Prevalence and Risk Factor Analysis of Resistant Escherichia coli Urinary Tract Infections in the Emergency Department

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Prevalence and risk factor analysis of resistant *Escherichia coli* urinary tract infections in the emergency department

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**ABSTRACT**

**Background:** *Escherichia coli* (E. coli) is a frequent uropathogen in urinary tract infections (UTI). Widespread resistance to sulfamethoxazole-trimethoprim (SMX-TMP) and increasing resistance to fluoroquinolones amongst these isolates has been recognized. There are limited data demonstrating risk factors for resistance to both SMX-TMP and fluoroquinolones.

**Objectives:** This study was conducted to assess for the prevalence of community resistance amongst E. coli isolates to SMX-TMP and levofloxacin in ambulatory patients discharged from the emergency department (ED).

**Methods:** Adults presenting for evaluation and discharged from the ED with a diagnosis of an E. coli UTI were retrospectively reviewed. Utilizing demographic and clinical data the prevalence of E. coli resistance and risk factors associated with SMX-TMP- and fluoroquinolone-resistant infection were determined.

**Results:** Among the 222 patients, the mean rates of E. coli susceptibility to levofloxacin and SMX-TMP were 82.4% and 72.5%, respectively. Significant risk factors for resistance to SMX-TMP included prior antibiotic use (p=0.04) and prior diagnosis of UTI (p=0.01). Significant risk factors for resistance to levofloxacin included: male gender, age, presence of hypertension, diabetes, chronic respiratory disease, nursing home resident, previous antibiotic use, previous diagnosis of UTI, existence of renal or genitourinary abnormalities, and prior surgical procedures (p<0.05 for all comparisons). The number of hospital days prior to initial ED evaluation (p<0.001) was determined to be a predictive factor in hospital and ED readmission.

**Conclusions:** These results suggest that conventional approaches to monitoring for patterns of susceptibility may be inadequate. It is imperative that practitioners develop novel approaches to identifying patients with risk factors for resistance. Identification of risk factors from this evaluation should prompt providers to scrutinize the use of these agents in the setting of patients presenting with an uncomplicated UTI in the ED.

**Keywords:** Drug Resistance, Bacterial; Risk Factors; Urinary Tract Infections; Uropathogenic Escherichia coli; Trimethoprim-Sulfamethoxazole Combination; Fluoroquinolones; Emergency Service, Hospital; United States.

**ANÁLISIS DE PREVALENCIA Y factores de riesgo de infecciones del tracto urinario por escherichia coli en el servicio de urgencias**

**RESUMEN**

**Antecedentes:** *Escherichia coli* (E. coli) es un uropatogénico frecuente en infecciones del tracto urinario (UTI). Se ha reconocido la resistencia generalizada al sulfametoaxazol-Trimetoprim (SMX-TMP) y la existencia creciente a fluoroquinolonas entre los aislados. Hay datos limitados que muestran los factores de riesgo para la resistencia tanto a SMX-TMP como a fluoroquinolonas.

**Objetivos:** Este estudio fue realizado para evaluar la prevalencia de resistencia en la comunidad en aislamientos de E. coli a SMX-TMP y levofloxacino en pacientes ambulatorios dados de alta en un servicio de urgencias (ED).

**Métodos:** Se revisió retrospectivamente a los adultos que se presentaron para evaluación y fueron dados de alta del ED con un diagnóstico de una UTI con E. coli. Utilizando datos demográficos y clínicos se calculó la prevalencia de resistencias a E. coli y los factores de riesgo asociados a infecciones resistentes a SMX-TMP y fluoroquinolonas.

**Resultados:** Entre los 222 pacientes, las tasas medias de susceptibilidad a levofloxacino y SMX-TMP fueron de 82.4% y 72.5%, respectivamente. Los factores de riesgo significativos para la resistencia a SMX-TMP incluyen el uso previo del antibiótico (p=0.04) y el diagnóstico previo de UTI (p=0.01). Los factores de riesgo significativos para resistencia a levofloxacin incluyen sexo masculino, edad, presencia de hipertensión, diabetes, enfermedad respiratoria crónica, vivir en residencia de ancianos, uso previo del antibiótico, diagnóstico previo de UTI, existencia de anomalías renales o genitourinarias , y cirugías previas (p<0.05 para todas las asociaciones). El número de días anteriores a la evaluación inicial en el ED (p<0.001) se identificó como un factor predictivo de readmisión hospitalaria y al ED.
INTRODUCTION

Escherichia coli (E. coli) is the most notable pathogen that results in a frequently diagnosed community-acquired infection, the urinary tract infection (UTI). The recommended first line agents for uncomplicated UTI include sulfamethoxazole/trimethoprim (SMX-TMP) or nitrofurantoin. However, decreasing susceptibilities of common pathogens to these pharmacologic agents for the treatment of UTIs has complicated empiric drug therapy decisions.

