A Comparison of Antimicrobial Susceptibility Profile of Urinary Pathogens for the Years, 1999 and 2003

FA Orrett,[1] GK Davis[1]

ABSTRACT

Urinary tract infection is a common condition worldwide; responsible for significant morbidity in both hospitalized and community patients. The laboratory records, for microbial isolates of infected urine and their susceptibility profiles for the years 1999 and 2003 were retrospectively reviewed and compared. In 2003, there was a significant decline in recovery of Citrobacter *spp compared to 1999. Conversely, the proportion of* K pneumoniae, E coli *and* Enterococci *increased dramatically in 2003, in both practices. For* Proteus vulgaris *and* Proteus mirabilis*, rates of isolation were increased in 2003, in hospital practice and community practice, respectively. Significant changes in antimicrobial susceptibility were also evident. A greater proportion of isolates from both practices were resistant to ampicillin, amoxicillin-clavulanic acid, cefuroxime, ceftazidime and cotrimoxazole in 2003 when compared to 1999. With respect to* E coli, *there were significant increases in prevalence of resistance to cefuroxime and amoxicillin-clavulanic acid. The overall resistance rate for norfloxacin remained relatively low and was unchanged for* E coli. *Continued surveillance of uropathogen resistance trends is important and this information should be communicated to clinicians. The feasibility of using the fluoroquinolones as a first line of therapy in urinary tract infection should be considered.*

Una Comparación del Perfil de Susceptibilidad Antimicrobiana de los Patógenos Urinarios en los Años 1999 y 2003

FA Orrett,[1] G Davis[1]

RESUMEN

La infección del tracto urinario es una condición común a nivel mundial. Esa condición es significativamente responsable de la morbilidad, tanto en los pacientes hospitalizados como en los no hospitalizados. Los datos de laboratorio en relación con los aislados microbianos de la orina infectada y sus perfiles de susceptibilidad en los años 1999 y 2003, fueron revisados y comparados de manera retrospectiva. En 2003, se produjo un descenso significativo de la recuperación de infecciones por Citrobacter *spp, en comparación con 1999. En contraste con ello, la proporción de* K pneumoniae, E coli *y* Enterococci *en ambas prácticas, aumentó dramáticamente en 2003. En el caso de Proteus vulgaris y Proteus mirabilis, las tasas de aislamiento aumentaron en el año 2003 en la práctica médica hospitalaria y comunitaria respectivamente. También aquí se hicieron evidentes cambios significativos en la susceptibilidad antimicrobiana. Una proporción mayor de aislados de ambas prácticas resultó ser resistente a la ampicilina, la combinación amoxicilina/ácido clavulánico, la ceftazidima y el cotrimoxazol en 2003, en comparación con 1999. Con respecto al* E coli, *hubo aumentos significativos en la prevalencia de la resistencia a la cefuroxima y la asociación amoxicilina/ácido clavulánico La tasa de resistencia general frente a la norfloxacina permaneció relativamente baja y no presentó variaciones frente al* E coli. *La vigilancia permanente de las tendencias de la resistencia a los patógenos es importante, y la investigación así obtenida, debe ser comunicada a los clínicos. Debe considerarse la factibilidad de usar fluoroquinolonas como terapia de primera línea.*

From: Department of Paraclinical Sciences,[1] Faculty of Medical Sciences, The University of the West Indies, Eric Williams Medical Sciences Complex, Champs Fleurs, Trinidad and Tobago, West Indies.

Correspondence: Dr GK Davis, Department of Paraclinical Sciences, Faculty of Medical Sciences, The University of the West Indies, Eric Williams Medical Sciences Complex, Champs Fleurs, Trinidad and Tobago, West Indies. E-mail: gershwindavis@yahoo.com

INTRODUCTION

Bacterial infections of the urinary tract (UTI) whether hospital-acquired or community-acquired, occur in all age groups in both genders, and usually require urgent treatment. In males, the prevalence of UTI is about 0.3%, but increases (13–40%) in the older age group ($\geq$ 65 years) because of

prostatic diseases and urologic manipulations (1–3). Among young men who develop UTI, homosexuality, as a result of exposure of the urethra to micro-organisms (*eg Escherichia coli*) during receptive rectal intercourse, lack of circumcision and human immunodeficiency virus (HIV) infection, are recognized risk factors (4, 5). In fact, the prevalence of UTI increases sharply in both elderly men and women with rates of 15–31% and 17–55% respectively, being reported from many studies (1, 6, 7).

