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Original Article

Pathogen Occurrence and Antimicrobial Susceptibility of Urinary Tract Infection Cases during a 20-Year Period (1983 - 2002) at a Single Institution in Japan

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SUMMARY: Urinary tract infections are one of the most common infectious diseases diagnosed in outpatients as well as in hospitalized patients. Recently, urinary tract infections have become more complicated and difficult to treat. Therefore, the present study analyzed the occurrence and antimicrobial susceptibility of uropathogens isolated at Kobe University Hospital between 1983 and 2002. This study was performed with three patient groups: urology inpatients, urology outpatients, and inpatients of other departments. During the 20-year study period, we studied 15,925 urine isolates obtained from those patients who were diagnosed with urinary tract infection. Overall, *Enterococcus faecalis* was the most frequently isolated pathogen, followed by *Pseudomonas aeruginosa* and *Escherichia coli*. The frequency of *Staphylococcus aureus* increased over time, corresponding to an increase in the occurrence of methicillin-resistant *S. aureus* (MRSA). In addition, the rate of isolation of *Serratia marcescens* also increased over time, especially among patients with urinary tract catheters. Our results demonstrate that the uropathogens isolated at a single institution have shown a trend of increasing resistance to various classes of antimicrobial agents. In addition, serious problems should be anticipated in the treatment of multidrug-resistant *P. aeruginosa*, fluoroquinolone-resistant *E. coli*, and arbekacin-resistant MRSA.

INTRODUCTION

Urinary tract infection (UTI) is one of the most common reasons for adults to seek medical consultation and is also one of the most frequently occurring nosocomial infections (1). Since isolated pathogen frequency and antimicrobial resistance rates can vary dramatically, even within the same nation, certain potentially resistant strains, such as those causing UTI among hospitalized patients, require worldwide surveillance of the most common causative species (2-9).

Recently, the incidence of nosocomial UTI has been increasing and its treatment has become more complicated because of the appearance of pathogens with increasing resistance to antimicrobial agents (10). Nosocomial UTI consists almost exclusively of complicated UTI caused by a wide range of bacteria. Empirical antimicrobial therapy must be initiated when urosepsis is likely to develop or when the patient's general status is deteriorating. Such conditions are likely to improve significantly with the immediate use of appropriate antimicrobial agents.

Several studies have demonstrated that the geographical variability of pathogen occurrence in cases of UTI among inpatient and outpatient populations is limited by the predominance of Gram-negative species, usually *Enterobacteriaceae* and particularly *Escherichia* and *Enterobacter* spp., in various regions of the world (5,6). In general, however, *Pseudomonas aeruginosa* and *Enterococcus* spp. are usually ranked among the top five pathogens and the resistance patterns of these organisms can vary significantly between hospitals, countries, and continents (11-13).

In order to treat UTI with a rational empirical therapy, it is necessary to identify the bacterial spectrum and antimicrobial susceptibilities of the uropathogens. Because this spectrum may vary among hospitals and in terms of UTI incidents, each institution must examine and assess its own facilities. Such an evaluation is useful for the establishment of indicators of hospital-wide spread of infection as well as for defining a hospital's antimicrobial policy. Herein, we studied the chronological transition and antimicrobial susceptibilities of bacteria isolated from the urine of patients with UTI over a 20-year period.

MATERIALS AND METHODS

Bacterial isolates: A total of 15,925 bacterial UTI isolates were isolated from patients at Kobe University Hospital between 1983 and 2002. The isolates were divided into the following three groups: isolates from urology inpatients, isolates from urology outpatients, and isolates from inpatients of other departments. We studied isolated strains with more than 10^4 colony forming units/ml urine and excluded repeat samples from the same infected patient. Upon receipt at the monitoring laboratory, isolates were subcultured onto blood agar to ensure viability and purity. Confirmation of species identification was performed with the Vitek™ system (bioMérieux, St. Louis, Mo., USA) or conventional methods

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as required. Frequencies of isolates were calculated for the following 5-year periods: 1983 - 1987; 1988 - 1992; 1993 - 1997; and 1998 - 2002.

