Antibiotic Resistance Patterns of Pediatric Community-Acquired Urinary Infections

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Knowledge about antimicrobial resistance patterns of the etiological agents of urinary tract infections (UTIs) is essential for appropriate therapy. Urinary isolates from symptomatic UTI cases attended at Santa Casa University Hospital of São Paulo from August 1986 to December 1989 and August 2004 to December 2005 were identified by conventional methods. Antimicrobial resistance testing was performed by Kirby Bauer's disc diffusion method. Among the 257 children, *E. coli* was found in 77%. A high prevalence of resistance was observed against ampicillin and TMP/SMX (55% and 51%). The antibiotic resistance rates for *E. coli* were: nitrofurantoin (6%), nalidixic acid (14%), 1st generation cephalosporin (13%), 3rd generation cephalosporins (5%), aminoglycosides (2%), norfloxacin (9%) and ciprofloxacin (4%). We found that *E. coli* was the predominant bacterial pathogen of community-acquired UTIs. We also detected increasing resistance to TMP/SMX among UTI pathogens in this population.
Key-Words: Urinary tract infection, pediatrics urinary tract infection, bacterial resistance, *Escherichia coli*.

Urinary tract infection (UTI) is a common cause of fever and one of the most common community-acquired infections. *In vitro* resistance is a significant problem, not only in complicated UTIs, but also in community-acquired urinary infections. *Escherichia coli* is the most frequent etiological agent, accounting for 65%-90% of urinary infections [1-4]. Frequent use of wide-spectrum antibiotics may change the intestinal flora, and as a consequence, induce bacterial resistance [5,6].

The American Academy of Pediatrics, the Royal College of Physicians of London and the National Guideline Clearinghouse recommend empirical and precocious treatment of UTI, based on the susceptibility standard to the antimicrobials that are habitually utilized, with the objective of reducing risks of pyelonephritic scarring [7]. There is a paucity of literature concerning antibiotic therapy for uncomplicated UTI in the developing world. Increasing rates of resistance among bacterial uropathogens has caused growing concern in both developed and developing countries [8]. We evaluated the frequency of uropathogens in a community of São Paulo, Brazil, and we examined the antimicrobial susceptibility of *E. coli* and other uropathogens. Additionally, we compared the antimicrobial susceptibility of *E. coli* between two periods.

Material and Methods

Patients

The study population consisted of children younger than 17 years old, who had culture-proven UTI evaluated in the pediatrics department of Santa Casa Hospital, from August 2004 to December 2005 and August 1986 to December 1989. The exclusion criteria were previous hospitalization (<30 days), presence of catheters and vesicle continent derivation (Mitrofanoff procedure).

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Urine Culture

Episodes of UTI were identified by positive urine culture. Cultures were obtained from midstream-collected urine or transurethral bladder catheterization. Bacterial identification and determination of antimicrobial susceptibility by the disk diffusion technique were performed according to National Committee for Clinical Laboratory Standards. A uroculture was considered positive when it presented a bacterial count of more than 100,000 colony-forming units (CFU)/mL in a urine specimen collected midstream, or more than 10,000 CFU/mL in a urine specimen collected by transurethral bladder catheterization [1,7].

The antimicrobial susceptibility tests included the following drugs: amikacin (an aminoglycoside), cephalexin, cefuroxime and cephotaxime (1st, 2nd and 3rd generation cephalosporins, respectively), norfloxacin, ciprofloxacin and nalidixic acid (fluoroquinolines), nitrofurantoin, ampicillin, and trimethoprim-sulfamethoxazole (TMP/SMX). The results were interpreted in accordance with the criteria established by the International Committee on Laboratorial Standardization. Organisms with intermediate susceptibility were considered resistant. All of the results were initially analyzed descriptively as absolute and relative frequency. The chi-square test or the Fisher exact test were used, with a significance level of 5%, to compare the proportions.

Results

We analyzed 100 subjects from 2004-2005 and 157 from 1986-89. Among these, 74% were female and 26% male (3.2 girls: 1 boy). The age range was from two months to 15 years (mean=four years and three months).

The most frequently isolated microorganism was *E. coli*, found in 129 (82%) children in the first period and in 77 (77%) in the second period. The resistance rate of *E. coli* to several antibiotics during these two periods is described in Table 1. There was no significant change in antimicrobial resistance rate between the two periods, with the exception of TMP/SMX, against which there was increased resistance in the second period (p=0.03). Aminoglicosides and 3rd generation cephalosporins were the most efficient antimicrobials against *E. coli*.

Table 1. Bacterial resistance of *E. coli* to the antimicrobials tested in the two studies performed in 1986 - 89 and 2004-2005 in São Paulo, Brazil.

***E. coli* Resistance**	**1986 - 1989 (n = 129)**	**2004 - 2005 (n = 77)**
Nitrofurantoín	12 (9%)	5 (6%)
Nalidixic acid	19 (13%)	11 (14%)
1st generation Cephalosporin	-	10 (13%)
2nd generation Cephalosporin	-	5 (7%)
3rd generation Cephalosporin	4 (3%)	4 (5%)
Norfloxacin	-	7 (9%)
Ciprofloxacin	-	3 (4%)
Amicacin	3 (2%)	0 (0%)
Ampicillin	52 (40%)	42 (55%)
Trimethoprim-Sulfamethoxazole	46 (36%)	39 (51%)

Table 2. Resistance to the habitual antimicrobials of urobacteria isolated from children with acquired urinary tract infection (UTI) in a community in São Paulo, Brazil, 2004-2005.