In sexually active women between the ages of 16–35 years, the prevalence of UTI is between 20–50% (8–10), and the major risk factors among this age group appear to be sexual intercourse and the use of contraceptive devices such as the diaphragm and spermicide (11, 12). Among elementary school boys, UTI is rare, but among school girls, it is approximately one percent (13).

Urinary pathogens from hospitalized and community patients have included strains that are resistant to many commonly prescribed antimicrobials. Accurate identification of uropathogens rely heavily on the laboratory, and most clinical laboratories perform primary susceptibility testing to provide therapeutic guidance usually within 24 hours. This 24-hour delay is unacceptable to most clinicians and patients, and so, patients are usually treated without recourse to laboratory guidance and their progress is monitored by their clinical response to therapy. Current thinking in the management of uncomplicated UTI is to use shorter courses of antimicrobial agents. This makes an appropriate empiric choice assume greater importance.

Recent review of the laboratory data at the Eric Williams Medical Sciences Complex (EWMSC) has shown changes in the spectrum of uropathogens and increasing resistance of such pathogens to some commonly prescribed antimicrobial agents. The purpose of this study therefore, is to review the isolates from urinary tract infections and compare their antibiogram in 2003 with that which was documented in 1999.

MATERIALS AND METHODS

The laboratory records for the years 1999 and 2003 were reviewed at the EWMSC. Urine specimens were derived from patients on the wards or from outpatient clinics, general practitioners offices and health centres. Urine samples from patients attending outpatient clinics, general practitioners offices and health centres in the community were all classified as "community practice" isolates, while isolates from inpatients were labelled as "hospital practice" isolates.

The method used in this laboratory had not changed since the commissioning of the hospital in the summer of 1991. Since January 1992, manual record-keeping of antimicrobial profiles of all urinary isolates have been kept. All specimens were examined by microscopy for the presence of leukocytes, erythrocytes, casts and bacteria. Quantitative bacteriologic cultures were performed according to standard laboratory procedures (14). A standard calibrated loop de-

livering 0.001 mL of urine was used to inoculate sheep blood agar and cysteine lactose electrolyte deficient agar. These plates were incubated aerobically at 37°C for 18 – 24 hours, and colony counts were expressed in colony–forming units (CFU) per millilitre (mL) of urine. A midstream ("clean catch") urine specimen containing $ 10^5$ CFU per mL or > 3000 CFU per mL in catheter specimen of a single specie were considered as having significant bacteriuria. Organisms identified were based on Gram stain reaction, colonial morphology and biochemical characterization. Repeated recovery of the same organism from the same patient was considered as a single isolate. Isolates were tested for susceptibilities by the disk diffusion technique, on Mueller–Hinton agar using the following discs and concentrations (in brackets): ampicillin (10 µg), augmentin (amoxicillin – clavulanic acid) (30 µg), ceftazidime (30 µg), gentamicin (10 µg), nalidixic acid (30 µg), norfloxacin (10 µg), tetracycline (30 µg), co-trimoxazole (trimethoprim – sulfamethoxazole) (25 µg), nitrofurantoin (300 µg) and cefuroxime (30 µg). The control organism was *Escherichia coli* ATCC 25922 strain supplied by the Caribbean Epidemiology Centre (CAREC), a branch of the Pan American Health Organization/World Health Organization. Statistical significance of changes was calculated using the chi-squared test and Fisher exact probability test, where appropriate, using the actual numbers.

RESULTS

The number and type of micro-organisms recovered from infected urine from hospital and community patients for the years 1999 and 2003 are shown in Tables 1 and 1a. The

Table 1:   Distribution of causative agents in urinary tract infections in hospital practice, [1]EWMSC, 1999 and 2003.

