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Urinary tract infection pathogens and antimicrobial susceptibilities in Kobe, Japan and Taipei, Taiwan: an international analysis

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Abstract

Objective: This study compared urinary tract infection (UTI) pathogens and antibiotic susceptibilities between Kobe, Japan and Taipei, Taiwan to investigate the regional resistance pattern of UTI-causative bacteria.

Methods: UTI-causative bacteria and antibiotic susceptibility for 4519 samples from Kobe University Hospital, Kobe and 25,131 samples from Shuang-Ho Hospital, Taipei from 2015 to 2017 were retrospectively analyzed to compare the differences between these hospitals.

Results: *Escherichia coli* was the most common pathogen in both areas (30.0% in Kobe, 41.2% in Taipei). The prevalence of cephalosporin and gentamicin-resistant *E. coli* tended to be higher in Taipei than in Kobe. Additionally, antibiotic susceptibilities of *Klebsiella pneumonia* and *Pseudomonas aeruginosa* tended to be higher in Kobe than in Taipei. The ratio of extended-

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spectrum β-lactamase-producing *K. pneumoniae* was significantly higher in Taipei than in Kobe (up to 40% vs. 14.8%), but this was not observed for *E. coli*.

Conclusion: Variations in the type of UTI-causative bacteria and antibiotic susceptibility between the two hospitals may be influenced by the use of different antibiotics. Further surveillance of resistance patterns is necessary for effective treatment.

Keywords

Urinary tract infection, susceptibility, antimicrobial resistance, extended-spectrum β-lactamase, international comparison, university hospitals

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Introduction

Urinary tract infections (UTIs) are the most common infectious disease among the general population.[1] For example, the annual prevalence of cystitis in North America is 3% to 4.3% in women and 0.5% to 1.7% in men.[2,3] Self-reported histories of physician diagnoses are even higher, with approximately 12.6% of women and 3.0% of men reporting episodes of community-associated UTIs in the US each year.[4] Moreover, the estimated lifetime risk of UTIs in women may be more than 60%.[5]

In the hospital setting, UTIs are most common in catheterized patients. Other causes of healthcare-associated UTIs include stones, genitourinary tract operations, voiding problems, and an immunocompromised status. Antibiotic treatment remains the gold standard for therapy and is effective for uncomplicated UTIs.[6] For complicated UTIs, broad-spectrum antibiotics should be administered quickly because of the increasing resistance of bacterial strains. *Escherichia coli*, *Enterococcus faecalis*, *Klebsiella pneumoniae*, *Proteus mirabilis*, and *Pseudomonas aeruginosa* are the most common causative bacteria in healthcare-associated UTIs.

The epidemiology of UTIs varies among countries. However, most studies focusing on UTI-causative bacteria are restricted to a single hospital or multiple centers in the same region or country. Only a few studies have investigated the differences in UTI-causative bacterial strains and antibiotic susceptibilities between different countries.[7] We previously compared causative bacteria and antimicrobial susceptibilities in UTI patients in Kobe, Japan and Surabaya, Indonesia with *E. coli* infections showing higher resistance to ampicillin and the first-generation cephalosporin, and found that *E. coli* and *K. pneumonia* extended-spectrum β-lactamase (ESBL) production rates were higher in Indonesia than in Japan.[7]

Japan and Taiwan are geographically close and their medical systems are more similar than that of Indonesia. For example, most of the population is covered by health insurance and there are many medical institutions in both countries, so treatment is easy to obtain. Patients must also have prescriptions from physicians to acquire antibiotics. Kobe and Taipei both have well-developed medical systems and a high quality medical service. However, the weather, geography, and lifestyle differs between the two cities. The present study gathered microbiologic data from UTI patients in Kobe and Taipei, then compared the causative bacteria and their susceptibility patterns between these two regions.

