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Original Contribution

Antimicrobial resistance in urinary tract infections at a large urban ED: Factors contributing to empiric treatment failure☆

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ABSTRACT

Objective: To calculate the emergency department (ED)-level *Escherichia coli* percentage of isolates susceptible to commonly used antibiotics and to determine the risk factors associated with inadequate empiric antibiotic therapy among patients treated for urinary tract infections (UTIs) in our ED.
Methods: Retrospective cohort study conducted at a large tertiary teaching hospital. Participants included patients older than 18 years of age who had a urine culture with growth of >100,000 colonies of *E. coli*. Demographic and therapeutic choices associated with inadequate empiric antibiotic therapy were explored. Antimicrobial susceptibility pattern of *E. coli* isolates recovered from ED patients were calculated, and stratified by gender and age.
Results: A total of 300 unique patients had *E. coli* bacteriuria during the study period. Among patients who received at least one dose of antibiotic in the ED, variables independently associated with an increased risk of inadequate empiric therapy were age (relative risk [RR] 1.016; 95% confidence interval [CI] 1.001–1.031; $P = 0.032$), male gender (RR 2.507; 95% CI 1.470–4.486; $P = 0.001$), and use of fluoroquinolones (RR 2.128; 95% CI 1.249–3.624 $P = 0.005$). Sub-group analysis of patients discharged from the ED showed that definitive therapy with nitrofurantoin decreased the risk of inadequate empiric antibiotic therapy by 80% (RR 0.202; CI 0.065–0.638; $P = 0.006$). ED-level antibiograms showed differences in antimicrobial susceptibility of *E. coli* by age and gender.
Conclusions: Development of ED-level antimicrobial susceptibility data and consideration of patients' clinical characteristics can help better guide selection of empiric antibiotic therapy for the treatment of UTIs.

1. Introduction

Urinary tract infections (UTIs) are among the leading causes of emergency department (ED) visits in the United States with an estimated two million visits in 2011 [1]. *Escherichia coli* (*E. coli*) is the main cause of UTIs across different populations, settings, and age groups. Acute cystitis and pyelonephritis in healthy premenopausal, nonpregnant women with no urinary tract abnormalities are generally classified as uncomplicated [2]. UTI in men are usually considered complicated, since they frequently occur in elderly patients in the context of urologic abnormalities and only a small fraction affect healthy younger men [3]. This classification serves as the basis for antibiotic choice and duration.

Recent studies conducted among ED patients have reported an increase in the percentage of *E. coli* isolates resistant to first and second-line antibiotics for the treatment of uncomplicated UTIs: trimethroprim-sulfamethoxazole and fluoroquinolones [4], while resistance rates to nitrofurantoin and fosfomycin among ambulatory patients remain low [5]. In our institution, according to the hospital-wide antibiogram, only 54% of the *E. coli* isolates are susceptible to trimethroprim-sulfamethoxazole and 60% to fluoroquinolones. This level of resistance limits the effectiveness of these antibiotics as ideal options to treat common UTIs in hospitalized patients. Antibiotic resistance percentages in urine isolates from patients seen in our ED are unknown, limiting the knowledge to appropriately select the best empiric antibiotic for the treatment of patients with UTIs. Therefore we aimed to calculate the ED-level *E. coli* percentage of isolates susceptible to

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commonly used antibiotics and to determine the risk factors associated with inadequate empiric antibiotic therapy among patients treated for UTIs in our ED.

2. Material and Methods

2.1. Study Design and Setting

Retrospective cohort study conducted at a large tertiary teaching hospital. The emergency department has approximately 100,000 visits annually. The study period spanned from May 1, 2014 to October 31, 2014.

2.2. Selection of Participants

Patients were identified from the microbiology laboratory database. We evaluated all consecutive patients older than 18 years examined in the ED who had a urine culture with growth of >100,000 colonies of *E. coli*. Only the first culture per patient was included in the final cohort. This study was reviewed and approved by the local Institutional Review Board.