Micro-organism	1999		2003	
	[2]n	%	n	%
Gram-negative				
Escherichia coli	45	17.3	83	28.5
Klebsiella pneumoniae	19	7.3	37	12.7
Citrobacter spp	63	24.2	11	3.9
Pseudomonas aeruginosa	19	7.3	12	4.1
Enterobacter spp	35	13.5	18	6.2
Proteus mirabilis	21	8.1	19	6.5
Proteus vulgaris	6	2.3	12	4.1
Acinetobacter spp	0	0.0	7	2.4
Providencia spp	1	0.4	0	0
Morganella morganii	0	0.0	2	0.7
[3]Other	1	0.4	2	0.7
Subtotal	210	80.8	203	69.8
Gram-Positive				
Enterococci	12	4.6	29	10.0
Group B Streptococci	6	2.3	8	2.7
Group D Streptococci	2	0.8	13	4.5
[4]CoNS	26	10.0	10	3.4
[5]*S aureus*	2	0.8	4	1.4
[6]*S saprophyticus*	1	0.4	3	1.0
[7]Other	1	0.4	5	1.7
Candida spp	1	0.4	16	5.5

Subtotal	51	19.2	88	30.2
Total	**261**	**100**	**291**	**100**

[1]EWMSC = Eric Williams Medical Sciences Complex; [2]N = total isolate; [3]Other = Non-typhoidal salmonella, *Serratia marcescens*, Acinetobacter spp. [4]CoNS = coagulase-negative staphylococci; [5]*S aureus = Staphylococcus aureus;* [6]*S saprophyticus = Staphylococcus saprophyticus;* [7]Other = Group A streptococci, Corynebacterium spp.

Table 1a: Distribution of causative agents in urinary tract infections in community practice at the EWMSC, 1999 and 2003

	1999		2003	
Micro-organism	[2]n	%	n	%
Gram-negative				
Escherichia coli	157	31.5	193	33.0
Klebsiella pneumoniae	8	1.6	78	13.4
Citrobacter spp	100	20.1	48	8.2
Pseudomonas aeruginosa	13	2.6	11	2.0
Enterobacter spp	63	12.7	54	9.2
Proteus mirabilis	38	7.6	64	11.0
Proteus vulgaris	5	1.0	2	0.3
Acinetobacter spp	1	0.2	3	0.5
Providencia spp	3	0.6	0	0
Morganella morganii	1	0.2	2	0.3
[3]Other	0	0	2	0.3
Subtotal	389	78.2	457	78.2
Gram-Positive				
Enterococci	22	4.4	30	5.1
Group B streptococci	19	3.8	10	1.7
Group D streptococci	1	0.2	6	1.0
CoNS	37	7.4	42	7.2
[4]*S aureus*	19	3.8	17	3.0
[5]*S saprophyticus*	7	1.4	19	3.3
Candida spp	0	0	1	0.2
[6]Other	4	0.8	2	0.3
Subtotal	109	21.0	127	21.8
Total	**498**	**100**	**584**	**100**

[1]EWMSC = Eric Williams Medical Sciences Complex; [2]N = total isolate; [3]Other = Alkaligenes spp. *S aureus = Staphylococcus aureus;* [5]*S saprophyticus = Staphylococcus saprophyticus.* [6]Other = Group A streptococci, Corynebacterium spp.

Gram – negative enteric organism, *E coli,* was the predominant isolate in both practices for both years. The rate of isolation of *Citrobacter* species from hospital and community practices fell sharply from 24.2% in 1999 to 3.9% in 2003 ($p < 0.001$). A similar decrease in recovery rate was also evident in community practice (20.1% in 1999 to 8.2%) ($p < 0.001$). The rate of isolation of *K pneumoniae* in both practices in 2003 was relatively stable, but when compared with 1999, the rates were significantly increased, 7.3% *vs* 12.7% ($p < 0.001$) for hospital practice isolates and 1.6% *vs* 13.4% ($p < 0.001$), for community isolates, respectively. Among the Gram – positive bacteria, Enterococci were the major isolates

in both hospital and community practices in 1999 (4.6 *vs* 4.4) and 2003 (10.0 *vs* 5.1), respectively. The rates of isolation of other organisms remain relatively stable during both periods, except for Enterobacter species that showed a fall in isolation between 1999 and 2003 among hospital patients.

The proportion of all micro-organisms recovered from infected urine that were resistant to various antimicrobials in hospital and community practices are shown in Table 2. Both

Table 2: Prevalence of resistance among causative organism of urinary tract infection to various antimicrobial agents at the [1]EWMSC, 1999 and 2003

