The Changing Patterns of Antimicrobial Susceptibility of Urinary Pathogens in Trinidad

F A Orrett, S M Shurland

ABSTRACT

Objective: The prevalence of antimicrobial resistance in urinary pathogens is increasing worldwide. Accurate bacteriologic records of culture results may provide guidance on empirical therapy before sensitivity patterns are available. We report the changing antibiograms of pathogens associated with urinary tract infections (UTI) over a 4-year period at a newly commissioned hospital complex diagnostic laboratory in Trinidad.

Methods: From January 1992 to December 1995, kept records of antibiograms of all urinary pathogens isolated were examined. Samples were derived from hospital sources (wards and out-patient clinics) and general practice sources (health centers and general practitioners). Quantitative bacteriologic cultures were performed according to standard laboratory procedures, and identification of isolates were based on Gram reaction, morphology and biochemical characteristics. Significant bacteriuria was defined as the presence of greater than 100,000 organisms per mL of a midstream urine specimen or more than 3000 bacteria per mL in a catheter specimen of a single specie. Antimicrobial sensitivities were done using the following antibiotics: norfloxacin, ampicillin, tetracycline, nitrofurantoin, gentamicin, co-trimoxazole (sulfamethoxazole-trimethoprim), trimethoprim, nalidixic acid, cephalexin and augmentin (amoxicillin-clavulanic acid). Control organism was *E coli* NCTC 10418 strain.

Results: The total number of specimens for the 4-year period in hospital was 14,181 with an isolation rate of 17%, and a general practice isolation rate of 67% from a total of 5,088 specimens. *E coli* was the most frequent isolate in both hospital (40%) and general practice (30%). There was an increase isolation of *P aeruginosa* from community practice reflecting an increase in home care catheterised male patients. Resistance to tetracycline was most significant in hospital (99%) and general practice (81%). Similar trend was observed for trimethoprim in hospital, and co-trimoxazole in both practices. Resistance to ampicillin, augmentin and cephalexin was relatively stable over the 4-year period.

Conclusion: We conclude that laboratories should encourage accurate bacteriologic record keeping of urinary isolates and their antibiograms to serve as guidance in empirical treatment in UTI. Also, urine microscopy may reduce the number of specimens sent for culture which are not cost-effective.

Keywords: urinary tract infections, uropathogens, urinary antimicrobial resistance, Trinidad

Department of Microbiology/ Pathology
Faculty of Medical Sciences
University of West Indies
St Augustine, Trinidad
West Indies

F A Orrett, MBBS, MS, Dp Bact
Lecturer

NIHERST
College of Health Sciences
EWMSC
Champs Fleurs
Trinidad, West Indies

S M Shurland, MSc
Lecturer

Correspondence to:
Dr F A Orrett

INTRODUCTION

Micro-organisms causing urinary tract infections (UTI) vary in their susceptibility to antimicrobials from place to place and from time to time[1]. Over the past four years, the microbiology laboratory of the Eric Williams Medical Sciences Complex (EWMSC), a 560-bed newly commissioned institution, isolated and reported the antibiotic sensitivities of a large number of urinary pathogens. The data analyses show changes in sensitivity patterns which may reflect alterations in intestinal flora[2] as a result of the changing order of human behaviour which include hospital hygiene practices and use of antimicrobial agents[3]. Accurate up-to-date bacteriological statistical record keeping of culture results may provide guidance on empirical treatment of UTI when therapy must be started before laboratory reports are available. In the absence of this guidance, the initial choice of antibiotics may descend to the level of emotional guesswork. It is not only important that commencement with therapy likely to be effective, but also to recognise failure as soon as possible[4], at which time, laboratory assistance should be sought. This study reports the changing antibiograms of pathogens associated with UTI based on isolates from the microbiology laboratory of EWMSC in Trinidad.

METHODS

The EWMSC is located in the north-western part of the country and is the largest of the 4 major hospitals in Trinidad and Tobago, a country of approximately 1.25 million people, located about 7 miles off the northern coast of Venezuela (South America). The EWMSC houses a 560-bed medical center, including a dental and veterinary hospitals. The medical hospital was opened in the summer of 1991 and the microbiology laboratory commenced the processing of specimens from November of that year. Since January 1992, records of antimicrobials sensitivities of all urinary pathogens isolated have been kept. Urine samples were derived from patients in the wards or attending outpatient clinics. For this investigation, no attempt was made to differentiate between inpatient and outpatient-derived isolates; instead, they were being classified as "hospital isolates". Urine samples were also received from patients attending health centers in the communities as well as those seen by general practitioners. All these isolates were classified as "general practice" isolates.

