Community-acquired urinary tract infection: age and gender-dependent etiology

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ABSTRACT

Introduction: Choosing the antimicrobial agent for initial therapy of urinary tract infection (UTI) is usually empirical and should consider the prevalence of uropathogens in different age groups and gender. **Objective:** To establish prevalence rates of uropathogens in community-acquired UTI in relation to age and gender. **Methods:** Cross-sectional study conducted in the emergency department (ED) of a general hospital, from January to December, 2010, in patients younger than 15 years old who had clinical suspicion of UTI and collected quantitative urine culture. UTI was defined as urine culture with growth of a single agent ≥ 100.000 colony forming units (cfu)/mL in a midstream collection or ≥ 50.000 cfu/mL in urethral catheterization. **Results:** There were 63.464 visits to ED. 2577 urine cultures were obtained, of whom 291 were positive for UTI (prevalence = 11.3% of clinical suspicion and 0.46% of visits), 212 cases (72.8%) in females, median age = 2.6 years. The predominant uropathogen was *E. coli* (76.6%), followed by *Proteus mirabilis* (10.3%) and *Staphylococcus saprophyticus* (4.1%). Among infants < 3 months, prevalence rates of *E. coli* were significantly lower (50% *vs* 78.4%; OR = 0.276; *p* = 0.006). Higher prevalences of *Staphylococcus saprophyticus* occurred among patients > 10 years (24.4% *vs* 0.4%; OR = 79.265; *p* < 0.0001). Proteus mirabilis was significantly more prevalent in boys than girls (24.0% *vs* 5.2%; OR = 5.786; *p* < 0.001). **Conclusions:** *E. coli* was the most prevalent community-acquired uropathogen. Nevertheless, initial empiric antimicrobial treatment of UTI should consider the significant prevalence of other agents different from *E. coli* in infants < 3 months, the high prevalence of *Staphylococcus saprophyticus* in patients > 10 years and *Proteus mirabilis* in males.

Keywords: bacteriuria; child; Escherichia coli; Proteus mirabilis; Staphylococcus saprophyticus; urinary tract infections.

INTRODUCTION

Urinary tract infections (UTI) are frequently seen in the pediatric care practice.[1,2] Classic symptoms such as dysuria, urinary frequency, urinary urgency and lower back pain are not always present in preverbal children, and fever may be the only symptom in infants.[3] The importance of early diagnosis and treatment has been described in the literature, along with the increased risk of kidney injury when treatment is delayed.[3-6]

The diagnosis of UTI relies on the presence of significant bacteriuria in clean catch samples of adequately collected quantitative urine cultures. Urine culture and antibiogram results usually take four days to be published; therefore, the initial choice of antimicrobial therapy is usually empirical.

The empirical choice of antimicrobial therapy is based on two basic principles: first, the prevalence of etiologic agents for each age range and gender; and second, the antimicrobial susceptibility of these uropathogens, which may vary between communities and with time.

Brazilian and international studies have identified *Escherichia coli* (*E. coli*) as the main UTI etiologic agent, with prevalence rates ranging between 60% and 90% depending on the region where the study was carried out and the age range of the enrolled subjects.[7-16] Knowledge on the antimicrobial susceptibility of *E. coli* plays a key role in the initial empirical choice of therapy. However, other uropathogens such as *Proteus mirabilis* (*P. mirabilis*) and *Staphylococcus saprophyticus* (*S. saprophyticus*) may be frequently seen in subjects of specific age

ranges and genders. The prevalences of these pathogens must be considered in the empirical choice of treatment, as their susceptibility to antibiotics may differ significantly from that of *E. coli*.

This study aimed to look into the prevalence rates of UTI uropathogens and their correlations with age and gender, in order to provide additional input to the empirical choice of antimicrobial agents in the early treatment of patients with UTI.

METHODS

This study was carried out in 2010 at the teaching Hospital of the University of São Paulo, a medium complexity care center located in the city of São Paulo at which 4.200 to 6.600 patients are seen per month in the emergency department.

This cross-sectional retrospective study included cases seen between January 1, 2010 and December 31, 2010. All quantitative urine cultures of pediatric patients aged up to 15 years seen in the emergency department were selected. The patients whose cultures were selected had complaints and clinical findings consistent with urinary tract infection (fever, abdominal pain, or urinary signs and symptoms). UTI was characterized by urine cultures with counts greater than 100.000 colony-forming units/mL (CFU/mL) of one type of bacteria for midstream urine samples or counts greater than 50.000 CFU/mL for samples collected with a catheter.