	Community 1999 [2]n = 498	Practice 2003 n = 584	Hospital 1999 n = 260	Practice 2003 n = 291
Number of organisms				
Resistant to antimicrobials	**Number (%)**			
Ampicillin	273 (54.9)	509 (87.1)	144 (55.4)	265 (91.0)
Augmentin[3]	79 (15.9)	180 (30.8)	59 (22.7)	200 (69.0)
Cefuroxime	118 (23.7)	438 (75.0)	93 (35.8)	169 (58.1)
Ceftazidime	167 (33.5)	234 (40.0)	105 (40.4)	189 (64.9)
[3]Co-trimoxazole[4]	167 (33.5)	428 (73.3)	49 (18.8)	84 (28.7)
Tetracycline	176 (35.3)	233 (39.9)	104 (40.0)	175 (60.1)
Nitrofurantoin	84 (16.9)	NT	42 (16.2)	NT
Nalidixic acid	143 (28.7)	NT	75 (28.8)	NT
Norfloxacin	46 (9.2)	58 (19.9)	15 (5.8)	38 (13.0)
Ofloxacin	*NT	98 (16.8)	NT	24 (8.2)
Ciprofloxacin	NT	101 (17.3)	NT	28 (9.6)
Gentamicin	25 (5.0)	NT	43 (16.5)	NT

[1]EWMSC = Eric Williams Medical Sciences Complex; [3]N = total number of isolates; [2]Augmentin = amoxicillin – clavulanic acid; *NT = not tested; [4]Co-trimoxazole = trimethoprim-sulfamethoxazole.

community-practice and hospital-practice uropathogens showed significant increases in resistance to ampicillin, amoxicillin-clavulanic acid, cefuroxime and co-trimoxazole for both 1999 and 2003. Although resistance rates were relatively low for norfloxacin, resistance among 1999 community isolates rose steadily from 9.2% to 19.9% in 2003. A similar trend was also observed among 1999 hospital isolates (5.8%) and 2003 isolates (13.0%). Prevalence rates were stable for the other drugs.

Because *E coli* was the principal isolate from infected urine in both practices, susceptibility of strains of this specie are shown in Table 3. There were significant increases in prevalence of resistance ($p < 0.001$) to cefuroxime and augmentin among isolates from both practices during the study period. Susceptibility to co-trimoxazole was relatively stable in community practice, but decreased significantly from 1999 to 2003 in hospital practice ($p < 0.001$). There were no substantial changes in susceptibility to gentamycin and nalidixic acid among isolates during the study period. Similar observations were noticed for tetracycline among hospital practice strains, but among community strains, the prevalence of susceptibility was significantly reduced ($p < 0.001$).

Table 3:   Proportion of urinary *Escherichia coli* resistant to various antimicrobials at the [1]EWMSC, 1999 and 2003

Significance 1999 *vs* 2003		Community Practice 1999 157 1999	Practice 2003 193 2003	Number of *E coli* % *E coli* resistant to	Hospital 1999 45 1999	Practice 2003 83 2003	Significance 1999 *vs* 3002	
X^2	*P* - value						X^2	*P* - value
4.85	< 0.05	71	56	Ampicillin	76	62	4.58	< 0.05
20.7	< 0.001	12	40	Augmentin[2]	13	31	9.44	< 0.001
21.17	< 0.001	43	75	Tetracycline	67	59	1.37	NS
0.25	** NS	25	22	Co-trimoxazole[3]	71	30	33.62	< 0.001
1.41	NS	26	19	Nalidixic acid	22	12	3.54	NS
0.65	NS	9	6	Gentamycin	13	12	0.046	NS
10.98	< 0.001	9	27	Cefuroxime	38	61	10.58	< 0.001
–	–	9	NT	Nitrofurantoin	9	NT	–	–
0.48	NS	12	9	Norfloxacin	18	8	4.42	NS
–	–	*NT	5	Ofloxacin	NT	4	–	–
–	–	NT	4	Ciprofloxacin	NT	8	–	–

[1] EWMSC = Eric Williams Medical Sciences Complex;   [2] Augmentin = amoxicillin – clavulanic acid;
[3] Co-trimoxazole = trimethoprim- sulfamethoxazole;   *NT = not tested; **NS = not significant.

DISCUSSION

Urinary tract infection is a common condition worldwide and the epidemiology and pattern of antimicrobial resistance varies from region to region and may be different depending on whether it occurs in the community or in hospital. It has been advocated that there should be surveillance of the bacterial spectrum and resistance pattern of uropathogens on both a global and local level (18). All isolates that were recovered in our laboratory were considered in this study, and the majority caused uncomplicated urinary tract infection; there being no recent instrumentation or antimicrobial treatment, and no known functional or anatomic abnormalities of the urinary tract.