Susceptibility testing: Antimicrobial susceptibility testing was performed and results were interpreted using the reference broth microdilution method as described by the National Committee for Clinical Laboratory Standards (NCCLS) M7-A5 and M100-S12 (National Committee for Clinical Laboratory Standards In: Methods for dilution antimicrobial susceptibility test for bacteria that grow aerobically. Approved standard M7-A5 and M100-S12, NCCLS, Wayne, Pa., USA) in 1987-2002 and the KB disc method in 1983-1986. The minimal inhibitory concentration (MIC) was defined as the lowest antimicrobial concentration that totally inhibited bacterial growth. We tested bacterial strains against the following antimicrobial agents: penicillin G, piperacillin, cefmetazole, ceftazidime, erythromycin, amikacin, gentamicin, clindamycin, minocycline, imipenem/cilastatin, ofloxacin, arbekacin, and vancomycin. Other compounds were also tested, however, these data are not dealt with here because of their limited potency. For quality control, *E. coli* ATCC 25922, *S. aureus* ATCC 29213, *P. aeruginosa* ATCC 27853, and *E. faecalis* ATCC 29212 were used. The antimicrobial susceptibilities of the five most frequently isolated bacteria (*Escherichia coli*, *P. aeruginosa*, *Serratia marcescens*, *Enterococcus faecalis*, and *Staphylococcus aureus*) were summed for each of the 5-year periods indicated above.

Statistical analysis: Statistical analysis was conducted using Student's *t* test with the StatView software package (Abacus Concepts, Berkeley, Calif., USA). The relative frequencies of isolates and the susceptibility of isolated strains to antimicrobial agents were analyzed in each period. Statistical significance was established at the 0.05 level.

RESULTS

Isolation rates of UTI bacteria for urology inpatients: The isolation rate for *P. aeruginosa* in each of the 5-year periods ranged from 13.1 - 20%. During the 20-year period of the study, *P. aeruginosa* was ranked as the most frequently isolated pathogen among Gram-negative bacteria. The isolation rate for *E. coli* in each of the 5-year periods ranged from 4.4 - 9.2%. In 1998 - 2002, *E. coli* was ranked as the third most frequently occurring pathogen isolated from the urine of urology inpatients (Table 1). The isolation rate for *S. marcescens* in each of the 5-year periods ranged from 4.7 - 11.7%. In 1993 and 1994, *S. marcescens* was ranked as the most frequently isolated pathogen among Gram-negative bacteria (data not shown). The isolation rate for *S. aureus* in each of the 5-year periods ranged from 1.9 - 6.6% and showed an increasing trend in the most recent 5 years ($P < 0.05$). In 1998 - 2002, *S. aureus* was the sixth most frequently isolated pathogen. The rate of methicillin-resistant *S. aureus* (MRSA) showed a similar increasing trend. In 2002, it accounted for 82.2% of the entire *S. aureus* population (data not shown). *E. faecalis* was one of the most frequently isolated bacteria during the 20-year period, with an isolation rate in each of the 5-year periods ranging from 13.3 - 21%. *E. faecalis* was ranked as the most frequently isolated pathogen in 9 years (data not shown). *E. faecium* was isolated approximately half as often as *E. faecalis*.

Isolation rates of UTI bacteria for urology outpatients: The isolation rate for *E. coli* in each of the 5-year periods ranged from 22.2 - 37.9%. *E. coli* was ranked as the most frequently isolated pathogen in this patient group (Table 2). The isolation rate for *P. aeruginosa* in each of the 5-year periods ranged from 6.7 - 11% and increased during the last 5-year period ($P < 0.05$). *Klebsiella pneumoniae* was isolated more often than *S. marcescens* during all periods with an isolation rate ranging from 6.2 - 8.5%. The isolation rate for *S. aureus* in each of the 5-year periods ranged from 1.5 - 6% and has been increasing recently from a rate of 1.5% for 1983 - 1987 to a rate of 6% for 1998 - 2002 ($P < 0.05$). *E. faecalis* was the second most frequently isolated pathogen after *E. coli* and was ranked first in 2000 (data not shown). The isolation rate for *E. faecalis* in each of the 5-year periods ranged from 8.5 - 18.6% and recently increased to 18.6% for 1998 - 2002 ($P < 0.05$). *Streptococcus* spp. and *Staphylococcus*