Children without urinary sphincter control (under two years of age) had urine samples collected with the aid of a catheter, whereas individuals with sphincter control had midstream urine samples collected. Antisepsis was carried out with chlorhexidine in neonates aged up to 28 days and with topical povidone-iodine in children above 28 days old. After collection, the samples were immediately forwarded to the hospital's microbiology laboratory and cultured in MacConkey blood agar medium (Plastlabor®, Rio de Janeiro); the identification and susceptibility of the isolated strains were determined using the Vitek® 2 system (bioMérieux, Marcy l'Etoile, France).

STATISTICAL ANALYSIS

Clinical and lab test results were analyzed in statistical package WINKS 4.80, WINKSTAT, MS. The results for continuous variables were presented in the form of medians, mean values, and standard deviations, with a 95% confidence interval (CI 95%). The results for categorical variables were expressed in the form of histograms and ratios. The Chi-square test, Yates' chi-squared test, and Fisher's exact test were used to compare categorical variables as needed. The differences between categorical variables were noted in odds ratios (OR). Fisher's exact test or the Mann-Whitney U-test was used to compare continuous variables as applicable. Significance level was set at 0.05.

This study was approved by the Research Ethics Committee of the institution and granted permit 622/05.

RESULTS

In 2010, 63.464 visits to the pediatric emergency department were recorded. A total of 2.577 urine culture sample collections were done due to suspicion of UTI, 1.304 (50.6%) of which with the aid of a catheter and 1.273 (49.4%) through midstream sample collection. UTI was confirmed in 137 of the cases collected with a catheter and in 154 of the midstream samples, adding to a total of 291 cases (prevalence = 11.3% of the clinically suspicious cases and 0.46% of all cases seen in the emergency department); patient median age was 2.6 years (ranging between 11 days and 14.99 years). Urine culture test results were released within 72 hours when no bacterial growth was observed; positive tests and their corresponding antibiograms were made available in five days.

UTI was more prevalent in females, with 212 cases (72.6%). *E. coli* was found in 76.6% of the cases of UTI, followed by *P. mirabilis* (10.3%), and *S. saprophyticus* (4.1%). Table 1 shows the incidence rates of each pathogen according to gender.

Antimicrobial susceptibility testing revealed that up to 70% of the *E. coli* isolates were susceptible to ampicillin, sulfamethoxazole-trimethoprim, and cephalothin. *E. coli* susceptibility was greater than 90% for second and third generation cephalosporins, aminoglycosides, quinolones, nitrofurantoin, and nalidixic acid. *E. coli* susceptibility for amoxicillin/clavulanic acid was 83.4%. No statistically significant difference was observed between subject age ranges (Figure 1).

Different uropathogen prevalence patterns were observed in each age range: infants under three months of age (n = 18), subjects aged between three months and ten years (n = 228), and individuals aged between 10 and 15 (n = 45), as described on Table 2. Patients aged between three months and ten years were grouped

TABLE 1		GENDER DISTRIBUTION OF UROPATHOGENS IDENTIFIED IN URINE CULTURES OF PATIENTS DIAGNOSED WITH UTI		
Uropathogens	Total isolated strains		Gender	
	n	%	F (n)	M (n)
Escherichia coli	223	76.6	176	47
Proteus mirabilis	30	10.3	11	19
Staphylococcus saprophyticus	12	4.1	11	1
Klebsiella pneumoniae	7	2.4	3	4
Enterococcus faecalis	4	1.4	1	3
Enterobacter cloacae	2	0.7	2	0
Proteus vulgaris	2	0.7	1	1
Serratia marcescens	2	0.7	1	1
Staphylococcus warnieri	2	0.7	1	1
Staphylococcus aureus	1	0.34	1	0
Morganella morgani	1	0,34	0	1
Pseudomonas aeruginosa	1	0.34	1	0
Citrobacter freundii	1	0.34	1	0
Citrobacter koseri	1	0.34	1	0
Pantoea spp	1	0.34	0	1
Raoultella ornithinolytica	1	0.34	1	0
Total	291	100	212	79

Figure 1. Antimicrobial susceptibility of E.coli isolates (n = 223) of patients diagnosed with UTI - SMX-TMP: sulfamethoxazole-trimethoprim; AMX-CLV: amoxicillin-clavulanic acid.

