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# Urine pH and treatment outcomes in women with uncomplicated acute pyelonephritis

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**Abstract**

Urine alkalinisation is commonly used in some countries for treatment of the symptomatic uncomplicated UTI. However, there is lack of evidence to support their use for UTI and lack of evidence to support the association between urine pH and treatment outcomes. Therefore, in this study, authors aimed to investigate the associations between urine pH and 1) treatment outcomes, 2) clinical symptoms after treatment and 3) cure of disease within 48 hours. A retrospective-cohort study was done using Khon Kaen Hospital inpatient electronic database registration from 1st January 2014 to 31st December 2016. One hundred and eight women with first diagnosis of uncomplicated acute pyelonephritis were divided by the range of urine pH into quartiles (Q) (1st Q = urine pH < 5.50, 2nd Q = urine pH 5.50-6.00, 3rd Q = urine pH 6.01-7.00, 4th Q = urine pH 7.01-8.00). The associations between urine pH in each Qs and treatment outcomes, clinical symptoms, and cure within 48 h, were analyzed. There was an association between each quartile of urine pH before and after treatment ($p$= 0.024). After treatment, patients that changed their urine pH to higher quartiles were found in 19.6% more than to lower quartiles. Second and 3rd Qs before treatment were associated with clinical improvement of dysuria ($p < 0.001$, both) and suprapubic pain ($p < 0.001$, and $p = 0.008$, respectively). In conclusion, there was no association observed between each Qs of urine pH and cure of disease within 48 h, in women with uncomplicated acute pyelonephritis.

**Keywords:** Urine pH, Acute pyelonephritis, Treatment outcomes

## 1. Introduction

Acute pyelonephritis (APN) is an infection of the upper urinary tract, specifically the renal parenchyma and renal pelvis [1,2]. Women are significantly more likely to experience urinary tract infection (UTI) than men and almost half of all women will experience UTI during their lifetime [3]. The microbial spectrum of pyelonephritis consists mainly of ascending urethral infection with *Escherichia coli* (75-95%), and occasional other species of Enterobacteriaceae, such as *Proteus mirabilis* and *Klebsiella pneumoniae* [4]. Clinical manifestations of pyelonephritis are fever, chills, flank pain, and irritative voiding symptoms (e.g., urgency, frequency, and dysuria) [5,6]. Approximately two-thirds of women who present classic symptoms of acute UTI have bacterial infection of the bladder and urinalysis can improve the accuracy of clinical symptoms to diagnose acute UTI [7,8].

Standard conventional management of suspected UTI is to treat empirically with antibiotics [1,5,6]. On the other hand, uncomplicated UTIs often remit spontaneously without antibiotics. Therefore, some studies have challenged this standard approach and tried to use other interventions to treat only symptoms of UTI. Urine alkalinization is one of those that are very commonly used in some countries for treatment of the symptomatic uncomplicated UTI [9-12]. Spooner studied in 205 women aged 18 to 60 years presenting with symptoms of cystitis and for whom there was no clear clinical evidence of a bacterial infection were treated with a 48-hour course of sodium citrate and found that symptoms were relieved in about 80% of cases. If failure to respond, a course of antibacterial therapy would be indicated [12]. However, there is lack of evidence to support their use for UTI and lack of evidence to support the association between urine pH and treatment outcomes. Therefore, in this study, authors aimed to investigate the associations between urine pH and 1) treatment outcomes, 2) clinical symptoms after treatment and 3) cure of disease within 48 h.

## 2. Materials and methods

After approval by the Institute Review Board in Human Research, Khon Kaen Hospital on 10th August 2017 (KE60117), this retrospective-cohort study was conducted by searching the Khon Kaen Hospital inpatient electronic database entries from 1st January 2014 to 31st December 2016. Raw data of this study are also available at https://figshare.com/articles/UrinepHRawData/11897193 (doi: 10.6084/m9.figshare.11897193).There were 3,543 patients diagnosed with APN and admitted to Khon Kaen Hospital.