The present study revealed that members of the *Enterobacteriaceae* family were the predominant bacterial pathogens of community-acquired (76%) and hospital-acquired (69.7%) urinary tract infections, a pattern seen in reports from both developed and other developing countries (1, 15–17). *E coli,* K *pneumoniae* and *Citrobacter* species were the most frequent isolates, and the recovery rates of these organisms from hospital practice were significantly more in 2003 than in 1999. Among community strains of *K pneumoniae* a similar increase was noticed in 2003 when compared to isolates in 1999. *E coli, Klebsiella pneumoniae* and *Proteus mirabilis* were the most frequent gram – negative isolates in hospital and community practices in 2003, respectively.

A large body of literature reflecting studies in various communities has found that *E coli* was by far the most common cause of UTI and the present study agrees with these findings. The top seven pathogens isolated from hospital patients accounted for 72.5% of all isolates in 2003 and the rank order was *E coli,* 28.5%; *Klebsiella pneumonia,* 12.7%; *Enterococci,* 10%; *Proteus mirabilis,* 6.5%; *Entero-*

bacter spp, 6.2%; *Group D streptococci,* 4.5% and *Proteus vulgaris,* 4.1%. The SENTRY Antimicrobial Surveillance Program that reviewed 2780 uropathogens from North America, Europe and Latin America (21) showed that the top seven pathogens accounted for 90% of all isolates, and the top three organisms were the same as in this study.

Changes were detected in the resistance of certain antimicrobials frequently used in the empirical treatment of UTI in the study hospital. Compared to 1999, the prevalence of resistance to all the antimicrobials tested among community practice and hospital practice uropathogens increased in 2003. Continued increase in resistance among bacteria from any source could have serious implications for a developing country such as ours, where this may lead to an increase in the healthcare budget as healthcare providers seek more high-powered antimicrobials with its attendant higher cost (2, 20, 22).

There were twice as many isolates from community practice compared to hospital practice for both years. For community-acquired cases, the empiric choice of antimicrobial is essential since the patient may not be seen again after the initial presentation. In a study from Senegal (23), it was reported that antimicrobial resistance among *Enterobacteriaceae* isolated from infected urine of community-practice patients, was steadily increasing. Resistance rates of 77.3%, 55% and 34.7% for ampicillin, co-trimoxazole and amoxicillin-clavulanic acid, were seen respectively. A similar pattern of resistance was observed in this study among community practice isolates, which increased from 54.8% in 1999 to 87.2% in 2003 for ampicillin, 15.9% in 1999 to 30.8% in 2003 for amoxicillin-clavulanic acid and 33.5% in 1999 to 73.3% in 2003 for co-trimoxazole. The researchers in Senegal suggested that fluoroquinolones be used as first line therapy in their population since it had the lowest level of

resistance of 13.3%. In this study norfloxacin not only had the lowest prevalence of resistance in both practices in both years, but remained relatively stable during the study period.

Among *E coli* strains, there was a significant increase in resistance to amoxicillin-clavulanic acid and cefuroxime for both community and hospital practices in 2003 compared to 1999 ($p < 0.001$). Resistance to tetracycline in 2003 increased significantly for *E coli* in community practice only ($p < 0.001$). An interesting finding was the fact that the resistance to ampicillin decreased significantly for both community and hospital practice and co-trimoxazole showed a significant decrease in resistance for hospital practice. The reason for this is not entirely clear, but may be a reflection of the changing patterns of prescribing of these common antibiotics due to the laboratory's frequent discussions with the clinicians as to the empiric choices of antimicrobial therapy and the strict adherence to the policy of restrictive reporting by the hospital microbiologist. The results of this study are similar to other reports in the literature. A report from Tunisia (24) showed that from among 6994 urinary *E coli* strains, 33.6% were resistant to amoxicillin-clavulanic acid; a finding similar to the result of 31% from the present study. About 37.3% of *E coli* strains were resistant to co-trimoxazole compared to 30% in 2003 in this study.

One of the issues pertinent to developing countries such as Trinidad and Tobago is providing economical care while trying to minimize the risk of contributing to the development of drug resistance in organisms isolated from clinical specimens. This study reinforces the need for on-going local surveillance of pathogens resistance trends and education of clinicians and general practitioners about the determinants of resistance such as patterns of antibiotic usage, which has a direct impact on the management of urinary tract infection. The feasibility of using the fluoroquinolones as a first line of therapy should be considered.

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