Original Article

Frequency and antibiotic susceptibility patterns of urinary pathogens in male outpatients in Argentina

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Abstract

Introduction: Knowledge of the etiology and antimicrobial susceptibility patterns of uropathogens is important for determining the best treatment option. This study aimed to determine the distribution and antibiotic susceptibility patterns of bacterial strains isolated from adult male outpatients.

Methodology: Between November 2012 and April 2013, 3,105 community urine samples were analyzed from adult male patients who attended the Laboratorio Hidalgo, Buenos Aires, Argentina. Antimicrobial susceptibility testing was performed by the Kirby-Bauer disc diffusion method. Isolates resistant to third generation cephalosporin were tested for extended-spectrum beta-lactamase (ESBL) production using the double-disk synergy test.

Results: Of the 3,105 urine samples analyzed, 791 (25.5%) had significant bacteriuria. The frequency of positive urine cultures increased significantly with patient age. *Escherichia coli* was isolated most frequently (47.3%), followed by *Enterococcus faecalis* (13.6%), and *Klebsiella pneumoniae* (11.9%). Gram-negative organisms represented 78.8% of urinary pathogens. The highest activities against Gram-negative bacteria were found with imipenem (99.0%), amikacin (98.1%), ertapenem (94.2%), fosfomycin (90.7%), and piperacillin-tazobactam (90.1%). The frequencies of ESBLs among *E. coli*, *K. pneumoniae,* and *P. mirabilis* were 15.2 %, 22.3%, and 8%, respectively. Fosfomycin, piperacillin-tazobactam, and nitrofurantoin were most effective against Gram-positive organisms.

Conclusions: Fosfomycin may be an excellent option for cystitis treatment in patients without risk factors, whereas piperacillin-tazobactam is preferred for the treatment of parenchymatous UTIs, complicated UTIs, and UTIs associated with risk factors. To ensure the optimal selection of antibiotics, physicians should have access to up-to-date information about the local prevalence of antimicrobial resistance.

Key words: antimicrobial susceptibility; community-acquired urinary tract; empirical treatment; infection; uropathogen

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Introduction

Urinary tract infections (UTIs) are among the most prevalent infectious diseases in the general population [1-2]. UTIs impose a substantial financial burden on the community and are associated with significant morbidity and mortality, particularly in hospitals [3-4]. The pathogenesis of uncomplicated UTIs remains unclear in men and it has been hypothesized that all UTIs in men must be considered complicated because they result from an anatomical or functional anomaly. Twenty percent of diagnosed uncomplicated UTIs occur in men, among whom the prevalence increases with age [5]. UTIs with bacteremia are linked with high mortality in the older population, among whom studies report a 28-day mortality of 5% [6]. However, many studies have failed to distinguish between urinary isolates recovered from adult female outpatients (most of whom have uncomplicated UTIs) and those recovered from men, children, or inpatients (most of whom have complicated UTIs). Most UTIs that occur in developing countries are treated on an empirical basis. The Infectious Diseases Society of America (IDSA) also recommends that physicians obtain information on local resistance rates and that ongoing local, regional, and national surveillance should be conducted to monitor changes in susceptibility of uropathogens and the suitability of empirical therapy recommendations [7]. Surveillance at the institutional level may be particularly important since previous studies have shown that the activity of antibiotics against urinary isolates of *E. coli* can vary considerably by geographic location [8-9]. A national surveillance initiative that specifically describes antimicrobial resistance among common urinary pathogens in adult male outpatients in Argentina has not been published. Therefore, the present study aimed to assess the etiology and antimicrobial susceptibility of a large number of urinary pathogens recovered from male outpatients aged > 50 years who had positive urine cultures.

Methodology

The study participants were ambulatory patients who attended the Laboratorio Hidalgo, Buenos Aires, Argentina, between November 2012 and April 2013. Freshly voided midstream urine specimens (n = 3,105) were submitted to the clinical microbiology laboratory for processing. Semi-quantitative urine culture with a calibrated loop was used to inoculate blood agar and/or chromID CPS plates (bioMérieux, Marcy-l'Étoile, France). Significant bacteriuria was defined as culture of a single bacterial species from a urine sample with a concentration of $\geq 10^5$ cfu/ml. The exclusion criteria included the presence of fungi, mixed cultures, multiple isolates from a given patient (in which case only the first isolate per patient was used), age less than 50 years, history of admission to the hospital and/or insertion of a urinary catheter in the previous 15 days, residence in a nursing home, and use of antibiotics in the previous 7 days.