Inclusion criteria were (1) women at 18 years of age or older who were diagnosed with APN; presence of 4 major and ≥ 2 minor clinical or laboratory signs or symptoms suggestive of APN. The 4 major criteria included the abrupt onset of fever (≥ 38.0°C), flank pain, costovertebral angle tenderness, and pyuria (> 10 WBCs per high-power field) [13]. The minor criteria included dysuria, urinary urgency and frequency, suprapubic tenderness, leukocytosis, and a positive urine culture with > $10^5$ colony-forming units/mL of a uropathogen; (2) having initial treatment with appropriated antibiotics [14,15]; and (3) having reports of urinalysis before and after usage of antibiotics.

Exclusion criteria were complicated pyelonephritis including; pregnancy, functional abnormality (neurogenic bladder, end stage renal disease), anatomical abnormality (polycystic kidney disease, horseshoe kidney, double ureter, ureterocele), urinary tract obstruction (calculus, indwelling catheter, stent, nephrostomy tube), immunosuppressed state (on steroid drug, cancer, diabetic mellitus, organ transplant, human immunodeficiency virus infection), extended-spectrum beta-lactamase (ESBL)-producing strains organism found in urine culture.

All patients' data including medical history, physical examination data and laboratory data, were documented using the hospital database. All continuous variables were presented as means ± SD or medians (interquartile ranges), and all categorical variables were presented as numbers (percentage). Comparisons between groups were performed using ANOVA or Kruskal-Wallis tests for continuous variables. The primary outcome, the association between baseline urine pH before treatment and treatment outcomes, was analyzed using test of marginal homogeneity. Secondary outcome, the association between urine pH and clinical symptoms after treatment, was analyzed using McNemar test. Tertiary outcome, the association between urine pH and cure (< 10 WBCs per high-power field [13]) within 48 h, was analyzed using multiple logistic regression to estimate crude and adjusted (if feasible) odd ratios and their 95% CIs. All analyses were conducted using IBM SPSS Statistics version 21. $p < 0.05$ in a 2-tailed test was considered as statistically significant.

## 3. Results

In the search for acute pyelonephritis 3,543 patients were found, 1,676 patients are men and/or aged lower than 18, which did not meet the inclusion criteria. The remaining 1,867 did meet the inclusion criteria, but 1,759 of them were then excluded due to their complicated UTIs. Therefore, only 108 patients could qualify for the study (Figure 1). All the 108 patients were then taken as study samples and divided by the range of urine pH into quartiles (Q); 1st Q (Q1) = urine pH < 5.50, 2nd Q (Q2) = urine pH 5.50-6.00, 3rd Q (Q3) = urine pH 6.01-7.00, and 4th Q (Q4) = urine pH 7.01-8.00. This dividing was similar to Lai et al. [16]. These patients were also divided into two subgroups for analysis. The first subgroup was "cured within 48 h" and the second subgroup was "cured after 48 h." Except for these "cure", not all 108 patients were analyzed, as only recorded available data were used.

Table 1 shows characteristics of the study patients by quartiles of urine pH at the first day of admission. There were no statistical differences in number of patients, age, comorbidities, body temperature, supra-pubic pain, baseline biological variables, intravenous antibiotics treatment, urine culture, and hospitalization days. However, there were significant differences of dysuria among different quartiles ($p < 0.001$).