From 1999-2002, in-vitro rates of resistance to SMX-TMP were noted to be increasingly prevalent, while treatment failure rates remained stable. Although, since that time rates of treatment failure have risen in proportion to escalating in-vitro resistance which now approaches or exceeds 20% across the nation. Nevertheless, despite diffuse SMX-TMP resistance E. coli resistance rates to fluoroquinolones in North America have remained low (3-6%) and trepidation concerning increasing rates of resistance was primarily isolated to areas outside of North America.

This has changed in the last five years as clinical data from North America has been presented identifying changing susceptibility patterns in gram negative bacilli to both SMX-TMP and fluoroquinolones. Despite these publications, the most recent guidelines continue to recommend the selective use of SMX-TMP for the treatment of uncomplicated cystitis. The recommendation for the use of fluoroquinolones is for complicated infections, such as pyelonephritis, or if the local resistance to SMX-TMP is ≥20%.

Presently practitioners are faced with widespread resistance to SMX-TMP outside of the hospital and increasing resistance to fluoroquinolones both within and outside the hospital setting. It was the aim of this study to assess for the prevalence of community resistance amongst E. coli isolates to SMX-TMP and levofloxacin in ambulatory patients discharged from the emergency department (ED) with urinary tract infections; while also analyzing if any risk factors were associated with readmission to the ED and the hospital.

METHODS

Design

Following the obtainment of institutional review board approval, patients aged ≥18 years who were evaluated and discharged from the ED with a discharge diagnosis of a UTI and a positive urine culture for Escherichia coli from 2009-2011 were retrospectively reviewed. Patients were identified using an existing culture database that houses all positive cultures from ambulatory patients seen through, and discharged from, the ED. Only patients with a positive urine culture were selected from the database for further evaluation. Patients were excluded for pregnancy or if their initial evaluation resulted in an admission to the hospital.

Measurements

The primary objective of this study was to assess the prevalence of and risk factors for E. coli resistance to SMX-TMP and levofloxacin. The secondary objectives included: assessing risk factors for readmission, comparing the institutional antibiogram to ED specific resistance rates, and evaluating this resistance profile in six month increments over three years to discern any possible evolving resistance patterns. As part of the secondary objective, a susceptibility profile was created from the isolates collected, which permitted the detection of resistance patterns of E. coli to SMX-TMP and levofloxacin in ambulatory patients presenting to the ED.
Data collected included patient demographic information, co-morbid disease state diagnoses, surgical procedures within 30 days prior to visit, previous diagnosis of UTI within 90 days, renal or genitourinary abnormalities, utilization of immunosuppression or antimicrobial prophylaxis, history of antibiotic use within 90 days, pertinent laboratory data, pertinent culture data with reported susceptibility patterns, antibiotic prescribed upon discharge and duration of therapy, and number of hospital days prior to the initial ED evaluation. The number of hospital days was calculated based on the total number of documented visits to the institution within the last year with one day being equivalent to either a single ED visit or an admission to the hospital.

### Statistical Analysis

Analyses were conducted using SigmaStat 3.5 Software® (Systat Software; San Jose, CA). Analyses were conducted using chi-square and multilogistic regression analysis was used to compile risk factors for antimicrobial resistance and risk factors for readmission. The level of significance was set at a p-value of <0.05.

### RESULTS

A total of 222 patients were identified as having positive urine cultures and meeting all inclusion criteria. According to the ED susceptibility profile, levofloxacin- and SMX-TMP-susceptible E. coli urinary tract infections were identified in 82.4% and 72.5% of cultures, respectively. According to the institution’s hospital-wide antibiogram (January 1, 2010-December 31, 2010), levofloxacin- and SMX-TMP-susceptible E. coli comprised 73% and 71% of all isolates, respectively. There was noted to be a significant difference in the rate of levofloxacin susceptibility between these two groups (82.4% versus 73%, p=0.003) but a non-significant difference in the rate of levofloxacin resistance rates over 6- (p=0.655) or 12-month (p=0.333) time periods (Table 3).

Risk factors for E. coli resistance to SMX-TMP are outlined in Table 4. Prior antibiotic use (p=0.038) and prior diagnosis of UTI (p=0.012) were found to be significantly different between these two groups. No significant difference was found in SMX-TMP resistance rates over 6- (p=0.655) or 12-month (p=0.548) time periods (Table 5).

