Should Nitrofurantoin Be Used to Treat Alkaline Urinary Tract Infection?

Johnathan M. Sheele, MD, MPH, MHS; Mayur Vallabhaneni, BS

Abstract

Our analysis of 1,331 adult patients who were diagnosed with a urinary tract infection (UTI) in the ED found that 90% (n = 1,194/1,331) had a urine pH between 5.0 and 7.0. The majority of these UTIs were caused by ***Escherichia coli***. In addition, we noted that ***Proteus mirabilis***, which is intrinsically resistant to nitrofurantoin, was the most common cause of UTI in patients who had a urine pH was over 8.5.

Background

Urinary tract infections (UTIs), one of the most common human bacterial infections, affect approximately 150 million people annually worldwide.[1,2] In the United States, UTIs account for approximately 1% of all outpatient clinic visits and about 2 to 3 million ED visits annually.[1,3-5]

Although the urine pH level is frequently assessed in urinalysis, it is rarely considered in the management of a patient with a UTI.

Reports correlating urine pH with urine culture data from ED patients with UTIs are lacking. While poorly studied, there are multiple factors that could potentially alter the urine pH of patients with a UTI, including blood pH, diabetes, dehydration, ketosis, drugs, and renal function, as well as factors related to the infecting microorganism. For instance, *Proteus mirabilis* produces urease, an enzyme that hydrolyzes urea to ammonia and carbon dioxide.[6-8]

Objective

The objective of this study is to assess the relationship between the urine pH and the infecting microbe in ED patients diagnosed with UTIs, and to determine if *P mirabilis* is associated with alkaline urine.

Methods

We obtained approval from our Institutional Review Board to retrospectively obtain electronic medical record data from patients aged 18 years and older who presented to our institution's ED and who were diagnosed with either cystitis or a UTI between January 1, 2012 and March 31, 2015. Both urine pH level and a urine culture were obtained for all patients.

The results of all of the patients' urinary cultures in our study were positive for one bacterial species or genera (≥100,000 CFU/mL). The *International Classification of Disease, Ninth Revision/Tenth Revision* codes used to identify patients with cystitis and UTI were as follows: 595.0, 595.1, 595.9, 599.0, N30.91, N30.90, N30.80, N30.81, N30.00, N30.01, N30.20, N30.20, and N39.0.

To ensure that the focus of our study was limited to cystitis and UTIs, we excluded patients who were diagnosed with pyelonephritis, sexually transmitted infection,

Dr Sheele is an assistant professor and research director, department of emergency medicine, University Hospitals Cleveland Medical Center and Case Western Reserve University, Cleveland, Ohio. **Mr Vallabhaneni** is a medical student at Case Western Reserve University, Cleveland, Ohio.

Authors' Disclosure Statement: The authors report no actual or potential conflict of interest in relation to this article.

DOI: 10.12788/emed.2018.0099

Table. Bacterial Species and Genera Causing UTIs and Associated Urine pH Values

	Mean pH	Median pH	Mode pH	pH 5-7	pH 7.5-9	pH 8-9	pH 8.5-9	Percent of total urines with pH 5-7	Percent of total urines with pH 7.5-9	Percent of total urines with pH 8-9	Percent of total urines with pH 8.5-9
Escherichia coli (n = 818)	6.0	6.0	6.0	765	53	30	6	64%	39%	36%	23%
Klebsiella (n = 167)	5.9	6.0	5.5	156	11	6	1	13%	8%	7%	4%
Proteus mirabilis (n = 88)	7.0	7.0	6.0	50	38	26	9	4%	28%	31%	35%
Enterococcus (n = 50)	6.2	6.0	5.5	43	7	5	2	4%	5%	6%	7%
Coagulase-negative *Staphylococci* (n = 42)	6.3	6.0	6.0	39	3	2	2	3%	2%	2%	8%
Citrobacter (n = 38)	5.9	6.0	6.0	37	1	1	0	3%	1%	1%	0%
Enterobacter sp. (n = 31)	5.7	5.5	6.0	31	0	0	0	3%	0%	0%	0%
Pseudomonas (n = 26)	6.2	6.0	6.0	22	4	1	0	2%	3%	1%	0%
Group B Streptococcus (n = 16)	6.6	6.3	6.0	11	5	1	1	1%	4%	1%	4%
Staphylococcus aureus (n = 11)	6.4	6.0	6.0	9	2	2	1	1%	2%	2%	4%
Streptococcus viridans (n = 9)	6.8	7.0	7.0	7	2	2	0	1%	2%	2%	0%
Escherichia fergusonii (n = 8)	5.7	5.8	6.0	8	0	0	0	1%	0%	0%	0%
Morganella morganii (n = 8)	6.5	6.3	6.0	5	3	1	0	<1%	2%	1%	0%
Serratia (n = 7)	6.1	5.5	5.5	6	1	1	0	1%	1%	1%	0%
Providencia stuartii (n = 7)	6.9	7.0	6.0	4	3	1	0	<1%	2%	1%	0%
Providencia rettgeri (n = 5)	8.3	9.0	9.0	1	4	4	4	<1%	3%	5%	15%

Abbreviation: UTI, urinary tract infection

pelvic inflammatory disease, or vaginal discharge. The urine pH values reported from the clinical laboratory were 5.0, 5.5, 6.0, 6.5, 7.0. 7.5, 8.0, 8.5, and 9.0. Our dataset contained 1,331 clinical encounters. We used descriptive statistics and unpaired *t*-tests to evaluate the associations between urine pH values and the different microbes.