**Table 1** Characteristics of the patients by quartiles of urine pH before treatment.

| Characteristics | Quartiles | | | | *p*-value |
|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | |
| Urine pH | < 5.50 | 5.50-6.00 | 6.01-7.00 | 7.01-8.00 | |
| Number of patients | 9 | 61 | 20 | 9 | 0.123 |
| Age (years), mean ± SD | 45.67±24 | 45.49±22 | 37.6±17 | 48.33±24 | 0.503 |
| Comorbidities, n (%) | | | | | |
| Hypertension | 0 (n=9) | 8/13.1 (n=61) | 1/5 (n=20) | 1/11.1 (n=9) | 0.542 |
| Anemia | 0 (n=9) | 6/9.8 (n=61) | 4/20 (n=20) | 0 (n=9) | 0.248 |
| Initial signs and symptoms | | | | | |
| Body Temperature (°C), mean ± SD | 39.17±0.9 | 38.99±0.7 | 39.13±0.9 | 39.19±+0.9 | 0.822 |

**Table 1** (continued) Characteristics of the patients by quartiles of urine pH before treatment.

| Characteristics | Quartiles | | | | *p*-value |
|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | |
| Initial signs and symptoms | | | | | |
| Dysuria, n (%) | 1/12.5 (n=8) | 30/49.2 (n=61) | 19/95 (n=20) | 4/44.4 (n=9) | <0.001 |
| Supra-pubic pain, n (%) | 1/11.1 (n=9) | 20/33.9 (n=59) | 12/60 (n=20) | 2/22.2 (n=9) | 0.050 |
| Baseline biological variables | | | | | |
| WBC ($10^3$ cells/$mm^3$), mean ± SD | 14689±5392 (n=9) | 14885±6365 (n=60) | 15250±6928 (n=20) | 17863±8884 (n=8) | 0.688 |
| Creatinine(μmol/L), mean ± SD | 0.92±0.3 (n=7) | 0.91±0.4 (n=55) | 1.03±1.1 (n=19) | 0.87±0.2 (n=8) | 0.881 |
| Initial urine WBC (cells per HPF) mean ± SD | 27.14±12 (n=7) | 48.14±32 (n=43) | 62.11±35 (n=19) | 28.33±18 (n=6) | 0.050 |
| IV antibiotics treatment, n (%) | | | | | 0.274 |
| Ceftriaxone | 8/88.9 | 53/86.9 | 13/65 | 7/77.8 | |
| Ceftazidime | 0 | 3/4.9 | 3/15 | 2/22.2 | |
| Ciprofloxacin | 1/11.1 | 3/4.9 | 2/10 | 0 | |
| Meropenem | 0 | 0 | 1/5 | 0 | |
| Piperacillin plus Tazobactam | 0 | 2/3.3 | 1/5 | 0 | |
| Urine culture, n (%) | | | | | 0.515 |
| *Escherichia coli* | 0 | 9/14.8 | 2/10 | 0 | |
| *Enterococcus faecalis* | 1/11.1 | 1/1.6 | 0 | 0 | |
| Gr. D streptococcus - not enterococci | 0 | 1/1.6 | 0 | 0 | |
| No growth or non-test | 8/88.9 | 50/82 | 18/90 | 9/100 | |
| Hospitalization days (median/min-max) | 2/2-10 | 3/1-8 | 3/1-12 | 3/2-5 | 0.946 |

IV = Intravenous, WBC = White blood cells.