E.coli Antimicrobial Susceptibility
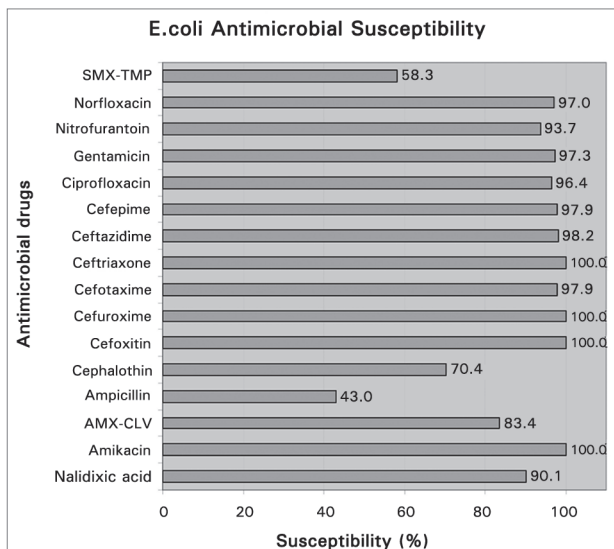
together due to etiologic similarity. This particular group was made up of 89 infants aged between three months and two years (64.0% females), and 139 children aged between two and 10 years (78.4% females).

More male subjects were affected by UTI in the group of infants aged three months and under (66.7% *vs*. 33.3%; OR = 6.149; 95% CI = [2.222-17.020]; p < 0.001), and *E. coli* prevalence was lower than in infants above the age of three months (50% *vs*. 78,4%; OR = 0.276; 95% CI = [0.105-0.726]; p = 0.006). The other uropathogens isolated in this age range were *Klebsiella pneumoniae* (four cases), *Enterococcus faecalis* (two cases: one patient aged 19 days and another aged 50 days), *Serratia marcescens* (one case), *Pantoea spp* (one case) and *P. mirabilis* (one case). Gram-negative enterobacteria were susceptible to amikacin and third generation cephalosporins, while *Enterococcus faecalis* was susceptible to penicillin and ampicillin.

In patients aged above ten years, *S. saprophyticus* was second only to *E. coli*, and accounted for 24.4% of the cases of UTI in this age range. Such prevalence was significantly greater than the rates seen in patients aged under 10 years (24.4% *vs*. 0.4%; OR = 79.265; CI 95% = [9.919-633.421]; p < 0.0001).

Gender-related prevalences of uropathogens can be seen in Figure 2. Statistically significant differences were seen in *E.coli* prevalence in females (83.0 *vs*. 59.5%; OR = 3.329; 95% CI = [1.874-5.914]; p < 0.001) and *P. mirabilis* prevalence in males (24.0% *vs*. 5.2%; OR = 5.786; 95% CI = [2.609-12.834]; p < 0.001). Statistically significant difference was not seen in the prevalence of *S. saprophyticus* in females and males (5.2 *vs*. 1.3%, p = 0.1906), but

	0-3 months		3 months to 10 years		10-15 years	
Uropathogen	F (n)	M (n)	F (n)	M (n)	F (n)	M (n)
Escherichia coli	4	5	148	40	24	2
Proteus mirabilis	0	1	8	17	3	1
Staphylococcus saprophyticus	0	0	1	0	10	1
Other	2	6	9	5	3	1
Total	6	12	166	62	40	5

TABLE 2 AGE AND GENDER DISTRIBUTION OF THE MAIN UROPATHOGENS IDENTIFIED IN URINE CULTURES OF PATIENTS DIAGNOSED WITH UTI

Figure 2. Gender distribution of the main uropathogens identified in urine cultures of patients diagnosed with UTI.
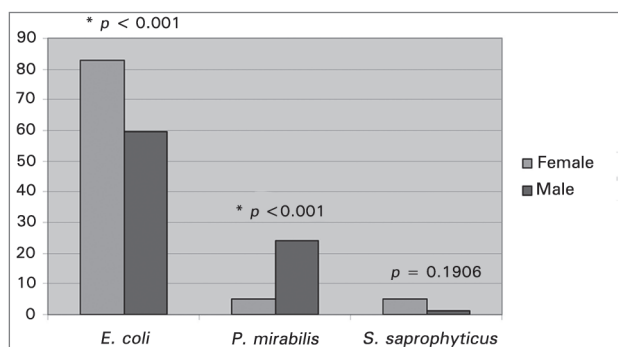
marked preponderance was seen in the number of cases involving females (11 females *vs.* one male).