Materials and methods

Study setting and sample collection

This is a Kobe University Hospital–Taipei Medical University international collaborative study. It was approved by the institutional review board of Kobe University (No. 170101) as an international study and was conducted in accordance with the ethical standards of the Declaration of Helsinki. This was a retrospective study and our institutional review board decreed that informed consent was not required. Patients were given the option of not participating.

Between 2015 and 2017, 4519 valid urine culture samples from Kobe University Hospital, Japan and 25,131 from Shuang-Ho Hospital, Taipei, Taiwan were collected and analyzed from patients with UTIs or suspected UTIs. Clean-catch midstream urine samples were collected from outpatients and inpatients or from catheters using a sterilized technique.

Bacterial culture and antimicrobial susceptibility tests

Urine cultures were tested by a standardized method using agar medium as described previously.[7] Microorganisms were isolated using standardized biochemical procedures[8] and identified by the automatic diagnostic BD Phoenix Automated Microbiology System (Becton, Dickinson and Co., Franklin Lakes, NJ, USA) according to published protocols.[9] Antimicrobial susceptibilities of isolates were assessed based on Clinical and Laboratory Standards Institute (CLSI) recommendations by the disk diffusion method using Mueller–Hinton medium.[10] Antimicrobial agents and testing were examined by BD BBL Sensi-Disc (Becton, Dickinson Sparks, MD, USA). Antibiotics used are listed in Table 1. The ESBL test was assessed by the formation of an inhibition zone (>5 mm) by clavulanic acid (CLA) on the middle CAZ/CLA disc surrounded by CTX, CTX/CLA, cefpodoxime, and cefepime discs based on the double disc synergy test in both Kobe and Taipei.[11]

Table 1. Antimicrobial agents and abbreviations.

Antimicrobial agents	Abbreviations
Amikacin	AMK
Cefotaxime	CTX
Ceftazidime	CAZ
Ciprofloxacin	CPFX
Gentamicin	GEN
Imipenem	IPM
Levofloxacin	LVFX

Sorted by alphabetical order.

Statistical analysis

Discrete variables were expressed as percentages and compared using the chi-squared test. Statistical significance was established at the 0.05 level.

Results

Comparison of UTI-causative bacteria

E. coli was the most common pathogen identified in UTI patients from Kobe University hospital, accounting for around 30% of all bacterial isolates (1354/4519, 29.9%). Other isolated bacteria included *E. faecalis* (678/4519, 15.0%), *K. pneumonia* (333/4519, 7.37%), *P. aeruginosa* (310/4519, 6.86%), *Staphylococcus aureus* (263/4159, 5.82%), and S*treptococcus* spp. (207/4519, 4.58%). Details of the bacteria isolates identified from Kobe are listed in Table 2.

E. coli (10,354/25,131, 41.2%) was also the most common pathogen identified in UTI patients from Shuang-Ho Hospital. *K. pneumonia* (2262/25,131, 9.0%) ranked second followed by *E. faecalis* (1757/25,131, 6.99%), *P. aeruginosa* (1555/25,131, 6.19%),

Table 2. Isolated bacteria from UTI urine samples in Kobe University Hospital.

Bacteria	No. of isolates	Ratio of isolates (%)
Escherichia coli	1354	29.96
Enterococcus faecalis	678	15.00
Klebsiella pneumoniae	333	7.37
Pseudomonas aeruginosa	310	6.86
Staphylococcus aureus	263	5.82
Streptococcus spp.	207	4.58
Enterobacter spp.	148	3.28
Staphylococcus epidermidis	137	3.03
Citrobacter spp.	103	2.28
Proteus mirabilis	95	2.10
Klebsiella oxytoca	75	1.66
Others	816	18.06
Total	4519	100.0

Sorted by percentage.

Table 3. Isolated bacteria from UTI urine samples in Shuang-Ho Hospital.