2.3. Data Extraction

Data were extracted from the electronic medical record (EMR) by 3 trained investigators. If documentation was unclear a senior investigator reviewed the available data. Diagnosis of UTI was ascertained from the EMR as documented by the treating ED physician and included: non-specific UTI, cystitis, pyelonephritis, prostatitis, urethritis and orchiepididymitis. Data on baseline demographic characteristics, pregnancy status, presence of indwelling urinary catheter at the time of ED presentation, and nursing home residency were obtained.

Antimicrobial susceptibility testing was performed using the Vitek 2 system (BioMériux®). Interpretative criteria for susceptibility and resistance were determined using the minimum inhibitory concentration breakpoint values established by the Clinical and Laboratory Standards Institute after 2010.

2.4. Definitions

The main outcome was inadequate empiric antibiotic therapy, defined as treatment with an agent reported to be intermediate or resistant against the isolated strain of *E. coli*. The adequacy of empiric antibiotic therapy was assessed in two scenarios: 1) antibiotic therapy administered in the ED (this outcome was registered among all patients who received at least one dose of antibiotic in the ED), and 2) antibiotic therapy prescribed upon discharge. The latter outcome was evaluated among patients who were discharged from ED and determined based on the antibiotic prescribed as definitive therapy. Antimicrobial susceptibility pattern of the *E. coli* isolates recovered from the study population were calculated, and antibiograms stratified by gender and age group were constructed.

2.5. Statistical Analysis

Comparisons between categorical variables were performed using Chi-square or Fisher's exact tests as appropriate. Differences in median among continuous variables were evaluated using Mann Whitney *U* test. Univariate analysis of risk factors associated with inadequate empiric antibiotic therapy at the ED level and upon discharge was performed. Multivariable analyses were done using logistic regression. A *P*-value of less than 0.05 was considered statistically significant. All analyses were performed using SAS University Edition (SAS Institute, Cary, NC).

3. Results

3.1. Patient Characteristics

A total of 300 unique patients had *E. coli* bacteriuria during the study period. Of these, 241/300 (80.3%) had a diagnosis of urinary tract infection documented as the reason for ED visit, while 18/300 (6%) were diagnosed with an infectious process other than UTI, and 41/300 (13.7%) had a non-infectious diagnosis. The types of UTI were distributed as follows: 147 (61%) were classified as non-specific UTI, 28 (11.6%) cystitis, 61 (25.3%) pyelonephritis, and the rest were 2 (8.3%) urethritis, 2 (8.3%) orchiepididymitis, and 1(4.1%) prostatitis. One hundred and thirteen (46.9%) of the patients were admitted and 128/241(53.1%) were discharged.

3.2. Factors Associated with Inadequate Empiric Antimicrobial Therapy

Among the patients with diagnosis of UTI, 239/241 (99.2%) received at least one dose of an antibiotic in the ED. One patient left against medical advice prior to receiving any therapy, and one patient did not receive antibiotics in the ED but was given a prescription upon discharge. Inadequate empiric antibiotic therapy was given to 41/241 (17%) of patients with *E. coli* UTI treated in the ED (Table 1). Patients who received inadequate empiric therapy had a median age of 59 years old (interquartile range [IQR] 47–65), compared to an age of 46 years old (IQR 31–62) among those who received adequate empiric therapy. On the univariate model, patient characteristics found to increase the risk of inadequate empiric antibiotic therapy were age (relative risk [RR] 1.021; 95% confidence interval [CI] 1.008–1.034; $P = 0.002$), male gender (RR 3.185; 95% CI 1.838–5.520; $P < 0.001$), and chronic indwelling catheterization (RR 2.269; 95% CI 1.243–4.140; $P = 0.008$).