Results

Data were categorized into 16 different bacterial genera or species. *Acinetobacter* (n = 1), *Kluyvera ascorbata* (n = 2), and *Stenotrophomonas maltophilia* (n = 3) were underrepresented in the dataset and therefore were not included in the data analysis. The data are summarized in the **Table**.

In our dataset, the most common bacteria associated with UTI, irrespective of urine pH, were *Escherichia coli* (n = 818/1,331; 62%), *Klebsiella* (n = 167/1,331; 13%), and *P mirabilis* (n = 88/1,331; 7%). The mean urine pH in our cohort was 6.1 (range, 5.0-9.0; SD, 0.88; median, 6; and mode, 6), and 1,194/1,331 (90%) of all urine samples had a urine pH of 5.0 to 7.0. Among patients who had a urine pH of 7.5 to 9.0, *E coli* was the cause of UTI in 39% (53/137) and *P mirabilis* was the cause of UTI in 28% (38/137). Likewise, among patients who had a urine pH of 8.0 to 9.0, *E coli* was the cause of UTI in 36% (30/83), and *P mirabilis* was the cause of UTI in 31% (26/83). Lastly, in patients who had a urine pH of 8.5 to 9.0, *P mirabilis* was the most common cause of UTI, present in 35% (9/26) patients.

The mean urine pH in our dataset for *P mirabilis* (n = 88) was 7.0, with a standard deviation (SD) of 1.03 and the standard error of the mean (SEM) of 0.11. The majority, 50/88 (57%) of *P mirabilis* UTIs were associated with a urine pH of 5.0 to 7.0. However, the urine pH for *P mirabilis* was significantly more alkaline than the combined urine pH from all of the other bacterial genera and species in our cohort ($P < .0001$). The mean urine pH in our cohort, excluding the *P mirabilis* data, was 6.01 with an SD of 0.828 and a SEM of 0.023.

Limitations

Our data were obtained retrospectively from a single ED, and did not include the following information: patient age and gender, and mode in which urine samples were obtained (eg, Foley catheter, clean catch). In addition, no reports were available regarding the sensitivity of the urine cultures with respect to urine pH.

Discussion

While alkaline urine was present in only 10% of patients, a high percentage of alkaline UTIs were associated with *P mirabilis,* an organism with intrinsic resistance to nitrofurantoin. Therefore, health care providers could consider obtaining a urine culture and/or prescribing an antibiotic other than nitrofurantoin for treating uncomplicated UTIs with alkaline urine. In addition, nitrofurantoin has been shown to be less effective against otherwise susceptible organisms in an alkaline urine.[9]

Conclusion

Our data demonstrates that urine pH of UTIs diagnosed in ED patients varied with the associated bacterial pathogen, and thus urine pH potentially could affect ED provider choice of antibiotics for the treatment of UTIs. Additional research is needed to confirm our results from a larger, more diverse dataset before changes in practice are recommended.

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(5):269-284. doi:10.1038/nrmicro3432.
2. Stamm WE, Norrby SR. Urinary tract infections: disease panorama and challenges. *J Infect Dis.* 2001;183 Suppl 1:S1-S4. doi:10.1086/318850.
3. Schappert SM, Rechtsteiner EA. Ambulatory medical care utilization estimates for 2007. *Vital Health Stat 13.* 2011;13(169):1-38.
4. Foxman B. Urinary tract infection syndromes: occurrence, recurrence, bacteriology, risk factors, and disease burden. *Infect Dis Clin North Am.* 2014;28(1):1-13. doi:10.1016/j.idc.2013.09.003.
5. Foxman B. The epidemiology of urinary tract infection. *Nat Rev Urol.* 2010;7(12):653-660. doi:10.1038/nrurol.2010.190.
6. Coker C, Poore CA, Li X, Mobley HL. Pathogenesis of *Proteus mirabilis* urinary tract infection. *Microbes Infect.* 2000;2(12):1497-1505.
7. Armbruster CE, Mobley HL. Merging mythology and morphology: the multifaceted lifestyle of *Proteus mirabilis. Nat Rev Microbiol.* 2012;10(11):743-754. doi:10.1038/nrmicro2890.
8. Schaffer JN, Pearson MM. *Proteus mirabilis* and urinary tract infections. *Microbiol Spectr.* 2015;3(5). doi:10.1128/microbiolspec.UTI-0017-2013.
9. Yang L, Wang K, Li H, Denstedt JD, Cadieux PA. The influence of urinary pH on antibiotic efficacy against bacterial uropathogens. *Urology.* 2014;84(3):731.e1-e7. doi:10.1016/j.urology.2014.04.048.