. 9th revision. World Health Organization; 1978.
17. . International Statistical Classification of Diseases. 10th revision. World Health Organization; 2010.
18. Oplinger M, Andrews CO. Nitrofurantoin contraindication in patients with a creatinine clearance below 60 mL/min: looking for the evidence. Ann Pharmacother 2013;47:106–11.
19. Conklin JD. The pharmacokinetics of nitrofurantoin and its related bioavailability. Antibiot Chemother (1971) 1978;25:233–52.
20. Richards WA, Riss E, Kass EH, Finland M. Nitrofurantoin; clinical and laboratory studies in urinary tract infections. AMA Arch Intern Med 1955;96:437–50.
21. Wijma RA, Fransen F, Muller AE, Mouton JW. Optimizing dosing of nitrofurantoin from a PK/PD point of view: What do we need to know? Drug Resist Updat 2019;43:1–9.
22. Marchant B, Sheele JM. A novel cause of pneumocephalus. J Emerg Med 2013;44:e381–3.
23. Mou TW. Effect of urine pH on the antibacterial activity of antibiotics and chemotherapeutic agents. J Urol 1962;87:978–87.
24. Schirmeister J, Stefani F, Willmann H, Hallauer W. Renal handling of nitrofurantoin in man. Antimicrob Agents Chemother (Bethesda) 1965;5:223–6.
25. Braunlich H, Bonow A, Schroter S. Age-dependence of renal tubular reabsorption of nitrofurantoin. Arch Int Pharmacodyn Ther 1978;232:92–101.