Table 1. Prevalences (%) of isolated urine pathogens among the urology inpatients

	1998 - 2002	1993 - 1997	1988 - 1992	1983 - 1987
P. aeruginosa	20	13.4	18.5	13.1
E. coli	9.2	4.8	4.6	4.4
S. marcescens	6.8	11.7	4.7	5.2
Enterobacter spp.	3.8	2.4	4.7	6
K. pneumoniae	3.7	2.3	3.4	4
P. mirabilis	2.4	0.9	0.2	1.7
K. oxytoca	1.4	0	0	0
Other *Pseudomonas* spp.	1.6	3.4	6.8	10
Citrobacter spp.	1.1	3.5	2.5	4.7
Other GNR	4.5	11.6	12.6	9.3
E. faecalis	15.7	13.3	14.7	21
E. faecium	7.6	9.2	10	8
S. aureus	6.6	5.3	4.6	1.9
S. epidermidis	3.2	4	6.3	6.2
Streptococcus	1	3.3	2.5	4.5
Other GPC	0.6	1.2	1	0
Others	10.8	9.7	2.9	0
No. of isolated strains	592	502	954	976

GNR, Gram-negative rods; GPC, Gram-positive cocci.

Table 2. Prevalences (%) of isolated urine pathogens among the urology outpatients

	1998 - 2002	1993 - 1997	1988 - 1992	1983 - 1987
E. coli	22.2	34.8	32.6	37.9
P. aeruginosa	11	6.7	8	6.8
K. pneumoniae	6.8	8.5	6.2	7.4
S. marcescens	3.9	6.2	3.9	3.9
Citrobacter spp.	3.6	3.6	2.4	2.6
Enterobacter spp.	2.5	2.2	4.6	3.6
P. mirabilis	2.4	2.2	3.1	3.7
K. oxytoca	1.4	1.5	0.2	0
Other *Pseudomonas* spp.	1.7	2.4	1.3	2.9
Other GNR	6.2	5	8.3	8.8
E. faecalis	18.6	8.5	12	11.7
S. aureus	6	4.3	3.7	1.5
Streptococcus	3.5	4.1	6.8	4.1
S. epidermidis	2.9	4	5.7	3.8
E. faecium	1.2	2.3	1	1.3
Other GPC	3.3	0.6	0.2	0
Others	2.8	3.1	0	0
No. of isolated strains	885	508	568	486

GNR, Gram-negative rods; GPC, Gram-positive cocci.

epidermidis were isolated more frequently than *S. aureus* between 1983 and 1992, but not during the last 10 years.

Isolation rates of UTI bacteria for inpatients from other departments: *E. coli* was one of the most frequently isolated bacteria, with an isolation rate in each of the 5-year periods that ranged from 10.4 - 13.7%; however, it has been decreasing in the most recent 5 years ($P < 0.05$) (Table 3). *P. aeruginosa* was one of the most frequently isolated pathogens in this patient group, surpassing *E. coli* in each of the 5-year periods except 1983 - 1987. *S. marcescens* tended to be most frequently isolated in *K. pneumoniae*, *S. marcescens*, and *Enterobacter* spp. *S. aureus* was isolated with increasing frequency; the average isolation rate for 1983 - 1987 was 1.3%, while that for 1998 - 2002 was 5.5%. *E. faecalis* was also one of the most frequently isolated bacteria, with an isolation rate of 15.1 - 20%.