Quantitative bacteriologic cultures were performed according to standard laboratory procedure[5]. A standard calibrated loop delivering 0.001 mL of uncentrifuged urine was used to inoculate sheep bloody agar and cysteine lactose electrolyte deficient (CLED) agar. These plates were incubated aerobically at 37°C for 18 – 24 hours. The colony count was expressed in colony-forming units per mL of urine. A midstream urine specimen containing more than $10^{(5)}$ bacteria per mL or more than 3000 bacteria per mL in cathether specimen of a single specie were considered as having significant bacteriuria[6]. Identification of organisms was based on Gram reaction, morphology and biochemical characteristics[7]. Isolates were tested for antimicrobial susceptibility by the Kirby-Bauer disc diffusion technique[8] on Mueller Hilton agar using the following discs and concentration: norfloxacin (introduced in 1994) 10 μg, ampicillin 10 μg, tetracycline 30 μg, nitrofurantoin 300 μg, gentamicin 10 μg, co-trimoxazole (sulfamethoxazole-trimethroprim) 25 μg, trimethoprim 5 μg, nalidixic acid 30 μg, cephalexin 30 μg and augmentin (amoxicillin-clavulanic acid) 30 μg. The control organism was *E coli* NCTC 10418 strain.

Statistical analysis of results was by Chi-square test.

RESULTS

Table I depicts the types and numbers of micro-organisms isolated from infected urine from general and hospital practices during the period 1992 –1995. The total number of specimens processed for the entire 4-year period in hospital practice was 14,181 with an average rate of infection of 17%. General practice isolation rate was 67% for a total number of 5,088 specimens over the same period. In general practice (Table I), approximately 40% of all urinary pathogens were by *E coli*, whereas in hospital practice, only about 30% were caused by the same organism.

Staphylococcus aureus and *Enterobacter* species were isolated from 8% of the urine specimens in 1992. They became numerically less important, being isolated in only 1% and 4% of the specimens respectively, in general practice in 1995. This pattern was also similar for hospital practice. The rate of isolation of *Staphylococcus saprophyticus* remained constant in general practice, but an increase was observed in hospital practice from 0% in 1993 to 5% in 1995. *Pseudomonas aeruginosa*, long considered uncommon general practice pathogen, increased in prevalence in general practice rising from 1% in 1992 to 3% in 1995. A similar pattern was seen in hospital practice; *P aeruginosa* was responsible for 3% of urinary infections in 1992 and 7% of infections in 1995. *Proteus mirabilis* and other *Proteus* species remained relatively constant in general practice, but were more frequently recovered in 1993 and 1994.

The proportions of all urinary pathogens resistant to the various antimicrobials in hospital and general practices between 1992 and 1995 are shown in Table II. For isolates of pathogens from both hospital and general practices, there were decreases in sensitivity to all antimicrobial agents tested from 1992 to 1995. While several of the drugs showed good invitro activity, others displayed decreased activities on isolates from both practices. Resistance to tetracycline ranged from 43% in 1992 to 99% in 1995 in general practice and from 48% (1992) to 81% (1995) for hospital practice isolates. A similar pattern was evident for co-trimoxazole and trimethoprim for the same period in hospital practice. Susceptibility to gentamicin and nalidixic acid was better maintained than that of augmentin and cephalexin over the same period.

The susceptibility pattern of *E coli* strains recovered from both hospital and general practices to antimicrobial agents are shown in Table III. *E coli* was less susceptible to cephalexin in hospital practice in 1994 and 1995 than in 1992, while maintaining approximately 50% susceptibility in general practice throughout the period of study. For *E coli* strains from general practice, there was a significant ($p < 0.001$) increase in prevalence of resistance to gentamicin, while for hospital isolates, there was a significant decline ($p < 0.05$) from 1992 to 1994. There was no substantial change in susceptibility to nalidixic acid and norfloxacin (introduced in 1994) of urinary pathogens in both situations to the drugs.