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26. Hoang P, Salbu RL. Updated nitrofurantoin recommendations in the elderly: a closer look at the evidence. Consult Pharm 2016;31:381–4.
27. The American Geriatrics Society Beers Criteria Update Expert PanelAmerican Geriatrics Society 2015 Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults. J Am Geriatr Soc 2015;63:2227–46.
28. Geerts AF, Eppenga WL, Heerdink R, et al. Ineffectiveness and adverse events of nitrofurantoin in women with urinary tract infection and renal impairment in primary care. Eur J Clin Pharmacol 2013;69:1701–7.
29. Singh N, Gandhi S, McArthur E, et al. Kidney function and the use of nitrofurantoin to treat urinary tract infections in older women. CMAJ 2015;187:648–56.
30. Taylor EN, Curhan GC. Differences in 24-hour urine composition between black and white women. J Am Soc Nephrol 2007;18:654–9.
31. Brumfitt W, Hamilton-Miller JM, Cooper J, Raeburn A. Relationship of urinary pH to symptoms of 'cystitis'. Postgrad Med J 1990;66:727–9.
32. Stuart 2nd RO, Hill K, Poindexter J, Pak CY. Seasonal variations in urinary risk factors among patients with nephrolithiasis. J Lithotr Stone Dis 1991;3:18–27.
33. Murayama T, Sakai N, Yamada T, Takano T. Role of the diurnal variation of urinary pH and urinary calcium in urolithiasis: a study in outpatients. Int J Urol 2001;8:525–31 discussion 32.
34. Murayama T, Taguchi H. The role of the diurnal variation of urinary pH in determining stone compositions. J Urol 1993;150:1437–9.
35. Cameron M, Maalouf NM, Poindexter J, Adams-Huet B, Sakhaee K, Moe OW. The diurnal variation in urine acidification differs between normal individuals and uric acid stone formers. Kidney Int 2012;81:1123–30.
36. Worcester EM, Bergsland KJ, Gillen DL, Coe FL. Mechanism for higher urine pH in normal women compared with men. Am J Physiol Renal Physiol 2018;314:F623–9.
37. Curhan GC, Taylor EN. 24-h uric acid excretion and the risk of kidney stones. Kidney Int 2008;73:489–96.
38. Lieske JC, Turner ST, Edeh SN, Smith JA, Kardia SL. Heritability of urinary traits that contribute to nephrolithiasis. Clin J Am Soc Nephrol 2014;9:943–50.
39. Johnston CS, Bliss C, Knurick JR, Scholtz C. Rapid Eating Assessment for Participants [shortened version] scores are associated with Healthy Eating Index-2010 scores and other indices of diet quality in healthy adult omnivores and vegetarians. Nutr J 2018;17:89.
40. Cosgrove K, Johnston CS. examining the impact of adherence to a vegan diet on acid-base balance in healthy adults. Plant Foods Hum Nutr 2017;72:308–13.
41. Chung SM, Moon JS, Yoon JS, Won KC, Lee HW. Low urine pH affects the development of metabolic syndrome, associative with the increase of dyslipidemia and dysglycemia: nationwide cross-sectional study (KNHANES 2013-2015) and a single-center retrospective cohort study. PLoS One 2018;13.
42. Lee J, Chang HK, Lee S. Association of low urine pH as a metabolic feature with abdominal obesity. J Int Med Res 2020;48 300060519898615.
43. Maalouf NM, Cameron MA, Moe OW, Sakhaee K. Metabolic basis for low urine pH in type 2 diabetes. Clin J Am Soc Nephrol 2010;5:1277–81.
44. Cameron MA, Maalouf NM, Adams-Huet B, Moe OW, Sakhaee K. Urine composition in type 2 diabetes: predisposition to uric acid nephrolithiasis. J Am Soc Nephrol 2006;17:1422–8.
45. Shimodaira M, Okaniwa S, Nakayama T. Fasting single-spot urine pH is associated with metabolic syndrome in the Japanese population. Med Princ Pract 2017;26:433–7.
46. Okamura T, Hashimoto Y, Hamaguchi M, Obora A, Kojima T, Fukui M. Low urine pH is a risk for non-alcoholic fatty liver disease: a population-based longitudinal study. Clin Res Hepatol Gastroenterol 2018;42:570–6.
47. Yoshida S, Miyake T, Yamamoto S, et al. Relationship between urine pH and abnormal glucose tolerance in a community-based study. J Diabetes Investig 2018;9:769–75.
48. Hashimoto Y, Hamaguchi M, Nakanishi N, Ohbora A, Kojima T, Fukui M. Urinary pH is a predictor of diabetes in men; a population based large scale cohort study. Diabetes Res Clin Pract 2017;130:9–14.
49. Tran TY, Flynn M, O'Bell J, Pareek G. Calculated insulin resistance correlates with stone-forming urinary metabolic changes and greater stone burden in high-risk stone patients. Clin Nephrol 2016;85:316–20.
50. Najeeb Q, Masood I, Bhaskar N, et al. Effect of BMI and urinary pH on urolithiasis and its composition. Saudi J Kidney Dis Transpl 2013;24:60–6.
51. Nakanishi N, Fukui M, Tanaka M, et al. Low urine pH Is a predictor of chronic kidney disease. Kidney Blood Press Res 2012;35:77–81.
52. Kadlec AO, Greco KA, Fridirici ZC, Gerber D, Turk TM. Effect of renal function on urinary mineral excretion and stone composition. Urology 2011;78:744–7.
53. Maalouf NM, Sakhaee K, Parks JH, Coe FL, Adams-Huet B, Pak CY. Association of urinary pH with body weight in nephrolithiasis. Kidney Int 2004;65:1422–5.
54. Maalouf NM, Cameron MA, Moe OW, Adams-Huet B, Sakhaee K. Low urine pH: a novel feature of the metabolic syndrome. Clin J Am Soc Nephrol 2007;2:883–8.
55. Cho YH, Lee SY, Jeong DW, et al. The association between a low urine pH and the components of metabolic syndrome in the Korean population: Findings based on the 2010 Korea National Health and Nutrition Examination Survey. J Res Med Sci 2014;19:599–604.
56. Pigna F, Sakhaee K, Adams-Huet B, Maalouf NM. Body fat content and distribution and urinary risk factors for nephrolithiasis. Clin J Am Soc Nephrol 2014;9:159–65.
57. Song JH, Doo SW, Yang WJ, Song YS. Influence of obesity on urinary pH with respect to sex in healthy Koreans. Urology 2011;78:1244–7.
58. Remer T, Berkemeyer S, Rylander R, Vormann J. Muscularity and adiposity in addition to net acid excretion as predictors of 24-h urinary pH in young adults and elderly. Eur J Clin Nutr 2007;61:605–9.
59. Berend K, de Vries AP, Gans RO. Physiological approach to assessment of acid-base disturbances. N Engl J Med 2014;371:1434–45.
60. Martin-Gutierrez G, Rodriguez-Beltran J, Rodriguez-Martinez JM, et al. Urinary tract physiological conditions promote ciprofloxacin resistance in low-level-quinolone-resistant *Escherichia coli*. Antimicrob Agents Chemother 2016;60:4252–8.
61. Losito A, Nunzi EG, Covarelli C, Nunzi E, Ferrara G. Increased acid excretion in kidney stone formers with essential hypertension. Nephrol Dial Transplant 2009;24:137–41.
62. Friedlander JI, Moreira DM, Hartman C, Elsamra SE, Smith AD, Okeke Z. Age-related changes in 24-hour urine composition must be considered in the medical management of nephrolithiasis. J Endourol 2014;28:871–6.
63. Abate N, Chandalia M, Cabo-Chan Jr AV, Moe OW, Sakhaee K. The metabolic syndrome and uric acid nephrolithiasis: novel features of renal manifestation of insulin resistance. Kidney Int 2004;65:386–92.
64. Hua Y, Krupp D, Esche J, Remer T. Increased body fatness adversely relates to 24-hour urine pH during childhood and adolescence: evidence of an adipo-renal axis. Am J Clin Nutr 2019;109:1279–87.