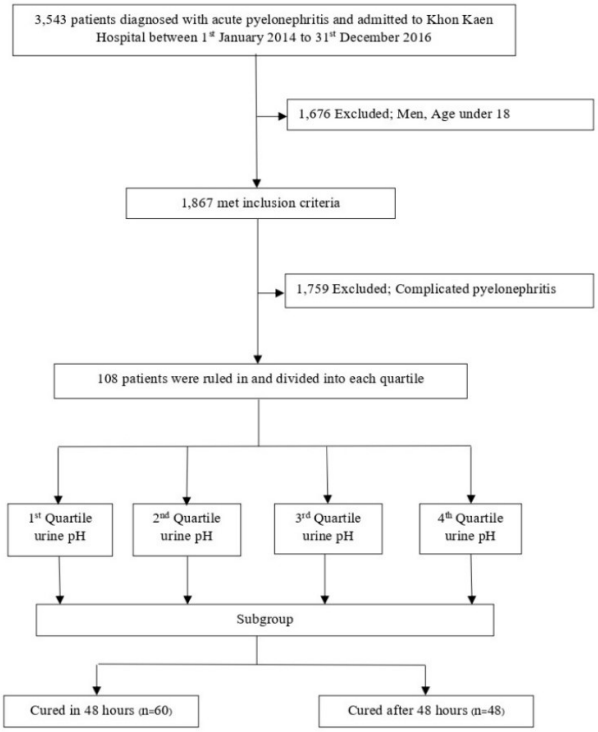


**Figure 1** The flowchart depicts the selection of participants.

Test of marginal homogeneity demonstrated that each quartile of urine pH after treatment was significantly changed from before treatment ($p = 0.024$) (Table 2). Comparison of each quartile after changing to higher pH and lower pH shows 36.6% of patients changed to higher pH (Table 2) while 17% of patients changed to lower pH (Table 2). Consequently, 19.6% of patients had changed their urine pH after treatment to higher quartiles than to lower quartiles.

**Table 2** The association between urine pH and treatment outcomes.

| Quartiles & Urine pH before treatment | | Quartile & Urine pH after treatment, n (%) | | | | *p*-value |
|---|---|---|---|---|---|---|
| | | 1 | 2 | 3 | 4 | |
| | | < 5.50 | 5.50-6.00 | 6.01-7.00 | 7.01-8.00 | |
| 1 | < 5.50 | 1/1.2 | 6/7.4 | 1/1.2 | 0 | 0.024 |
| 2 | 5.50 - 6.00 | 5/6.1 | 25/30.5 | 17/20.7 | 5/6.1 | |
| 3 | 6.01 - 7.00 | 1/1.2 | 4/4.9 | 9/11.0 | 1/1.2 | |
| 4 | 7.01 - 8.00 | 0 | 2/2.4 | 2/2.4 | 3/3.7 | |

McNemar test showed significant association between Q2 before treatment and improvement of dysuria ($p < 0.001$), also supra-pubic pain ($p < 0.001$). In Q3, there were also significantly changes from dysuria ($p < 0.001$) and suprapubic pain ($p = 0.008$) to no symptoms. There was no significant association between other quartiles and improvement of these symptoms (Table 3).

**Table 3** The association between urine pH and clinical symptoms after treatment.

| Quartiles & Urine pH before treatment | | Symptoms | Improvement of clinical symptoms after treatment | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | Dysuria, n (%) | | | Suprapubic pain, n (%) | | |
| | | | Absent | Present | *p*-value | Absent | Present | *p*-value |
| 1 | < 5.50 | Present | 1/12.5 | 0 | 1.000 | 1/12.5 | 0 | 1.000 |
| | | Absent | 7/87.5 | 0 | | 7/87.5 | 0 | |
| 2 | 5.50 - 6.00 | Present | 22/40.0 | 6/10.9 | <0.001 | 14/26.9 | 6/11.5 | <0.001 |
| | | Absent | 27/49.1 | 0 | | 32/61.5 | 0 | |
| 3 | 6.01 - 7.00 | Present | 16/88.9 | 2/11.1 | <0.001 | 8/47.1 | 2/11.8 | 0.008 |
| | | Absent | 0 | 0 | | 7/41.2 | 0 | |
| 4 | 7.01 - 8.00 | Present | 2/25 | 2/25 | 0.500 | 1/14.3 | 1/14.3 | 1.000 |
| | | Absent | 4/75 | 0 | | 5/71.4 | 0 | |

Multiple logistic regression analysis revealed no significant differences between urine pH and cure of disease in 48 h either with (not shown) or without adjusting for hypertension, anemia, antibiotic usage, body temperature, creatinine, serum WBC, urine culture, urine WBC, dysuria, and suprapubic pain (Table 4).