The significant pathogens were identified using standard biochemical procedures and/or the API 20 System (bioMérieux Marcy-l'Étoile, France). To analyze the culture results and the susceptibility rates, the patients were divided into the following age groups: 50–60, 61–70, 71–80, and ≥ 81 years. The antimicrobial susceptibility testing of all isolates used the Kirby–Bauer disk diffusion method. The following antibiotic discs were used: amikacin (30 µg), ampicillin (10 µg), ampicillin-sulbactam (20/10 µg), cefotaxime(30 µg), cefoxitin (30 µg), ceftazidime (30 µg) , cephalothin(30µg), ciprofloxacin (5 µg) , ertapenem(10 µg) , fosfomycin- glucose-6-phosphate (200/50 µg), gentamicin (10 µg), imipenem(10 µg), nitrofurantoin (300 µg) , piperacillin-tazobactam (100/10 µg), trimethoprim-sulphamethoxazole (1.25/23.75 µg). The antimicrobial discs were all purchased from Oxoid (Basingstoke, UK). *Escherichia coli* ATCC 25922, *Staphylococcus aureus* ATCC 29213, *Pseudomonas aeruginosa* ATCC 27853, *Enterococcus faecalis* ATCC 29212, and *E. coli* ATCC 35218 were used as the quality control strains. The interpretative criteria for the antimicrobial tests were those recommended by Clinical and Laboratory Standards Institute [10]. Intermediate susceptibility was classified as resistance. The production of extended-spectrum beta-lactamases (ESBLs) indicated resistance to third generation cephalosporins. To analyze the ESBL phenotypes, an overnight culture suspension of the test isolate was adjusted to a 0.5 McFarland's standard and inoculated onto the surface of a Mueller-Hinton agar plate. Cefotaxime (30 µg) and cefotaxime-clavulanic acid (30 µg/10 µg) disks were placed 20 mm apart on the agar. Similarly, ceftazidime (30 µg) and ceftazidime-clavulanic acid (30 µg/10 µg) disks were placed 20 mm apart on the plate. Plates were incubated for 24 hours at 35°C. An increase of ≥ 5 mm in the zones around the third generation cephalosporins when tested in combination with clavulanic acid versus the zone size when tested alone was considered to be an indicator of ESBL production [11]. *E. coli* ATCC 25922 was used as an ESBL-negative control whereas *Klebsiella pneumoniae* ATCC 700603 was used as an ESBL-positive reference strain. Detection of methicillin-resistant *Staphylococcus* was performed using cefoxitin disks (30 µg) as described by the National Committee for Clinical Laboratory Standards [10]. The frequencies of positive urine samples and the frequency of positive samples with each agent were compared using the chi-squared test. A P-value of ≤ 0.05 was considered statistically significant.

Results

During 6 months 3,105 urine samples were analyzed and 791 (25.5%) had significant bacteriuria. The frequency of positive urine cultures increased significantly with patient age (Table 1). Overall, the two older patient age groups accounted for 73% of the total isolates. Of the 791 isolates, 623 (78.8 %) were

Table 1. Frequencies of positive urine cultures based on patients' age

Age (in years)	Samples	Positive samples (%)	P
50-60	634	101 (15.9%)	NS
61-70	1002	162 (16.2%)	NS
71-80	927	318 (34.3%)	< 0.05
≥ 81	542	210 (38.7%)	< 0.05
Total	**3105**	**791 (25.5%)**	

P-values (chi-square) are based on comparisons between age groups. NS, not significant.