A total of 35 (15.8%) patients returned to the ED with a diagnosis of a UTI. Of these 22 had an initial prescription for levofloxacin and 11 had one for TMP-SMX (62.9% vs. 31.4%, p=0.169, respectively). Characteristics that were found to be significantly different between these two groups are described in Table 6. Significantly higher percentages of patients returned to the emergency department if they had a previous diagnosis of a urinary tract infection, renal or genitourinary abnormalities, or prior antibiotic use. Logistic regression analysis found that the number of hospital days prior to the ED visit (p<0.001) was a predictive factor in readmission (Table 7).

Of those patients prescribed a medication to which their culture demonstrated susceptibility, 25 (13.7%) returned to the ED with a diagnosis of a UTI and of those prescribed inappropriate empiric therapy, 10 (25%) returned (p=0.126). Inappropriate empiric therapy had a non-significant impact on hospital length of stay if the patient had a return visit to the ED or readmission to the hospital (OR: 1.222 [95% CI 0.589-2.537]; p=0.590).

### DISCUSSION

The findings of the present evaluation support existing reports, which demonstrate changes in resistance patterns of gram negative bacilli to fluoroquinolones, particularly E. coli. The results of the evaluation from Rattanaumpawan and

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**Table 2. Logistic Regression Analysis of Risk Factors for Levofloxacin and SMX-TMP Resistance**

| Variable                  | Levofloxacin Resistance | SMX-TMP Resistance |
|---------------------------|-------------------------|--------------------|
|                           | OR          | 95% CI  | P value | OR          | 95% CI  | P value |
| Age                       | 0.972       | 0.952-0.991 | 0.005   | 0.988       | 0.969-1.009 | 0.006 |
| Height                    | 0.875       | 0.759-1.009 | 0.067   | 1.079       | 0.954-1.228 | 0.156 |
| Weight                    | 1.03        | 0.963-1.203 | 0.156   | 1.03        | 0.963-1.103 | 0.313 |
| Body Mass Index (BMI)      | 0.753       | 0.622-1.088 | 0.131   | 0.923       | 0.753-1.128 | 0.553 |
| Hospital days prior        | 1.014       | 0.961-1.071 | 0.614   | 0.979       | 0.924-1.041 | 0.325 |
| Number days after emergency department | 1.003   | 0.996-1.010 | 0.391   | 0.997       | 0.991-1.003 | 0.358 |

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The results of this investigation identified the prevalence of resistance amongst E. coli isolates in discharged patients, as SMX-TMP and levofloxacin resistance rates exceeded guideline standards for empiric therapy in the treatment of urinary tract infection. In order to offer guidance on the selective use of SMX-TMP and fluoroquinolones, previous studies have attempted to identify risk factors for resistance. Out of those evaluations, risk factors identified for SMX-TMP resistance included: SMX-TMP use within 30 days, diabetes mellitus, and recent hospitalization.16-18 Age, fluoroquinolone use within the past year, prior hospitalization, diabetes mellitus, hypertension, use of a foley catheter, and urolithiasis were identified as risk factors for levofloxacin resistance.19 However, these studies were either conducted outside of the United States or before fluoroquinolone resistance was as widespread as it is presently. This prevented evaluators from determining the existence of common risk factors for both SMX-TMP and fluoroquinolones. In addition, neither inquiry examined which risk factors were associated with the most costly consequence of treatment failure, hospital readmission rates. It was the intent of this evaluation to assess whether any patient-specific characteristics could be associated with antimicrobial resistance. Those significant risk factors that were identified included: age, co-morbid conditions such as hypertension, diabetes, and chronic respiratory disease, residing in a nursing home, previous antibiotic use, previous diagnosis of UTI, and existence of renal or genitourinary abnormalities. Shared risk factors for SMX-TMP and fluoroquinolone resistance included both previous diagnosis of UTI and prior antibiotic use. This study is limited by its retrospective nature and its assessment of only the population treated by a Level I Trauma Center. This evaluation was also unable to characterize resistance rates for patients admitted through the ED in addition to those patients discharged from the ED. However, any analysis of antimicrobial resistance rates must always be institution specific and the identification of risk factors for resistance has potential applicability beyond single centers.