Table 3. Prevalences (%) of isolated urine pathogens among inpatients of other departments

	1998 - 2002	1993 - 1997	1988 - 1992	1983 - 1987
P. aeruginosa	15.6	13.8	14.3	11
E. coli	10.4	10.9	12.3	13.7
S. marcescens	7.5	6.9	5.2	8.6
K. pneumoniae	5.2	3.6	5.2	5.7
Enterobacter spp.	4.6	4.4	6.6	5
Citrobacter spp.	1.8	2.6	2.6	4.3
P. mirabilis	1.4	1.7	1.5	3.4
K. oxytoca	0.5	1.5	1.1	2.3
Other *Pseudomonas* spp.	2.7	3	3.3	8.7
Other GNR	5.3	12.3	11.9	12.8
E. faecalis	15.4	15.4	20	15.1
S. aureus	5.5	3.3	4	1.3
E. faecium	5	3.5	4	3.4
S. epidermidis	2	3.4	3.8	2.3
Streptococcus	1.3	2.1	2.2	2.3
Other GPC	1.4	1	1.1	0
Others	14.4	10.6	0.9	0.1
No. of isolated strains	2,266	1,941	2,661	3,576

GNR, Gram-negative rods; GPC, Gram-positive cocci.

Susceptibility of five isolated UTI bacteria to antimicrobial agents: We studied the chronological changes in susceptibility to antimicrobial agents among the following five bacteria: *E. coli*, *P. aeruginosa*, *S. marcescens*, *E. faecalis*, and *S. aureus*. The study was divided into the same 5-year periods as used for totaling detection frequencies. The results are presented as the susceptibility rates for each period. For *E. coli*, the susceptibility rate to ampicillin was 71.3 - 72.6% during the initial two periods, 78.6 - 79.2% to piperacillin during the last two periods, and 98.2 - 100% to cefmetazole and 93.7 - 100% to amikacin during all periods. The susceptibility rate to gentamicin was 91.1 - 98.9% but decreased over time, from 96.8% in 1983 - 1987 to 91.1% in 1998 - 2002 ($P < 0.05$). The susceptibility rate to minocycline was 80.2 - 96.7%; with respect to the period of 1998 - 2002, it was 100% every year from 1998 to 2001, but fell to 85.6% in 2002 (data not shown). Susceptibility to imipenem/cilastatin was 100% during the last two periods. Although susceptibility to ofloxacin was 82.8 - 98.8% in every year-study, it declined from 98.8% in 1995 to 89.2% in 2001 and 87.4% in 2002 (data not shown). For *P. aeruginosa*, the susceptibility rate to

Table 4. Antimicrobial susceptibility rates (%) of representative 5 species of uropathogens

Period	(N[1])	ampicillin	penicillin G	piperacillin	cefmetazole	amikacin	erythromycin	gentamicin	clindamycin	minocycline	imipenem/ cilastatin	ofloxacin
E. coli												
1998 - 2002	(484)	N/D	N/D	78.6	100	93.7	N/D	91.1	N/D	96.7	100	88.9
1993 - 1997	(408)	N/D	N/D	79.2	98.5	100	N/D	98.6	N/D	83.9	100	94.4
1988 - 1992	(786)	72.6	N/D	N/D	100	100	N/D	98.9	N/D	85.3	N/D	N/D
1983 - 1987	(719)	71.3	N/D	N/D	98.2	99.7	N/D	96.8	N/D	80.2	N/D	N/D
P. aeruginosa												
1998 - 2002	(538)	N/D	N/D	89.5	N/D	96.8	N/D	81.4	N/D	9.5	92.6	70
1993 - 1997	(365)	N/D	N/D	90.1	N/D	84.5	N/D	79.5	N/D	21.7	91.1	54.4
1988 - 1992	(862)	N/D	N/D	70.2	N/D	87.6	N/D	75.6	N/D	3.4	N/D	N/D
1983 - 1987	(550)	N/D	N/D	64.2	N/D	88.6	N/D	65.1	N/D	7.4	N/D	N/D
S. marcescens												
1998 - 2002	(240)	N/D	N/D	44.6	26.1	70	N/D	96	N/D	87.8	96	68.7
1993 - 1997	(229)	N/D	N/D	64.3	18.8	81.8	N/D	97	N/D	91.7	97	58.3
1988 - 1992	(259)	3	N/D	N/D	18.8	87.9	N/D	96	N/D	76	N/D	N/D
1983 - 1987	(379)	1.7	N/D	N/D	10.8	82.7	N/D	77.6	N/D	64.8	N/D	N/D
S. aureus												
1998 - 2002	(222)	6.8	7.3	N/D	31.7	N/D	41.5	N/D	43.9	90.5	28.6	33.7
1993 - 1997	(113)	N/D	5	N/D	40	N/D	40	N/D	65	70	40	35
1988 - 1992	(253)	4.9	2.4	N/D	24.4	N/D	29.2	N/D	46.3	N/D	52	N/D
1983 - 1987	(68)	N/D	N/D	N/D	N/D	N/D	N/D	N/D	N/D	N/D	N/D	N/D
E. faecalis												
1998 - 2002	(622)	100	99.1	N/D	1.9	N/D	36.9	3.9	0	91.7	98	69.3
1993 - 1997	(407)	N/D	97.3	N/D	1.4	N/D	47.9	5	1.4	88.9	98.5	72.3
1988 - 1992	(1096)	94.8	83.7	N/D	1.1	N/D	52.3	N/D	2.2	22.2	96.2	N/D
1983 - 1987	(801)	95.8	92.5	N/D	0.6	N/D	58.7	N/D	1.3	39	N/D	N/D