Based on the age distribution observed on the descriptive analysis, age was also explored by categorizing it into a binary variable using 45 years of age as the cutoff. When age was treated as a categorical variable, gender was found to be an effect modifier of the association between age older than 45 years and inadequate empirical therapy. Effect modification occurs when the effect of an exposure on an outcome varies according to the level of a third variable [6]. We found that among male patients, an age greater than 45 years was associated with a non-statistically significant risk of inadequate empiric therapy of 1.087 (95% CI 0.480–2.463; $P = 0.842$). However, when looking at female patients only, an age greater than 45 years old tripled the risk of receiving inadequate empiric therapy (RR 3.341; 95% CI 1.146–9.742; $P = 0.027$). No effect modification was found between age and gender when age was analyzed as a continuous variable. Regarding therapeutic choices, use of fluoroquinolones conferred a risk of inadequate empiric therapy of 1.839 (95% CI 1.060–3.191; $P = 0.030$). In the adjusted model, variables independently associated with an increased risk of the inadequate empiric therapy were age (continuous variable) (RR 1.016; 95% CI 1.001–1.031; $P = 0.032$), male gender (RR 2.570; 95% CI 1.472–4.486; $P = 0.001$), and use of fluoroquinolones (RR 2.128; 95% CI 1.249–3.624; $P = 0.005$).

We then analyzed the adequacy of the antibiotics prescribed as definitive therapy among patients who were discharged and found that 33/128 (25.8%) had inadequate empiric antibiotic therapy. In the unadjusted analysis, the variables associated with increased risk of inadequate empiric antibiotic therapy were: 1. age (RR1.020; 95% CI 1.004–1.036; $P = .013$); 2. male gender (RR 1.951; 95% CI 1.097–3.470; $P = 0.023$); and 3. presence of a urinary catheter at the time of infection (RR 2.382; 95% CI 1.300–4.367; $P = 0.005$). Use of nitrofurantoin decreased the risk of inadequate empiric therapy (RR 0.184; 95% CI 0.060–0.571; $P = 0.003$) (Table 2). Once again, based on age distribution observed on the descriptive analysis, age was also explored as a categorical variable, with a cutoff of 45 years old. Among discharged patients, gender again was found to be an effect modifier of the

Table 1
Risk factors for inadequate empiric antimicrobial therapy among patients with *Escherichia coli* UTI treated in the emergency department.

Variable	Inadequate empiric antimicrobial therapy n = 41(%)	Adequate empiric antimicrobial therapy n = 200(%)	Univariate analysis		Multivariate analysis	
			RR (95% CI)	*P*-value	RR (95% CI)	*P*-value
Demographics						
Age, median (IQR)	59(47–65)	46(31–62)	1.021(1.008–1.034)	0.002	1.016(1.001–1.031)	0.032
Male gender	23(56.1)	46(23.0)	3.185(1.838–5.520)	<0.001	2.570(1.472–4.486)	0.001
Pregnant	1(2.4)	9(4.5)	0.578(0.088–3.787)	0.567		
Urinary catheter	10(24.4)	20(10.0)	2.269(1.243–4.140)	0.008	1.706(0.945–3.078)	0.076
Nursing home	4(9.8)	9(4.5)	1.896(0.797–4.512)	0.148		
Type of urinary tract infection						
Non-specific UTI	30(73.2)	117(58.5)	1.744(0.919–3.309)	0.089		
Pyelonephritis	7(17.1)	54(27.0)	0.608(0.284–1.299)	0.199		
Cystitis	4(9.8)	24(12.0)	0.822(0.317–2.134)	0.688		
Orchiepididimitis	0	2(1.0)	NA			
Urethritis	0	2(1.0)	NA			
Prosthatitis	0	1(0.5)	NA			
Antibiotics						
Nitrofurantoin	3(7.1)	39(19.5)	0.374(0.121–1.155)	0.087		
SXT	2(4.9)	10(5)	0.979(0.268–3.580)	0.974		
Fluoroquinolone	19(46.3)	58(29)	1.839(1.060–3.191)	0.030	2.128(1.249–3.624)	0.005
Ceftriaxone	13(31.7)	82(41)	0.713(0.390–1.307)	0.274		
Cefepime	0	4(2)	NA			
TZP	1(2.4)	19(9.5)	0.276(0.040–1.905)	0.192		