Table 5. SMP-TMP Resistance over Time

| No. of total patients | 1/09-6/09 | 7/09-12/09 | 1/10-6/10 | 7/10-12/10 | 1/11-6/11 | 7/11-12/11 |
|-----------------------|----------|------------|----------|------------|----------|------------|
| 31                    | 82.5%    | 73%        | 71%      | 73%        | 73%      | 72%        |
| 30                    | 83%      | 74%        | 72%      | 73%        | 73%      | 72%        |
| 31                    | 82.5%    | 73%        | 71%      | 73%        | 73%      | 72%        |
| 37                    | 81%      | 72%        | 70%      | 72%        | 72%      | 71%        |
| 66                    | 81%      | 72%        | 70%      | 72%        | 72%      | 71%        |
| 27                    | 80%      | 71%        | 69%      | 71%        | 71%      | 70%        |

Table 4. Risk Factors for E. coli Resistance to SMX-TMP

| Category | SMX-TMP resistant (n=61) | SMX-TMP susceptible (n=161) | p-value |
|----------|--------------------------|-----------------------------|---------|
| Sex, Male |                         |                             | 0.928   |
| Race     |                         |                             |         |
| White    | 49 (80.3%)               | 121 (75.2%)                 | 0.526   |
| African-American | 5 (8.2%) | 25 (15.5%) |           |
| Other    | 7 (11.5%)                | 15 (9.3%)                   |         |
| Diabetes mellitus | 13 (21.3%) | 28 (17.4%) | 0.633   |
| Hypertension | 18 (29.5%) | 52 (32.3%) | 0.812   |
| Chronic respiratory disease | 12 (19.7%) | 20 (12.4%) | 0.247   |
| Benign prostatic hypertrophy (BPH) | 3 (4.9%) | 6 (3.7%) | 0.984   |
| Nursing home resident | 5 (8.2%) | 4 (2.5%) | 0.122   |
| Antibiotic use within 90 days | 32 (52.5%) | 58 (36.0%) | 0.038   |
| Previous UTI within 90 days | 29 (47.5%) | 46 (28.6%) | 0.012   |
| Renal or genito-urinary abnormality | 25 (41%) | 67 (41.6%) | 0.946   |
| Immunosuppression | 8 (13.1%) | 19 (11.8%) | 0.970   |
| Home use of antibiotics | 4 (6.6%) | 9 (5.6%) | 0.963   |
| Surgical procedures within 30 days | 7 (11.5%) | 19 (11.8%) | 0.868   |

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CONCLUSIONS
Identification of risk factors for resistance and readmission should prompt providers to scrutinize the use of these agents in the setting of patients presenting with an uncomplicated UTI. This is particularly imperative as the possibility of resistance in patients with multiple risk factors (prior UTI, antibiotic use within the previous 90 days, or renal or genitourinary abnormalities) can subsequently result in return visits to the ED or increased rates of readmission. In addition, the overall healthcare and financial impacts of choosing the inappropriate empiric therapy could be significant. Further study is needed to determine whether optimal antimicrobial therapy can be achieved through the risk stratification of patients meeting these criteria subsequently leading to a lower incidence of negative outcomes.

CONFLICT OF INTEREST
A.B.: No conflicts. K.W.: No conflicts. S.B: No conflicts.

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Table 7. Logistic Regression Analysis of Risk Factors for Readmission

| Characteristic                        | Return ED Visit (n=35) | No Return ED Visit (n=187) | p-value |
|---------------------------------------|------------------------|-----------------------------|---------|
| Demographic                           |                        |                             |         |
| Age                                   | 1.000                  | 0.980-1.022                 | 0.974   |
| Height                                | 1.127                  | 0.965-1.317                 | 0.131   |
| Weight                                | 0.896                  | 0.772-1.044                 | 0.162   |
| Body Mass Index (BMI)                 | 1.355                  | 0.906-2.028                 | 0.139   |
| Hospital days prior                   | 1.100                  | 1.053-1.149                 | <0.001  |

Table 6. Characteristics Associated with Return Visits to the Emergency Department (ED)

| Characteristic                        | Return ED Visit (n=35) | No Return ED Visit (n=187) | p-value |
|---------------------------------------|------------------------|-----------------------------|---------|
| Levofloxacin Resistance               | 9 (25.7%)              | 30 (16.0%)                  | 0.372   |
| SMX-TMP Resistance                    | 8 (22.9%)              | 53 (28.3%)                  | 0.757   |
| Previous Diagnosis of UTI             | 21 (60%)               | 54 (28.9%)                  | 0.030   |
| Renal/Genitourinary Abnormality        | 25 (71.4%)             | 67 (35.8%)                  | 0.029   |
| Antibiotic Use                        | 26 (74.3%)             | 64 (34.2%)                  | 0.013   |
| Surgical Procedure                    | 6 (17.1%)              | 20 (10.7%)                  | 0.503   |
| Immunosuppression                     | 5 (14.3%)              | 22 (11.8%)                  | 0.928   |
| Prophylactic Use of Antibiotics       | 0 (0%)                 | 3 (1.6%)                    | 1.000   |

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