Gram-negative and 168 (21.2 %) were Gram-positive. The most frequent pathogen was *E. coli* (47.3%), followed by *E. faecalis* (13.6%), *K. pneumoniae* (11.9%), *Proteus mirabilis* (6.3%), *P. aeruginosa* (3.5%), *Morganella morganii* (3.2%), and *Staphylococcus spp.* (4.5%) (Table 2), which altogether accounted for > 90% of all isolates.

The most prevalent bacterial species, with the exceptions of *K. pneumoniae* and coagulase-negative *Staphylococcus*, differed in their isolation rates among the four patient age groups. *Enterococcus spp.* and *P. mirabilis* were more frequent in the 71–80 and ≥ 81 years age groups. *P. aeruginosa, M. morganii,* and *S. aureus* were more prevalent in the ≥ 81 years age group. The frequency of *E. coli* decreased with patient age and was more prevalent in the 50–60 and 61–70 years age groups.

Stratification of the susceptibility results based on patient age detected differences among the subgroups. The susceptibility of *E. coli* to beta lactams, ciprofloxacin, and aminoglycosides declined progressively with increasing patient age (Table 3).

E. coli showed low susceptibility rate to ampicillin (34.0 %), ampicillin sulbactam (50.5 %), first-generation cephalosporins (52.9 %), trimethoprim-sulfamethoxazole (51.6 %), and ciprofloxacin (52.7 %). The most active antibiotics against *E. coli* were imipenem (100 %), ertapenem (99.5 %), amikacina (99.5 %), fosfomicina (97.6 %), nitrofurantoin (95.2 %), and piperacillin tazobactam (90.9 %). Of the 374 *E. coli* isolates, ESBL production was observed in 57 (15.2 %). Overall coresistance rates were as follows: ciprofloxacin, 70.2%; trimethoprim sulfamethoxazole, 68.4%; gentamicin, 26.3%; nitrofurantoin, 5.3%; fosfomycin, 1.8%; and amikacin, 1.8 %.

The antimicrobial susceptibility profiles of the main uropathogen isolates are shown in Table 4. The overall susceptibility rates of Gram-negative uropathogens were low with ampicillin (25.8%), ampicillin sulbactam (45.1%), cephalotin (47.4%), trimethophrim sulfamethoxazole (51.0%), ciprofloxacin (53.3%), nitrofurantoin (66.1%), and gentamicin (79.9%). Acceptable but suboptimal levels were detected with third generation cephalosporins (84.1%). The frequencies of ESBLs in *K. pneumoniae,* and *P mirabilis* were 22.3%, and 8% respectively. The

Table 2. Percentage of uropathogen isolates for each patient age group

Organism	Age group:50-60 (n = 101)	Age group:61-70 (n = 162)	Age group:71-80 (n = 318)	Age group:≥ 81 (n = 210)	All age groups (n = 791)
Escherichia coli	55.4 [a]	54.9 [a]	48.1 [a]	36.2	47.3
Enterococcus spp.	10.9	11.1	13.5	17.1 [a]	13.6
Klebsiella pneumoniae	7.9	13.6	13.2	10.5	11.9
Proteus mirabilis	3.0	3.1	5.7	11.4 [a]	6.3
Pseudomonas aeruginosa	2.0	2.5	2.2	7.1 [a]	3.5
Morganella morganii	3.0	2.5	1.6	6.2 [a]	3.2
Staphylococcus aureus	1.0	1.2	2.5	3.8	2.4
Coagulase-negative *Staphylococcus*	2.0	2.5	2.2	1.9	2.1
Other Gram-negative[b]	9.9	5.5	7.9	3.8	6.6
Other Gram-positive[c]	4.9	3.1	3.1	1.9	3.0

[a] $p < 0.05$ (comparison between age groups); [b] Other Gram- negative category was composed of 17 *Enterobacter spp*, 15 *Citrobacter spp*, 8 *Providencia spp*, 6 *Proteus spp. other than P. mirabilis*, 4 *Klebsiella oxytoca*, and 2 *Serratia marcescens*; [c] Other Gram- positive category was composed of 15 *Streptococcus agalactiae*, 6 *Streptococcus viridians*, and 3 *Corynebacterium spp*.