RR, relative risk; CI, confidence interval; IQR, inter-quartile range; NA, not applicable; SXT, trimethroprim-sulfamethoxazole TZP, piperacillin-tazobactam.

association between age older than 45 years and inadequate empiric therapy. Among male patients older than 45 years there was a statistically insignificant risk of 0.522 (CI 0.235–1.156; $P = 0.109$) of occurrence of inadequate empiric therapy. However, among female patients, an age greater than 45 years old doubled the risk of receiving inadequate empiric therapy upon discharge (RR 2.205; 95% CI 1.006–4.837; $P = 0.048$). In the adjusted analysis, the only variable that remained statistically significant was therapy with nitrofurantoin, which decreased the risk of inadequate empiric antibiotic therapy by 80% (RR 0.202; CI 0.065–0.638; $P = 0.006$) (Table 2).

3.3. Differences in Antimicrobial Susceptibility

We further explored the antimicrobial susceptibility pattern of the *E. coli* isolates recovered from the study population by constructing antibiograms stratified by gender and age group (Fig. 1). Among patients aged 45 years and younger percentages of antibiotic susceptibilities were comparable across different classes, except for fluoroquinolones, where we observed that only 59% of *E. coli* isolates recovered from male patients were susceptible, compared to 82% of the isolates from female patients ($P = 0.005$). In the 46–64 age group differences between male and female were seen in the susceptibility patterns to trimethroprim-sulfamethoxazole (30% versus 50% respectively; $P = 0.049$) and cefazolin (58% versus 78% respectively; $P = 0.020$). No differences in susceptibility percentages were seen between male and female patients older than 65. It should be noted that susceptibility rates to nitrofurantoin were above 90% across all age groups, while susceptibility to trimethroprim-sulfamethoxazole was under 60% among both men and women of all ages.

4. Discussion

Our results indicate that among patients treated for *E. coli* UTI in our ED use of fluoroquinolones, male gender and age are independent risk factors for inadequate empiric antibiotic therapy. Interestingly, when limiting the analysis to the subgroup of patients who were discharged

Table 2
Risk factors for inadequate empiric antimicrobial therapy among patients with *Escherichia coli* UTI discharged from the emergency department.

Variable	Inadequate empiric antimicrobial therapy n = 33(%)	Adequate empiric antimicrobial therapy n = 95(%)	Univariate analysis		Multivariate analysis	
			RR (95% CI)	*P*-value	RR (95% CI)	*P*-value
Demographics						
Age, median (IQR)	51(41–62)	43(29–58)	1.020(1.004–1.036)	0.013	1.016(0.999–1.032)	0.052
Male gender	12(36.4)	17(17.9)	1.951(1.097–3.470)	0.023	1.151(0.609–2.174)	0.665
Pregnant	0	5(5.3)	NA			
Urinary catheter	7(21.2)	6(6.3)	2.382(1.300–4.367)	0.005	1.717(0.922–3.195)	0.088
Type of urinary tract infection						
Non-specific UTI	21(63.6)	59(62.1)	1.050(0.569–1.937)	0.876		
Pyelonephritis	4(12.1)	17(17.9)	0.703(0.276–1.790)	0.460		
Cystitis	6(18.2)	17(17.9)	1.014(0.474–2.171)	0.970		
Orchiepididymitis	1(3)	1(1)	1.969(0.477–8.127)	0.349		
Urethritis	1(3)	1(1)	1.969(0.477–8.127)	0.349		
Antibiotics						
Nitrofurantoin	3(9.1)	42(44.2)	0.184(0.060–0.571)	0.003	0.202(0.065–0.638)	0.006
SXT	5(15.1)	7(7.4)	1.726(0.821–3.629)	0.150		
AMC	0	1(1)	NA			
Cephalexin	3(9.1)	10(10.5)	0.885(0.313–2.500)	0.817		
Fluoroquinolone	15(45.4)	34(35.8)	1.343(0.748–2.412)	0.323		

RR, relative risk; CI, confidence interval; IQR, inter-quartile range; NA, not applicable; SXT, trimethroprim-sulfamethoxazole; AMC, amoxicillin-clavulanate.