DISCUSSION

In most clinical circumstances, particularly in rural communities in Trinidad and Tobago, laboratory assistance is not readily available. Clinicians must rely on their "best guess" etiologic agent[9], and commence antimicrobial therapy without definitive laboratory diagnosis. In these circumstances, it would be helpful to the clinicians to have some information to guide empirical treatment. Sensitivity of urinary pathogens to antimicrobials are not only influenced by the choice of drug, but by the cost, patient compliance, frequency and route of administration and severity of side affects[10]. The most effective antimicrobial agents in both general and hospital practices were nalidixic acid, gentamicin and augmentin. The least effective in hospital practice in increasing order were cephalexin, ampicillin, trimethoprim, co-trimoxazole and tetracycline. The declining position of ampicillin and cephalosporins (first generation), may be due partly to an increased prevalence of more resistant bacterial species and partly to increasing resistance within bacterial species. Resistance rates in Trinidad ($\simeq$56% unpublished data) and some developing countries[11] (44% in Chile and 40% in Thailand) are in general, higher than in the United States[12] and Southern European countries (3% – 8%)[13,14], and is probably due to indiscriminate use of antimicrobials in the developing countries. The most popularly prescribed drugs for urinary tract infections in general practice were co-trimoxazole, ampicillin and tetracycline. Resistance to these agents are among the highest compared to the other drugs examined over the 4-

Table I – Frequency of isolation of urinary pathogens: 1992 – 1995

Hospital Practice					General Practice			
1992	1993	1994	1995		1992	1993	1994	1995
1154	2705	4937	5385	Number of specimens	472	1333	2116	1167
31	15	13	9	(%) Pathogens	90	67	35	76
1992	**1993**	**1994**	**1995**	**Pathogens (%)**	**1992**	**1993**	**1994**	**1995**
* 30	33	35	32	*E coli*	28	38	41	44
20	21	20	20	*Klebsiella sp*	13	16	15	14
9	8	5	8	*Group B strep*(1)	18	14	14	13
8	5	3	3	*Enterobacter sp*	8	6	3	4
6	8	10	6	*Proteus mirabilis*	5	5	4	5
5	5	5	7	*Enterococci*	4	4	6	5
3	4	6	7	*Pseudononas aerug*(2)	1	2	4	3
4	5	4	1	*Proteus vulgaris*	1	1	3	0
3	4	2	2	*Coag-Neg Staph*(3)	4	4	0	3
3	2	2	3	*Staph aureus*(4)	8	0	2	1
3	0	1	5	*Staph sapro*(5)	5	5	4	5
1	0	1	1	*Proteus spp.*	1	0	0	0
** 0	3	1	1	*Non-enterococci*	3	2	2	1
3	2	5	1	Others	3	2	2	1

* Percentages have been rounded off to the nearest whole number.
(1) *Group B Streptococcus*; (2) *Pseudomonas aeruginosa*; (3) *Coagulase-negative staphylococci*, (4) *Staphylococcus aureus*, *Staphylococcus saprophyticus*; (5) Others; occasional isolates of *Citrobacter* spp, *Group A streptococci. Serratia Marcescens, Acinetobacter spp.*
** No isolates

Table II – Proportions of all urinary pathogens resistant to various antimicrobials: 1992 – 1995

Hospital Practice					General Practice			
1992	1993	1994	1995		1992	1993	1994	1995
* 77	67	67	60	% Pathogen sensitive To all antimicrobials	79	75	70	66
1992	**1993**	**1994**	**1995**	**% Pathogens resistant to:**	**1992**	**1993**	**1994**	**1995**
27	32	18	27	Augmentin(1)	20	25	30	35
0	48	55	38	Ampicillin	18	46	41	42
17	30	27	28	Cephalexin	10	4	20	25
17	14	13	** -	Nalidixic Acid	+ 0	0	0	0
-	-	0	4	Norfloxacin	5	5	4	5
4	9	10	7	Gentamicin	4	9	5	10
19	22	53	47	Trimethoprim	46	36	38	35
53	44	37	71	Co-trimoxazole(2)	23	21	42	60
48	63	73	81	Tetracycline	43	61	76	99
-	-	-	-	Nitrofurantoin	-	-	30	20

* Percentages have been rounded off to the nearest whole number.
(1) Augmentin: amoxicillin – clavulanic acid; (2) Co-trimoxazole: sufamethoxazole-trimethoprim.
** Not tested.
\+ No resistance.

year period (Table II). The resistance to trimethoprim alone was decreasing, while resistance to the composite drug, co-trimoxazole, was on the rise. It is not clear why this was so. However, these high rates are in agreement with other reports[15-17], which also recommend a de-emphasis on reliance of these antimicrobials, although some centers still favour the use of co-trimoxazoles. The multi-resistance in the community may be due in part, to the large numbers of outpatients with chronic in-dwelling urethral Foley catheters who are put prophylactically on antimicrobial therapy[22]. These patients (mean age 69 years) either have out-flow obstruction or incontinence, and who either refuse surgery, are not fit for surgery or are awaiting elective surgery. Catheters are changed once in every six weeks in most places or earlier if complaints of fever, haematuria or acute blockage are made. *P aeruginosa* which was uncommon as a urinary pathogen in general practice in 1992 was more frequently isolated in 1995. This may be due in part to the increase in home-care catheterised male patients with prostatic disease as shown in an earlier study[22]. Since the majority of commonly prescribed antimicrobial drugs are given orally and since the anti-pseudomonal drugs are parenteral agents, eradication of these organisms from infected urine may be difficult due to poor patient compliance. But the changes observed in the overall susceptibility of the urinary pathogen may not be completely attributed to alterations in the different species as evidenced by the commonest urinary pathogen *E coli* (Table III).