Bacterial resistance in domiciliary UTI	***Escherichia coli* (n = 77)**	**Non-*coli* bacteria (n = 23)**	**p**
Nitrofurantoin	5 (6%)	11 (48%)	0.0002
Nalidixic acid	11 (14%)	1 (4%)	0.1
1st generation Cephalosporin	8 (10%)	6 (26%)	0.06
2nd generation Cephalosporin	4 (5%)	3 (13%)	0.19
3rd generation Cephalosporin	4 (5%)	5 (22%)	0.1
Norfloxacin	6 (8%)	1 (4%)	0.4
Ciprofloxacin	3 (4%)		00.5
Amicacin	0 (0%)	2 (9%)	0.05
Ampicillin	42 (55%)	15 (65%)	0.3
Trimethoprim-sulfa	39 (51%)	10 (43%)	0.3

Among the oral antibiotics, nitrofurantoin, fluoroquinolines and 2nd generation cephalosporins were the most active antimicrobials against *E. coli*, followed by nalidixic acid, 1st generation cephalosporins and TMP/SMX (Table 1).

Non-coli bacteria were obtained in 23 cases. Among the non-*coli* bacteria, we identified *Proteus* sp. (15 patients), *Klebsiella* sp. (three patients), *S. saprophyticcus* (two patients) and *Enterococcus*, *Providencia* sp. and *Morganella morganni* (one patient each).

Table 2 shows the bacterial susceptibility of the non-coli UTI. Compared to *E. coli* bacteria, the non-*coli* bacteria had a higher rate of resistance to nitrofurantoin (6% to 48%). There greater resistance to amicacin and 1st, 2nd and 3rd generation cephalosporins, although the difference was not significant (Table 2). Non-coli bacteria were found in 23 cases. Among the non-*coli* bacteria, we identified *Proteus* sp. (15 patients), *Klebsiella* sp. (three patients), *S. saprophyticcus* (two patients) and *Enterococcus, Providencia* sp. and *Morganella morganni* (one patient each). Table 2 shows the susceptibility of non-coli UTI bacteria.

Discussion

The main etiological agents of UTI have changed little during the last few decades [1]. We also found that *E. coli* is still the principal etiological agent of UTI, accounting for 77% of the cases. Most cases of UTI are treated empirically, especially in developing countries, where patients often cannot afford to consult a physician or have a laboratory analysis made. Consequently, when urine samples are collected for laboratory tests, there may be an overrepresentation of microorganisms that do not respond to treatment. In spite of this possible bias due to recruitment of patients in a laboratory setting, we can provide information about risk factors for urinary tract infection due to *E. coli* strains that are resistant to antimicrobial agents that are commonly used in developing countries [8].

Nitrofurantoin maintained good activity against *E. coli* during the two periods of study. Nitrofurantoin is not as widely used as TMP/SMX and results in low levels of intestinal selection. However this class of antimicrobial is excreted in the urine and fails to achieve therapeutic concentrations in the bloodstream; because of this pharmacokinetic profile, it is not recommended to treat febrile infants or children in whom renal involvement is suspected [1]. The aminoglycosides are

drugs that are considered safe for the treatment of UTI in children, because they do not negatively impact on the intestinal flora and the resistance rate against them has remained very low in the last few decades, being around 1 to 2% [3]. We found a resistance rate of 2% against amikacin for the bacteria *E. coli* from 1986-1989, and zero from 2004-2005. The 3rd generation cephalosporins were active against *E. coli* during both periods. Intravenous therapy should be considered in children who have failed oral therapy and continue to be febrile [1]. Other non-*E. coli* Gram-negative bacteria, particularly *Proteus mirabilis*, tend to be more frequently resistant to antibiotics.

Resistance to ampicillin and TMP/SMX has increased progressively in the last decade. In the United States, Gupta observed an increase from 7% in 1990 to 16%-18% in 1996-2001 in outpatient treatment of non-complicated UTIs [8]. This increase in the resistance rate is probably a consequence of indiscriminate use of this drug. We found a significant increase in the resistance of *E. coli* to TMP/SMX, from 36% in 1986-1989 to 51% in 2004-2005. These high rates advise against its use in our community.

Most studies have shown that the frequency of resistance of uropathogenic bacteria to fluoroquinolines is low. However, in some countries in Europe, such as Spain and Portugal, the resistance rate reaches 19.6% [9]. We observed more frequent resistance to nalidixic acid than to norfloxacin and ciprofloxacin (9% and 4%, respectively). There are restrictions against the routine use of these drugs in pediatric patients, due to demonstration of arthropathies associated with quinolones in animal models. However, fluoroquinolines can be used in complicated cases of UTI, as they decrease hospitalization time [10,11].

The WHO guidelines indicate TMP/SMX and ampicilin as first choice for treatment of UTI [12]. We conclude that the antibiotic sensitivity patterns to the habitual antimicrobials of community-acquired uropathogens in São Paulo, Brazil recommend against there use as first choice. Nitrofurantoin is an inexpensive antimicrobial agent with good activity against UTI etiological agents.

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