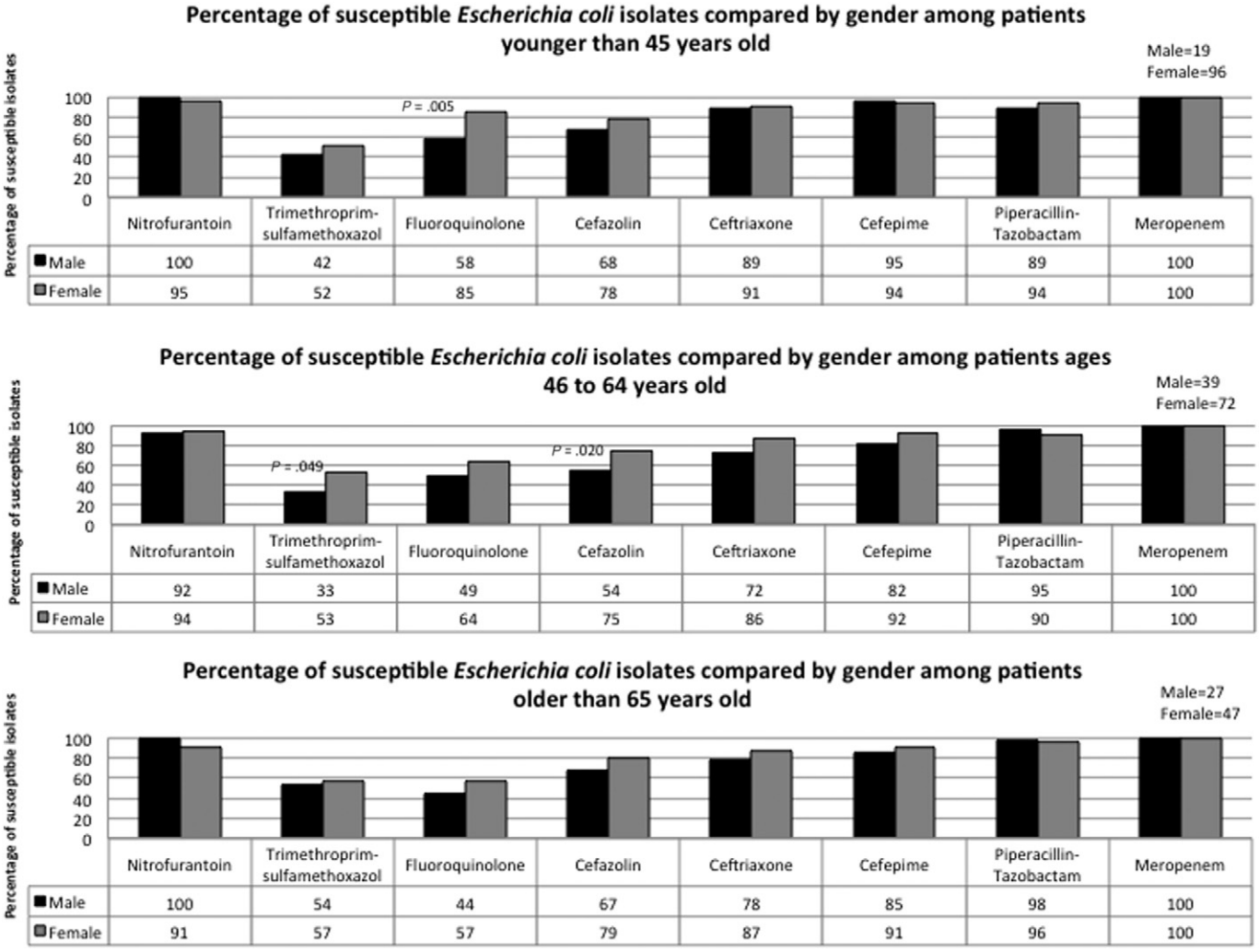

Fig. 1. Percentage of susceptible *Escherichia coli* isolates from patients who visited the emergency department stratified by gender and age group.

from the ED, use of nitrofurantoin significantly decreased the risk of inadequate therapy.

