Bailey AM, Weant KA, Baker SN. Prevalence and risk factor analysis of resistant Escherichia coli urinary tract infections in the emergency department. Pharmacy Practice 2013 Apr-Jun;11(2):96-101.

Original Research

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

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Received (first version): 18-Dec-2012 Accepted: 22-May-2013

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 uropatogeno frecuente en infecciones del tracto urinario (UTI). Se ha reconocido la resistencia generalizada al sulfametoxazol-Trimetoprim (SMX-TMP) y la resistencia creciente a fluoroquinolonas entre los aislados. Hay datos limitados que muestren 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 revisó 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 incluían 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 levofloxacino incluían 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.

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Conclusiones: Estos resultados sugieren que los abordajes convencionales para monitorizar los patrones de susceptibilidad pueden ser inadecuados. Es necesario que los facultativos desarrollen nuevos abordajes para identificar pacientes con factores de riesgo de resistencias. La identificación de los factores de riesgo para esta evaluación debería impulsar a los profesionales a examinar el uso de estos antibióticos en los pacientes que presentan una UTI no complicada en el ED.

Palabras clave: Farmacorresistencia Bacteriana; Factores de Riesgo; Infecciones Urinarias; Escherichia coli Uropatógena; Combinación Trimetoprim-Sulfametoxazol; Fluoroquinolonas; Servicio de Urgencia en Hospital; Estados Unidos.

INTRODUCTION

Escherichia coli (E. coli) is the most notable pathogen that results in a frequently diagnosed community-acquired infection, the urinary tract infection (UTI).[1] The recommended first line agents for uncomplicated UTI include sulfamethoxazole/trimethoprim (SMX-TMP) or nitrofurantoin.[2-5] 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.[1] 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.[2-5] 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.[6-9]

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.[10,11] Despite these publications, the most recent guidelines continue to recommend the selective use of SMX-TMP for the treatment of uncomplicated cystitis.[1] The recommendation for the use of fluoroquinolones is for complicated infections, such as pyelonephritis, or if the local resistance to SMX-TMP is ≥ 20%.[1]

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.[3,8,12] 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.

Table 1. Risk Factors for *E. coli* Resistance to Levofloxacin

Category	Levofloxacin resistance, n, % (n=39)	Levofloxacin susceptible, n, % (n=183)	p-value
Sex, male	13 (33.3%)	28 (15.3%)	0.016
Race			0.272
White	33 (84.6%)	137 (74.9%)	
African-American	4 (10.2%)	26 (14.2%)	
Other	2 (5.1%)	20 (10.9%)	
Diabetes mellitus	10 (25.6%)	31 (16.9%)	0.296
Hypertension	17 (43.6%)	25 (13.7%)	<0.001
Chronic respiratory disease	9 (23.1%)	7 (3.8%)	<0.001
Benign prostatic hypertrophy (BPH)	4 (10.3%)	1 (0.6%)	0.003
Nursing home resident	7 (17.9%)	0 (0%)	<0.001
Antibiotic use within 90 days	26 (66.7%)	11 (6.0%)	<0.001
Previous UTI within 90 days	22 (56.4%)	9 (4.9%)	<0.001
Renal or genito-urinary abnormality	27 (69.2%)	16 (8.7%)	<0.001
Immunosuppression	5 (12.8%)	7 (3.8%)	0.062
Home use of antibiotics	3 (7.7%)	2 (1.1%)	0.054
Surgical procedures within 30 days	8 (20.5%)	7 (3.8%)	<0.001