Table 3. Percentage of susceptibility in 374 *E. coli* isolates to various antibiotics according to the age of the patients

N	Age category	AMN	AMS	CEF	PTZ	ESC	ERT	IMI	TMS	NIT	FOS	CIP	GEN	AKN
56	50-60	44.7	57.2	60.7	98.7	87.5	100	100	53.6	94.7	98.2	62.5	87.5	100
89	60-70	41.6	55.1	59.6	92.1	88.8	100	100	51.7	95.5	97.8	58.6	87.7	100
153	70-80	31.5	45.8	49.9	90.2	84.3	99.3	100	52.3	95.4	97.4	48.6	81.7	99.3
76	≥ 81	22.4	50.0	47.3	88.2	79.9	98.7	100	48.7	94.8	97.4	46.1	76.3	98.7
374	All ages	34.0	50.5	52.9	90.9	84.8	99.5	100	51.6	95.2	97.6	52.7	82.4	99.5

AMN, ampicillin; AMS, ampicillin sulbactam; CEF, cephalothin; PTZ, piperacillin-tazobactam; ESC, extended-spectrum cephalosporins (cefotaxime-ceftazidime); ERT,ertapenem; IMI, imipenem; TMS, trimethoprim sulfamethoxazole; NIT, nitrofurantoin; FOS, fosfomycin; CIP, ciprofloxacin; GEN, gentamicin; AKN, amikacin highest activities against Gram-negative bacteria were found with imipenem (99.0%), amikacin (98.1%), ertapenem (94.2%), fosfomycin (90.7%), and piperacillin-tazobactam (90.1%).

The susceptibility rates of *Enterococcus spp.* to ampicillin and fosfomycin were high (95.4% and 97.2%, respectively), particularly when compared with that to ciprofloxacin (58.3%)

The susceptibility rates of *Streptococcus agalactiae* to ampicillin and levofloxacin were 100% and 86.7%, respectively. The rate of methicillin-resistant *Sthaphylococcus aureus* was 36.8% and that of Coagulase-negative staphylococci 52.9%. The susceptibility rates of *Staphylococcus spp.* to fosfomycin and trimethoprim sulfamethoxazole were high (97.2% and 94.3%, respectively). The susceptibility to nitrofurantoin was 100% for *Enterococcus spp.* and *Staphylococcus spp.*

Discussion

Knowledge of the etiological agents involved with UTIs and their antimicrobial resistance patterns in specific geographical locations may help clinicians to select appropriate antimicrobial treatments. The present study determined the distribution and antimicrobial susceptibility profiles of bacterial species isolated from 3105 urinary samples collected from community patients (males > 50 years old) who lived in an urban area of Buenos Aires.

In agreement with previous studies, the present investigation found that the frequency of positive urine cultures increased with patient age [12-14]. In the present study, the most frequently isolated organism was *E. coli,* which accounted for 47.3% of positive samples. *Enterococcus spp.* was the second most common organism, followed by *K. pneumonia,* and *P. mirabilis*. The proportions of the different bacterial species isolated were similar to those described in several previous studies [13,15-16]. However, the data stratification based on patient age showed that the *E. coli* isolation rates tended to be lower in males aged > 71 years, whereas *Enterococcus spp.*, *P. mirabilis,* and *P. aeruginosa* were more prevalent in this group.

Uncomplicated UTI is one of the most common reasons for prescribing antimicrobials [17]. However, the overuse of antibiotics, particularly broad-spectrum antibiotics, increases the risk of promoting resistance to particular drugs. The present study documented a remarkably high resistance to ciprofloxacin, trimethoprim-sulfamethoxazole, and cephalosporins including third-generation cephalosporins. ESBL in uropathogens isolated from the community is cause for concern due to the enormous potential for multidrug resistance from strains that produce these enzymes, which could lead to failure of empirically-administered therapies and development of complicated UTIs. [18-19]. The Infectious Diseases Society of America guidelines suggest that 10–20% resistance warrants a change in the recommended antibiotic used as the first-line therapy [7]. Piperacillin tazobactam, fosfomycin, ertapenem, imipenem, and amikacin were effective against > 90% of the Gram-negative isolates. In this group of patients, the frequency of Gram-positive bacterial isolates was