Choosing an appropriate antimicrobial for the management of UTIs takes into consideration gender, clinical presentation, local community resistance prevalence, and the presence of anatomic or functional abnormalities. For uncomplicated UTIs, first-line agents include nitrofurantoin (in patients with normal renal function), fosfomycin and pivmecinillam (not available in the United States) [7]. Reports of low resistance rates to nitrofurantoin are consistent with our results [5]. Moreover, we found that use of nitrofurantoin as definitive antimicrobial choice among patients discharged from the ED was associated with an 80% decrease in the risk of inadequate empiric antibiotic therapy.

Among our patient population, we found that use of fluoroquinolones doubled the risk of inadequate empiric antibiotic therapy. Fluoroquinolones have been recommended as second-line agents for the management of uncomplicated UTIs but growing rates of resistance [4], as well as increased recognition of their potential side effects [8] limit their use.

In patients with complicated UTIs, the variety of causal organisms, as well as increased rates of resistance, pose a greater challenge in choosing empiric antibiotic therapy. Male patients have traditionally been considered as having complicated UTIs, since these infections typically occur in the context of anatomic abnormalities [3]. As shown in our results, male gender was associated with an increased risk of inadequate empiric antibiotic therapy. Furthermore, we found significant differences in the susceptibility patterns of *E. coli* isolates between male and female patients, as well as across age groups. In a population with high-level resistance to fluoroquinolones, when a complicated UTI is suspected, we favor initial empiric antibiotic therapy with third or fourth generation cephalosporins such as ceftriaxone or cefepime, and piperacillin-tazobactam as a less ideal alternative. Empiric use of carbapenems is discouraged, unless there are known risk factors for infection with ESBL-producing bacteria, or a previous history of infection with this type of organism. According to the Drug Resistance Index-a composite measure that combines the ability of antibiotics to treat infection with the extent of their use in clinical practice-the number of "difficult to treat" infections has been steadily increasing across the United States since 1999 [9]. Therefore, consideration of demographic characteristics that increase the risk of inadequate empiric therapy, as well as the development and dissemination of ED-level specific antibiotic resistance data can then be used as part of a strategy to improve prescribing patterns among ED physicians [10,11]. Antimicrobial Stewardship Programs can lead efforts geared at recommending the use of antibiotics that remain active against the most common UTI causative agents, while also having the narrowest antimicrobial spectrum of activity and minimizing the negative impact on the gut microbiome [10, 12].

Limitations to our study include those inherent to its retrospective design in a single urban center. However, our ED is one of the busiest in the country serving a very large and ethnically diverse population. Also, our study was focused on *E. coli*, and adequacy of empirical

antimicrobial therapy of other uropathogens was not assessed. Data on antibiotic allergy and prior ED visit(s) was not collected. Delays in initiation of appropriate antimicrobial therapy, choice of antibiotic among patients who were admitted, and impact of antibiotic mismatch on hospital length of stay and mortality were not evaluated. Also, it is possible that some patients were empirically treated for UTI without obtaining a urine culture as it is not customary among all practitioners to obtain urine cultures in all patients especially when discharge from the ED is anticipated. Whether the patients in whom a urine culture was obtained systematically differ from those treated without obtaining cultures is unknown. The role of perception of severity of illness on the choice of empiric therapy was not explored.

5. Conclusion

Development of ED-level antimicrobial susceptibility data and consideration of patients' clinical characteristics can help better guide selection of empiric antibiotic therapy for the treatment of UTIs. As the number of effective treatment options dwindles, especially for patients who could otherwise be discharged from the ED, more studies addressing the effectiveness of different strategies for improvement in prescription patterns are needed.

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