Table 2. Logistic Regression Analysis of Risk Factors for Levofloxacin and SMX-TMP Resistance				
	Variable	OR	95% CI	P value
Levofloxacin Resistance	Age	0.972	0.952-0.991	0.005
	Height	0.875	0.759-1.009	0.067
	Weight	1.103	0.963-1.263	0.156
	Body Mass Index (BMI)	0.753	0.522-1.088	0.131
	Hospital days prior	1.014	0.961-1.071	0.614
	Number days after emergency department	1.003	0.996-1.010	0.391
SMX-TMP Resistance	Age	1.005	0.988-1.024	0.553
	Height	0.984	0.859-1.128	0.821
	Weight	1.026	0.898-1.174	0.702
	Body Mass Index (BMI)	0.938	0.653-1.346	0.728
	Hospital days prior	1.016	0.954-1.082	0.626
	Number days after emergency department	0.997	0.991-1.003	0.358

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). Antibiogram susceptibility rates and dichotomous variables were assessed 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.[13] 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 between the SMX-TMP groups (72.5% versus 71%, p=0.690).

Significant risk factors for E. coli 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 (Table 1). Logistic regression analysis of risk factors for levofloxacin resistance found that patient age was statistically significant (Table 2). No significant difference was found in levofloxacin resistance rates over 6- (p=0.145) 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 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

Table 3. Levofloxacin Resistance over Time						
	1/09-6/09	7/09-12/09	1/10-6/10	7/10-12/10	1/11-6/11	7/11-12/11
No. of total patients	31	30	31	37	66	27
No of patients with levofloxacin-resistant *E. coli*	0	7	6	8	12	6
Resistance rate (%)	0	23	19	21.6	18.2	22.2

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	11 (18.0%)	30 (18.6%)	0.928
Race			0.526
White	49 (80.3%)	121 (75.2%)	
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

colleagues confirmed fluoroquinolone resistance approaching 20%.[10,11] This is contrary to information captured from prior surveys in emergency departments spanning the years from 2000-2004 in which rates of E. coli susceptibility to fluoroquinolones approached 93-95%.[5,14] This drastic change over a relatively short period of time could be the result of increased fluoroquinolone use in response to declining SMX-TMP susceptibilities.

Antimicrobial resistance is no longer an anomaly seen only in the critically ill. It is important for practitioners to be aware of its existence outside of the hospital and for them to develop approaches to identifying patients with patterns and risk factors for resistance. Traditionally, guidance for identifying patterns of resistance has been derived from institutional antibiograms. An antibiogram provides direction regarding institutional trends in bacterial resistance and understanding these developments helps avoid treatment failure or readmission to the hospital.

Although this evaluation did not have the numbers to detect a significant difference on rates of readmission, understanding the association of inappropriate therapies on rates of readmission remains an important element in antimicrobial stewardship. However, global application of an institution-wide antibiogram to all patient populations does not always translate into clinical success. This is demonstrated by the ED susceptibility profile derived from this evaluation, as rates of fluoroquinolone resistance were significantly different between the overall institution and the ED. Per the hospital-wide antibiogram, E. coli susceptibilities to levofloxacin and SMX-TMP were 73 and 71%, respectively; whereas in the ED susceptibility profile, 82.4% and 72.5% of isolates were susceptible to levofloxacin and SMX-TMP, respectively.[13] Use of an inadequate antibiogram for a unique patient population could result in inappropriate empiric therapies, treatment failures, and readmissions to the hospital, yielding potentially significant healthcare and financial impacts.[15]

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.[16-19] 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						
	1/09-6/09	7/09-12/09	1/10-6/10	7/10-12/10	1/11-6/11	7/11-12/11
No. of total patients	31	30	31	37	66	27
No. of patients with levofloxacin-resistant *E. coli*	10	8	12	9	15	7
Resistance rate (%)	32.2	26.7	38.7	24.3	22.7	25.9

Table 6. Characteristics Associated with Return Visits to the Emergency Department (ED)			
Characteristic, n (%)	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

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.

Financial support: There are no pertinent financial relationships to disclose.

Table 7. Logistic Regression Analysis of Risk Factors for Readmission			
Demographic	OR	95% CI	P value
Age	1.000	0.980-1.022	0.974
Height	1.127	0.965-1.317	0.131
Weight	0.898	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

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