Table 4. Percentage of susceptibility in 791 community urinary isolates to different antibiotics

Organism	N	AMN	AMS	CEF	PTZ	ESC	ERT	IMI	TMS	NIT	FOS	CIP	GEN	AKN
Escherichia coli	374	34.0	50.5	52.9	90.9	84.8	99.5	100	51.6	95.2	97.6	52.7	82.4	99.5
Klebsiella pneumoniae	94	NR	53.2	57.4	83.0	77.7	97.9	98.9	48.9	12.8	94.7	45.8	75.6	96.8
Proteus mirabilis	50	54.0	72.0	78.0	94.0	92.0	100	100	78.0	0	72.0	74.0	90.0	100
Other Gram-negative [a]	105	NR	NR	NR	85.8	83.8	69.6	95.2	38.1	32.3	65.8	52.4	70.5	93.4
All Gram- negative	623	25.8	45.1	47.4	90.1	84.1	94.2	99.0	51.0	66.1	90.7	53.3	79.9	98.1
Enterococcus spp.	108	95.4	NR	NR	NR	NR	NR	NR	NR	100	97.2	58.3	NR	NR
Staphylococcus spp.	36	0	55.6	55.6	55.6	NR	NR	NR	94.3	100	97.2	40.0	45.7	NR
Streptococcus agalactiae	15	100	NR	NR	NR	100	NR	NR	NR	NR	NR	NR	NR	NR
Other Gram-positive [b]	9	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

AMN, ampicillin; AMS, ampicillin sulbactam; CEF, cephalothin; PTZ, piperacillin-tazobactam; ESC, extended-spectrum cephalosporins (cefotaxime-ceftazidime); ERT,ertapenem; IMI, imipenem; TMS, trimethoprim sulfamethoxazole; NIT, nitrofurantoin; FOS, fosfomycin; CIP, ciprofloxacin; GEN, gentamicin; AKN, amikacin; NR, Susceptibility test not reported.

[a] Other Gram-negative category was composed of 28 *Pseudomonas aeruginosa*, 25 *Morganella morganii*, 17 *Enterobacter spp*, 15 *Citrobacter spp*, 8 *Providencia spp*, 6 *Proteus spp. other than P. mirabilis*, 4 *Klebsiella oxytoca*, and 2 *Serratia marcescens;* [b] Other Gram- positive category was composed of 6 *Streptococcus viridians* and 3 *Corynebacterium spp*.

21.2%. However, an effective antimicrobial agent must have activity against all Gram-positive bacteria. Ertapenem and amikacin have poor activity against Gram-positive bacteria while imipenem should be reserved for serious intrahospitalary infections. In the present study, fosfomycin had excellent activity against Gram-positive bacteria and the results were comparable with previous studies [20-23]. It is reasonable to assume that piperacillin-tazobactam has a high activity against ampicillin-susceptible *Enterococcus spp.* and *Streptococcus spp.*, and methicillin-susceptible *Staphylococcus*.

The limitations of our study include the absence of clinical and outcome data describing the types and severity of the urinary tract infections from which the isolates were derived. In addition, it has been hypothesized that all UTIs in men must be considered to be complicated. Therefore, isolates tested for antimicrobial susceptibility may be predominantly from patients for whom previous antimicrobial treatment failed or from patients with other underlying risk factors. It is recognized that performing patient-based studies would be an optimal alternative but would be costly and likely not practical for regional data assimilation [24].

In conclusion, *E. coli* remains a common pathogen isolated from urine samples that are submitted to clinical laboratories for culture, although it is isolated less frequently in males (47.3%). The emergence of ESBLs, in addition to high rates of resistance to fluorquinolones and trimethoprim-sulfamethoxazole, in Gram-negative isolates is a cause for concern. Fosfomycin may be an excellent option for cystitis treatment in patients without risk factors, whereas piperacillin-tazobactam is preferred for the treatment of parenchymatous UTIs, complicated UTIs, and UTIs associated with risk factors. To ensure the optimal selection of antibiotics, physicians should have access to up-to-date information about the local prevalence of antimicrobial resistance.

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