**Table 4** The association of urine pH and cure within 48 h by univariate analysis.

| Quartiles & Urine pH before treatment | Cure within 48 h | | |
|---|---|---|---|
| | Crude OR | 95%CI | *p*-value |
| Q1 / 2+3+4 | 2.38 | 0.28-20.37 | 0.42 |
| Q1+2 / 3+4 | 0.76 | 0.24-2.39 | 0.64 |
| Q1+2+3 / 4 | 1.44 | 0.26-7.94 | 0.68 |

## 4. Discussion

### *4.1 Important findings*

These findings show (1) an association between urine pH before and after treatment of women with uncomplicated acute pyelonephritis which is increase urine pH after treatment in 19.6%; (2) an association between urine pH and improvement of dysuria or supra-pubic pain in patients with urine pH 5.50 - 6.00 before treatment; (3) no relation between urine pH and cure of disease within 48 h.

### *4.2 Strengths and limitations of the study*

Many studies have compared alkalinizing agent with treatment outcome, which is not proper to implicate that increasing of urine pH can be related to improve treatment outcome. Therefore, an association between urine pH and treatment outcome should be done first. The strength of this study is to explain the association between urine pH and treatment outcome. However, we acknowledge some important limitations. First, because of its

retrospective design, the study is limited since desired data such as information of urgency and frequency of symptoms are usually not asked from the patients and therefore not obtained by doctors in Khon Kaen Hospital are not usually ask patient. Second, the study may be subject to a selection bias. The data was from only the available patients' medical records. Not all 108 patients were analyzed except for cure. Third, the possibility of residual confounding due to unmeasured or poorly measured confounders such as frequency of sexual activity, catheter use in past medical history, and any history of recurrent UTI could not be ruled out. Multivariate analysis (adjusted OR) was not shown because there were no significant changes. Fourth, this study was restricted to an acute pyelonephritis, and the results may not be applicable to the general population of UTI. Finally, we did not analyze on culture outcomes as only 14% of patients were culture positive.

*4.3 Comparison with other studies*

It is difficult to compare these results to other previous studies because there is no study about urine pH and treatment outcome in women with uncomplicated acute pyelonephritis, but only similar to one study [17] where there is an association between urine pH and antibiotic efficacy against bacterial uropathogens which means urine pH can affect UTI treatment. This study also has similar outcomes when indirectly compared to other studies [12,18] which found urine alkalinizing agent can improve treatment outcome by increasing urine pH. However, their research was a single arm studies with lack of a comparison group which decreases the reliability of any conclusion. However, there was an observational study [19] of 128 women with uncomplicated UTIs and it found no correlation between urine pH and symptoms of UTI different from the result of this study.

*4.4 Possible explanations and implications*

Compared to the secondary outcome of this study with urine pH 5.50-6.00 we have demonstrated improvement of dysuria, Table 1 shows that there is significant difference in number of patients between each quartile in dysuria before treatment which could influence the result after treatment. Therefore, we cannot clearly say that urine pH 5.50-6.00 before treatment was related to an improvement of dysuria. Even in comparison to other cause of dysuria, Nguan et al. [20] had evaluated changes in urine pH for relieving the symptoms of interstitial cystitis and Wong et al. [21] had investigated the use of urinary alkalizers to reduce painful voiding after flexible cystoscopy in patient without UTI. These studies also failed to show any benefit of increasing urine pH. In addition, only adequate hydration can increase urine pH [22]. This might explain Table 2 findings. Regarding to the result of tertiary outcome in this study (Table 4) and considering other study results, we can probably conclude that urine pH can increase after treatment but there is no effect on duration of treatment and clinical improvement.

## 5. Conclusion

In conclusion, there was an association between urine pH before and after treatment however the increase of urine pH had no effect on duration of female uncomplicated acute pyelonephritis treatment. In addition, this study found that urine pH 5.5-7 was associated with improvement of dysuria and suprapubic pain. Research with well-constructed randomized controlled trials is needed to investigate urine pH and clinical symptoms for urinary tract infection.

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