In a survey of clinical isolates of *E coli* from various sources in central Europe[19] from 1975 to 1984, there was little change in susceptibility to various antibiotics with time. This was similar to the findings in our study. Presently, most urinary pathogens whether encountered in general or hospital practice remain sensitive to a range of different antibiotics. The carriage of antibiotic-resistant strains in the healthy community should alert us to the fact that antibiotic-resistant strains are not restricted to the hospital environment and that we should be cautious with the use of antimicrobial agents in general practice. Fortunately, although antibiotic resistance may be increasing among urinary pathogens, our study has shown that no patient has been identified with a urinary tract infection that could not be treated because of resistance to all antimicrobial agents.

The study also demonstrated that hospital clinicians' suspicions of urinary infections are less reliable than that of general practice practitioners. Of the 14,181 specimens processed over the 4-year period in hospital practice, only 17% registered infected urines; whereas, in general practice there was a 67% rate of infection from the 5,088 specimens processed for the same period. One possible explanation for the low positive isolation rate in hospital practice may be that most of these patients present with pyrexia and the urine forms part of the septic work up. Although urine culture may be the best method for determining an infected urine specimen (bacteriuria), this procedure is expensive and the 17% bacteriuric episode does not warrant this expense. Perhaps a screening urinalysis using a multi-pad "dipstick" reagent strip[20,21] which can detect bacteriuria (nitrate test) and pyuria (leukocyte esterase test) may help to choose only positive specimens to be sent for culture. One short coming of this study was that we did not correlate urine microscopy (urinalysis) with culture. This may have falsely identified patients with significant bacteriuria who did not have a UTI. Also, since both geographic and temporal variations can be expected in the susceptibility of urinary pathogens, clinical laboratories should keep a continuous record of isolates and their antibiogram.

Table III – The percentage of urinary *E coli* resistant to various antimicrobials: 1992 – 1995

Significnace 1992 vs 1995		Hospital Practice					General Practice				Significance 1992 vs 1995	
		1992	1993	1994	1995		1992	1993	1994	1995		
		105	138	1994	1995	Number of *E coli*	120	342	306	385		
		*75	67	78	71	% Sensitive	71	78	79	76		
X(2)	P	1992	1993	1994	1995	**% *E coli***	1992	1993	1994	1995	X(2)	P
NS	NS	20	24	20	26	Augmentin(1)	20	28	28	25	NS	NS
3.24	< 0.025	33	63	42	44	Ampicillin	47	48	58	48	NS	NS
112.68	< 0.001	11	75	46	78	Cephalexin	45	30	44	45	NS	NS
-	-	17	23	16	-	Nalidixic Acid	3	9	11	6	NS	NS
-	-	** -	-	6	9	Norfloxacin	-	-	3	1	-	-
6.81	< 0.05	26	10	14	13	Gentamicin	3	5	5	19	16.22	< 0.001
NS	NS	24	19	25	22	Trimethoprim	33	20	36	32	NS	NS
7,53	< 0.05	24	8	10	11	Co-trimoxazole(2)	35	20	2	17	19.07	< 0.001
-	-	47	-	-	-	Tetracycline	48	16	22	34	7.88	< 0.001
-	-	-	-	-	-	Nitrofurantoin	-	-	8	11	-	-

* Percentages have been rounded off to the nearest whole number.
(1) Augmentin: amoxicillin acid; (2) Co-trimoxazole: sufamethoxazole-trimethoprim.
** Not tested.
NS: Not significant.

ACKNOWLEDGMENT

The authors would like to thank Dr A A Adesiyun for his comments and critical analysis of this manuscript.