All identified strains of *P. mirabilis* showed resistance to nitrofurantoin and were susceptible to nalidixic acid, aminoglycosides, and second and third generation cephalosporins. *P. mirabilis* susceptibility to amoxicillin/clavulanic acid was 93.3%.

DISCUSSION

E. coli was the most prevalent uropathogen (76.6%) in our series. Brazilian[7-10] and international[11-15,17] series have described significant *E. coli* resistance to ampicillin and sulfamethoxazole-trimethoprim, as also seen in this study, in addition to high susceptibility to nitrofurantoin, nalidixic acid, aminoglycosides, quinolones (subject to use restrictions in pediatric subjects),[18] and second and third generation cephalosporins.

Half of the cases of UTI in infants under the age of three months - a group at higher risk for bacteremia and kidney sequelae[5,6,19,20] - were caused by uropathogens other than *E. coli*, namely seven Gram-negative and two Gram-positive enterobacteria (*Enterococcus faecalis*). Uropathogen incidence rates vary significantly between studies and patients in this age range,[12,19-22] and authors tend to recommend empirical therapies based on broad spectrum antimicrobial drugs.[23] According

to the National Institute for *Health and Clinical Excellence* (NICE) 2007,[3,24] such finding should entail early imaging of at least 50% of the described patients due to the presence of cultures positive for bacteria other than *E. coli*. In our series, empirical initial therapy with amikacin or cefotaxime combined with ampicillin was adequate for the identified pathogens. Our results showed higher prevalences of UTI in male infants, as also seen in the literature.[12,16,19-22] This study did not look into breastfeeding, circumcision, past use of antimicrobial drugs, history of UTI, or urologic imaging, all of which factors that could be associated with variations in prevalence and antimicrobial susceptibility of UTI pathogens.[1,4,15,21,25] However, the prevalences of etiologic agents observed in this study in regards to gender and age reflect the pattern seen in a population that spontaneously seeks care at a general hospital. The patients enrolled in this study were not referred to our service for having known risk factors.

P. mirabilis was the most important uropathogen in males and accounted for 24% of the cases of UTI in boys, as also described by other authors.[9,11] This is an important factor in the initial prescription of antimicrobial drugs to boys, once the antimicrobial susceptibilities of *P. mirabilis* and *E. coli* are different.

S. saprophyticus has been described as the most important uropathogen in sexually-active young women.[9,13,14,26] This retrospective study did not consider information on the start of the subjects' sex life. *S. saprophyticus* was highly prevalent and accounted for 24.4% of the cases of UTI in subjects above the age of ten years. Antibiograms were not ordered in these cases. However, unlike *P. mirabilis*, *S. saprophyticus* has been described to show resistance to nalidixic acid and susceptibility to nitrofurantoin,[13,14] a fact to remember in the empirical therapy of patients in this age range.

There has been a lot of debate on the best course of empirical therapy for UTI, but it is not

the purpose of this study to name the best choice of treatment for each gender, age, or region of the world. However, significant patterns of occurrence of the main uropathogens by age range and gender were observed in the community included in this study, and this information is valuable for the initial therapy rationale.

Our proposed empirical initial therapy for infants under the age of three months is aminoglycosides or third generation cephalosporins, possibly in association with ampicillin, depending on how the case progresses and on the presence of suspicion of UTI by *Enterococcus faecalis*. Children above the age of three months suspected for pyelonephritis are prescribed second or third generation cephalosporins or amoxicillin/clavulanic acid. Nitrofurantoin is a good option for girls with signs of cystitis; it is not good for boys, given the resistance to this antimicrobial drug shown by *P. mirabilis*. *In-vitro* resistance of a certain uropathogen to an antimicrobial drug does not necessarily translate into treatment failure, but empirical initial therapy with ampicillin or sulfamethoxazole-trimethoprim is not recommended due to the significant resistance shown by *E. coli* to these drugs. Empirical use of first generation cephalosporins must be done with caution, as the observed *E. coli* susceptibility to cephalothin was 70.4%. New prospective studies with larger samples are required to assess the in-vivo efficacy of the various therapy options in different age ranges, genders, and patient histories.

Conclusion

The choice of empirical initial antimicrobial therapy is significantly affected by uropathogen prevalences according to age and gender. *E. coli* was the most prevalent uropathogen in the cases of community-acquired UTI included in this study. Nonetheless, *E.coli* prevalence varies with gender and age. Uropathogens other than *E. coli* must be considered in patients under the age of three months. High prevalences of *S. saprophyticus* were seen in children above the age of 10 years, while *P. mirabilis* was an important uropathogen in male patients.

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