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65. Kovesdy CP. Metabolic acidosis and kidney disease: does bicarbonate therapy slow the progression of CKD? Nephrol Dial Transplant 2012;27:3056–62.
66. Singh I, Gautam LK, Kaur IR. Effect of oral cranberry extract (standardized proanthocyanidin-A) in patients with recurrent UTI by pathogenic *E. coli*: a randomized placebo-controlled clinical research study. Int Urol Nephrol 2016;48:1379–86.
67. De Lavallaz L, Musso CG. Chronobiology in nephrology: the influence of circadian rhythms on renal handling of drugs and renal disease treatment. Int Urol Nephrol 2018;50:2221–8.
68. AlRabiah H, Allwood JW, Correa E, Xu Y, Goodacre R. pH plays a role in the mode of action of trimethoprim on Escherichia coli. PLoS One 2018;13.
69. Zhanel GG, Karlowsky JA, Davidson RJ, Hoban DJ. Influence of human urine on the in vitro activity and postantibiotic effect of ciprofloxacin against *Escherichia coli*. Chemotherapy 1991;37:218–23.
70. Wagenlehner F, Nowicki M, Bentley C, et al. Explorative randomized phase II clinical study of the efficacy and safety of finafloxacin versus ciprofloxacin for treatment of complicated urinary tract infections. Antimicrob Agents Chemother 2018;62(4):e02317.
71. Cunha BA, Giuga J, Gerson S. Predictors of ertapenem therapeutic efficacy in the treatment of urinary tract infections (UTIs) in hospitalized adults: the importance of renal insufficiency and urinary pH. Eur J Clin Microbiol Infect Dis 2016;35:673–9.
72. Smith SM, Eng RH, Cherubin CE. Conditions affecting the results of susceptibility testing for the quinolone compounds. Chemotherapy 1988;34:308–14.
73. Zeiler HJ. Influence of pH and human urine on the antibacterial activity of ciprofloxacin, norfloxacin and ofloxacin. Drugs Exp Clin Res 1985;11:335–8.
74. So W, Crandon JL, Nicolau DP. Effects of Urine Matrix and pH on the potency of delafloxacin and ciprofloxacin against urogenic *Escherichia coli* and *Klebsiella pneumoniae*. J Urol 2015;194:563–70.
75. Vree TB, Hekster YA, Baars AM, Damsma JE, van der Kleijn E. Pharmacokinetics of sulphamethoxazole in man: effects of urinary pH and urine flow on metabolism and renal excretion of sulphamethoxazole and its metabolite N4-acetylsulphamethoxazole. Clin Pharmacokinet 1978;3:319–29.
76. Abbott JE, Miller DL, Shi W, et al. Optimization of urinary dipstick pH: are multiple dipstick pH readings reliably comparable to commercial 24-hour urinary pH? Investig Clin Urol 2017;58:378–82.
77. Omar M, Sarkissian C, Jianbo L, Calle J, Monga M. Dipstick spot urine pH does not accurately represent 24 hour urine PH measured by an electrode. Int Braz J Urol 2016;42:546–9.

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1. Why is this topic important?

Urinary tract infections (UTIs) are one of the most common bacterial infections treated in the emergency department (ED), and nitrofurantoin is one of the antibiotics most commonly used to treat UTIs. Predicting nitrofurantoin resistance from the urinalysis could potentially improve antibiotic stewardship for patients with UTI.

2. What does this study attempt to show?

The study examines whether alkaline urine in the ED is associated with nitrofurantoin resistance.

3. What are the key findings?

Patients with alkaline urine in the ED are more likely to have bacteriuria that is resistant to nitrofurantoin.

4. How is patient care impacted?

Emergency physicians should consider a urine culture or the choice of an antibiotic other than nitrofurantoin, or both, when treating patients with a UTI and alkaline urine in the ED. At urine pH $\geq$ 8, bacteriuria was less likely to be sensitive to nitrofurantoin than cefazolin, ciprofloxacin, and trimethoprim/sulfamethoxazole.

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