Bacteria	No. of isolates	Ratio of isolates (%)
Escherichia coli	10,354	41.20
Klebsiella pneumoniae	2262	9.00
Enterococcus faecalis	1757	6.99
Pseudomonas aeruginosa	1555	6.19
Proteus mirabilis	1391	5.53
Streptococcus agalactiae	748	2.98
Enterococcus faecium	700	2.79
Streptococcus anginosus	588	2.34
Staphylococcus haemolyticus	563	2.24
Staphylococcus epidermidis	516	2.05
Morganella morganii ss. morganii	495	1.97
Citrobacter koseri	392	1.56
Staphylococcus aureus ss. aureus	380	1.51
Acinetobacter baumannii	355	1.41
Enterobacter cloacae	347	1.38
Others	2728	10.85
Total	25,131	100.0

Sorted by percentage.

and *Proteus mirabilis* (1391/25,131, 5.53%). These isolated bacteria are listed in Table 3.

Antimicrobial susceptibility test

Regarding antimicrobial susceptibilities, resistance often occurs in Gram-negative bacteria (GNB).[6] *E. coli*, *K. pneumoniae*, and *P. aeruginosa* were the most common GNB UTI pathogens in both Kobe and Taipei. The antibiotic susceptibility rates of *E. coli* to CAZ and GEN were significantly lower in the Taipei group (76%–78%) than in the Kobe group (94.8%–96.5%) (Table 4, $P < 0.05$). *E. coli* in both Kobe and Taipei showed 28% to 48% resistance to fluoroquinolone antibiotics (CPFX and LVFX). There was also a trend of increasing resistance from 2015 to 2017, but this was not significantly different between the two hospitals.

The rates of susceptibility were significantly lower for *K. pneumoniae* in the Taipei group for CAZ, GEN, CPFX, and LVFX compared with Kobe (Table 5, $P < 0.05$). Only 62% to 72% of isolated *K. pneumonia* in Taipei was responsive to the above antibiotics compared with 84% to 94% in the Kobe group. *P. aeruginosa* responses to CPFX and LVFX were similar, with only 68.1% to 73.2% of all isolated *P. aeruginosa* showing susceptibility to the above antibiotics in the Taipei group which was significantly lower than in the Kobe group (82.8%–94%; $P < 0.05$, Table 6).

Comparison of ESBL-producing bacteria

We also compared the ESBL production rate of *E. coli* and *K. pneumoniae* in both hospitals. For *E. coli*, this was 14% to 26.4% in the Taipei group compared with 21% to 25.2% in the Kobe group, which was not significantly different (Figure 1). However, the ESBL production rate for *K. pneumonia* was significantly higher in the Taipei group (22%–40%) compared with the Kobe group (7%–14.8%; Figure 2, $P < 0.05$).

Table 4. Comparison of *Escherichia coli* susceptibility.

			Ratio of susceptibility (%)					
Bacteria	Area	Year	CAZ	AMK	GEN	CPFX	LVFX	IPM
E. coli	Taipei	2015	76.9*	99.6	77.3*	71.6*	72.4*	99.1
		2016	78.6*	99.6	77.8*	72.0*	72.9*	99.8
		2017	76.1*	99.5	74.3*	62.1*	62.9*	99.2
	Kobe	2015	94.8	94.8	87.4	66.3	67.0	95.1
		2016	95.4	96.1	8.35	56.2	56.6	96.5
		2017	95.8	96.5	80.6	52.2	52.9	96.5

*$P < 0.05$ between the two groups.

Table 5. Comparison of *Klebsiella pneumoniae* susceptibility.

			Ratio of susceptibility (%)					
Bacteria	Area	Year	CAZ	AMK	GEN	CPFX	LVFX	IPM
K. pneumoniae	Taipei	2015	62.5*	96.4	71.7*	69.7*	72.5*	86.3
		2016	63.2*	95.5	71.8*	70.0*	72.6*	94.5
		2017	58.8*	95.8	69.9*	65.7*	69.0*	85.3
	Kobe	2015	86.9	95.2	92.9	84.5	94.0	95.2
		2016	79.8	95.2	86.5	88.5	93.3	94.2
		2017	80.4	94.6	89.2	83.8	90.5	84.6

*$P < 0.05$ between the two groups.