REFERENCES

1. Gruneberg RN. Antibiotic sensitivities of urinary pathogens, 1971-1982. J Antimicrobiol Chemother 1984; 14:17-23.
2. Gruneberg RN, Leigh DA, Brumfitt W. Escherichia coli serotypes in urinary tract infection: studies in domicilliary antenatal and hospital practice. In: Urinary Tract Infection. O'Grady F., and Brumfitt W, eds. London: Oxford University Press, 1968:68-79.
3. Gruneberg RN, Smellie JM, Leakey A. Changes in antibiotic sensitivities of fecal organisms in response to treatment in children with UTI. In: Urinary Tract Infections Brumfitt W, Asscher AW eds. London: Oxford University Press 1993:131-6.
4. Garrod LP, O'Grady F. Antibiotic and Chemotherapy 3rd ed. Edinburgh and London: E & S Livingstone, 1973 Chap xxii: 368-84.
5. Baron EJ, Finegold SM, Martin WJ. Organisms encountered in the urinary tract. In: Bailey and Scotts, eds. Diagnostic Microbiology St. Louis CV Mosby, 1990: 253-62.
6. Maskell R. Diagnosis of urinary tract infections, its causes and consequences. In: Urinary tract infection. Current Topics in Infection Series 3. London: Edward Arnold. 1983: 21-41.
7. Cowan ST. Cowan & Steel's Manual for the identification of medical bacteria, 2nd Ed. New York: Cambridge University Press, 1974.
8. Bauer AW, Kirby WMM, Sherris JC, Turok M. Antibiotic susceptibility testing by a standardised single disk method. Am J Clin Pathol 1966; 45:493-6.
9. McAllister TA, Alexander JG, Percival A, Boyce JMH. Part 1: The sensitivities of urinary pathogens – A survey. Post Grad Med J 1971; 47:7-18.
10. Gruneberg RN. Changes in urinary pathogens and their antibiotic sensitivites, 1972-1992. J Antimicrobiol Chemother 1994; 33:1-8.
11. Murray BE, Alvarado T, Kim KH, Vorachit M, et al. Increasing resistance to trimethoprim sulfamethoxazole among isolates of Escherichia coli in developing countries. J Infect Dis 1985; 152:1107-12.
12. Mathewson JJ, Murray BE. Plasmid-mediated resistance to trimethoprim-sulfamethoxazole in Salmonella krefeld strains isolated in the United States. Antimicrob Agents Chemother 1983; 23:495-6.
13. Montefiore D, Ojeniyi A, Rotowa N, Adeyani-Dore F. Role of new antibiotics in tropical developing countries. In: Current chemotherapy and Immunotherapy. Proceedings of the 12th International Congress of Chemotherapy. Florence, Italy, 1981 Vol 1 Paris P & Grassi, GG, eds. 1981 319-21. American Society for Microbiology, Washington DC.
14. Cross AS, Opal S, Kopecko DJ. Progressive increase in antibiotic resistance of Gram-negative bacterial isolates. Walter Reed Hospital, 1976-1980: Specific analysis of gentamicin, tobramycin and amikacin resistance. Arch of Int Med 1983:2075-80.
15. Kocabiyik S, Akalin E, Alaeddinoglu (1987). Aminoglycoside - resistance profile of gentamicin resistant strains of Enterobacteriaceae and pseudomonas. In Progress of Antimicrobial and Anti-cancer Chemotherapy Proceeding of the 15th International Congress of Chematherapy, Istanbul. 1987, Vol 1 (Berkarda B & Kuemmerle HP., Eds. 777- 9. Ecomed, Landsberg/Lech, Federal Republic of Germany.
16. Young HK, Jesudason MV, Keshi G, Amyes SGB. Trimethoprim resistance amongst urinary pathogens in South India. J Antimicrob Chermother 1986; 17: 615-21.
17. Lamikanra A, Ndap RB. Trimethoprim resistance in urinary tract pathogens in two Nigerian hospitals. J Antimicrob. Chemother 1989; 3:151-4.
18. Hooton TM. Urinary infection in women: The best drugs. JAMA 1995; 273:41-5.
19. Kresken M, Weidemann B. Development of resistance in the past decade in Central Europe. J Antimicrob Chemother 1986; 18:235-42.
20. Leo SY, Scottolini AG, Luangphinith S, et al. Urine screening strategy employing dipstick analysis and selective culture: an evaluation. Am J Clin Pathol 1994; 81:634-42.
21. Sewell DL, Bust SP, Gabbert NJ, et al. Evaluation of the chemstrip 9 as a screening test for urinalysis and urine culture in men. Am J Clin Pathol 1985; 83:740-3.
22. Orrett FA, Premanand N. Bacteriuria in outpatients with chronic indwelling urethral catheters. Med Sci Res 1993; 21:333-4.