[1]: Number of isolated strains.
N/D, not done.

piperacillin was 64.2 - 90.1%, and increased over time, while that to ceftazidime was 89.5 - 90.1% but decreased in 2002 to 72% (data not shown). The susceptibility rate to amikacin was 84.5 - 96.8%, that to gentamicin was 65.1 - 81.4%, that to minocycline was 3.4 - 21.7%, that to ofloxacin was 54.4 - 70%, and that to imipenem/cilastatin was 91.1 - 92.6%; however, in 2002 the susceptibility to imipenem/cilastatin decreased to 75.5% (data not shown). The susceptibility rate of *S. marcescens* to ampicillin was 1.7-3% during the initial two periods, that to piperacillin was 44.6 - 64.3% during the last two periods, that to cefmetazole was 10.8-26.1%, and that to amikacin was 70 - 87.9%, although the susceptibility to amikacin fell to 52% in 2002 (data not shown). The susceptibility rate to gentamicin was 77.6 - 97%, that to minocycline was 64.8 - 91.7%, that to imipenem/cilastatin was 96 - 97% and that to ofloxacin was 58.3 - 68.7%.

S. aureus showed a susceptibility rate of 2.4-7.3% to penicillin G, 4.9 - 6.8% to ampicillin, 29.2 - 41.5% to erythromycin, 43.9 - 65% to clindamycin, and 24.4 - 40% to cefmetazole. Susceptibility to minocycline was 70 - 90.5%, but this rate decreased to 68.5% in 2002, as compared with 2000 and 2001 when it was 100% (data not shown). The susceptibility rate was 28.6 - 52% to imipenem/cilastatin, but decreased during the last 5 years, during which it was 33.7-35% to ofloxacin, 94.4 - 100% to arbekacin, and 100% to vancomycin (data not shown). For *E. faecalis*, the susceptibility rate to penicillin G was 83.7 - 99.1%, to ampicillin was 94.8 - 100%, to cefmetazole was 0.6 - 1.9%, to erythromycin was 36.9 - 58.7%, to gentamicin was 3.9 - 5%, and to clindamycin was 0 - 2.2%. The susceptibility rate to minocycline was 22.2 - 91.7% and increased over time, while it was 96.2 - 98.5% to imipenem/cilastatin and 69.3 - 72.3% to ofloxacin (Table 4).

DISCUSSION

Recently, growth in the variety of UTI characteristics has occurred as the result of an increase in hospital-acquired infections and types of resistant strains. This often causes difficulties for the treatment of UTI patients. Another particularly serious problem is that the increase in nosocomial UTIs has resulted in longer hospital stays and unexpectedly high health care costs for patients expecting to be treated only for their underlying disease (14). Recently, the development of new antimicrobial agents and improved surgical and pharmaceutical management of urinary tract disorders has progressed. However, this progression has been counteracted by an increase in the number of elderly patients, which has produced an increase in the isolation rates of UTI pathogens as well as in the range of susceptibility to antimicrobial agents (2,9,15-19). Furthermore, the number of reports regarding the transition of bacteria isolated from urine of UTI patients being published by various institutions has recently shown a declining trend (10,14,20-22). For these reasons, our study is especially meaningful because it provides crucial information about recent UTIs.

A remarkable characteristic of the past 20 years has been the increase in the isolation rates of *E. coli*, *S. marcescens*, and *S. aureus* in urology inpatients. In particular, the increase in the frequency of *S. aureus* has clearly been influenced by the increased isolation rate of MRSA.

Regarding urology outpatients, a major change over the past 20 years has been the decreasing isolation rate of *E. coli*. In contrast, the isolation rates of *P. aeruginosa* and *E. faecalis* have increased. These changes indicate that UTIs among outpatients have become more complicated and that these trends should be considered during the treatment of UTI patients. One factor in these trends has been the increasing number of older patients with complicated UTIs (23).

A major change for inpatients of other departments during the past 20 years has been the decrease in the isolation rate of *E. coli* and the increase in that of *S. aureus*. The increase of MRSA in *S. aureus* is particularly remarkable; therefore, all doctors treating UTI patients should be cognizant of this development.

The susceptibility of *E. coli* to newer fluoroquinolones has decreased 5.5 points (from 94.4% to approximately 88.9%) during the past 10 years, especially among outpatients. This suggests that although newer fluoroquinolones have long been recommended for treating UTIs caused by *E. coli*, antimicrobials must now be selected carefully (24). However, Gales et al. reported that the isolation rate of ciprofloxacin-resistant *E. coli* ranged from 18.1 - 18.9% in 1997 - 2000. Therefore, we must monitor this situation for further change (25).

In terms of *P. aeruginosa*, susceptibilities to antimicrobials, especially piperacillin, ceftazidime, and imipenem/cilastatin, have shown a decreasing trend over the past 20 years. The often-discussed multidrug-resistant *P. aeruginosa* is generally considered to be resistant to ciprofloxacin, imipenem/cilastatin, and amikacin (26). Since there is a strong possibility that this kind of resistant strain will continue to increase, detailed investigations of the use of antimicrobial agents are urgently needed before the emergence of multidrug-resistant *P. aeruginosa* and similar uropathogens.

The susceptibility of *E. faecalis* to antimicrobials has not undergone any remarkable changes and has remained at nearly 100%, especially to penicillin G, ampicillin, and imipenem/cilastatin. However, regarding susceptibilities to erythromycin and minocycline, the former decreased significantly in the last 5 years ($P < 0.05$) and the latter increased significantly in the last 10 years ($P < 0.05$). Nevertheless, we cannot overlook the possible emergence of resistant strains because of the frequent use of these antimicrobial agents to manage the frequently isolated *E. faecalis*.

S. marcescens, one of the bacteria most frequently isolated from urology inpatients, is often associated with UTIs in urinary tract catheterized patients. A multidrug-resistant strain of *S. marcescens* was recently reported, making it necessary to consider not only the selection of antimicrobial agents but also the management of urinary tract catheters (24,27). Additionally, those doctors who treat urinary tract catheterized patients should be informed of the most appropriate management of urinary tract catheters.

While the rate of MRSA isolation has been increasing in *S. aureus*, susceptibility to vancomycin and arbekacin has remained nearly 100%. However, in 2002, one strain resistant to arbekacin was detected. Moreover, an MRSA strain resistant to vancomycin has been reported in the United States, indicating that we should not only enforce proper urine culture and susceptibility testing but also make an effort to avoid the overuse of anti-MRSA drugs (28).

In conclusion, the present study demonstrated that the uropathogens isolated at a single institution have shown various trends in isolation rates and resistances to various classes of antimicrobial agents. Isolated uropathogens showed greater diversification, and a marked overall increase in isolated Gram-positive bacteria including MRSA was observed. In addition, multidrug-resistant *P. aeruginosa*, fluoroquinolone-resistant *E. coli*, and arbekacin-resistant MRSA can be ex-

pected to cause serious treatment problems. Therefore, it is essential to use the most appropriate antimicrobial management based on this data, in order to accurately assess the severity of patients' UTI, and to recognize the limits of conservative treatments.

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