Table 6. Comparison of *Pseudomonas aeruginosa* susceptibility.

			Ratio of susceptibility (%)					
Bacteria	Area	Year	CAZ	AMK	GEN	CPFX	LVFX	IPM
P. aeruginosa	Taipei	2015	83.7	95.8	79.0*	73.2*	72.2*	87.5
		2016	82.8	96.9	77.3	69.1*	69.1*	87.8
		2017	85.5	97.0	83.6	72.0*	68.1*	84.1
	Kobe	2015	86.9	95.2	92.9	84.5	94.0	95.2
		2016	89.9	93.9	80.8	82.8	83.8	82.8
		2017	80.4	94.6	89.2	83.8	90.5	84.6

*$P < 0.05$ between the two groups.

Discussion

UTIs are the most common infectious disease and antibiotics are the mainstay of treatment. However, different countries have varying treatment guidelines and choices of antibiotics. Geography, economic conditions, education levels, insurance coverage, and physician education also differ among countries or regions. Insufficient

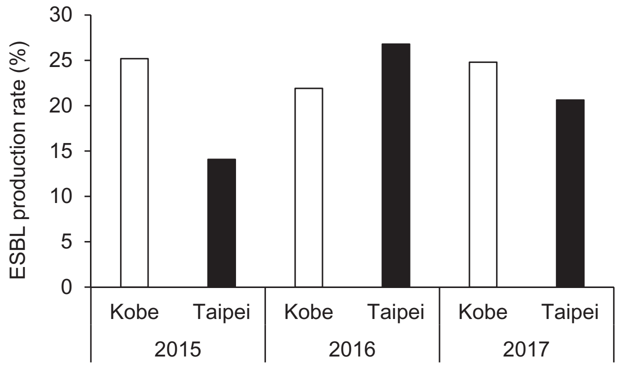

Figure 1. Ratio of ESBL-producing *Escherichia coli* according to region and year. No significant difference was found between Kobe and Taipei. ESBL, extended-spectrum β-lactamase.

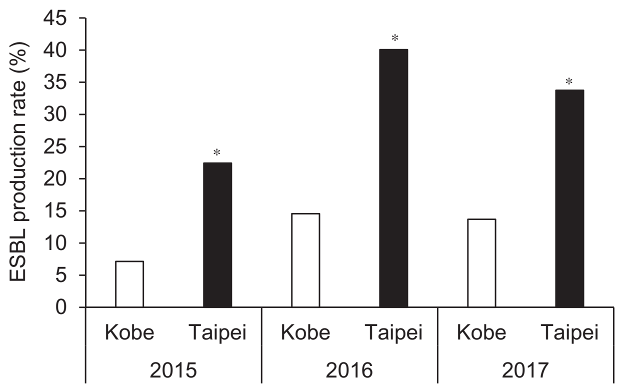

Figure 2. Ratio of ESBL-producing *Klebsiella pneumoniae* by region and year. The ratio was higher in Taipei in all years (*$P < 0.05$). ESBL, extended-spectrum β-lactamase.

antibiotic dosage or durations that result in suboptimal treatment are the main reasons for bacterial antibiotic resistance.

Physicians often base their UTI treatments on personal experience rather than guidelines.[12] In Taiwanese clinics, insurance reimbursements mean that physicians are restricted to administering medication for only 3 days. Therefore, some patients receive only partial treatments and do not return for further evaluation, which can lead to the development of antibiotic resistance. Conversely, Japanese patients may have better compliance and prescription-directed use of antibiotics.

In the present study, we found differences both in the causative bacteria of UTIs and in trends in antimicrobial susceptibilities between Kobe and Taipei. *E. coli* was the most common pathogen in both cities, accounting for around 30% to 40% of all bacteria. *E. faecalis* was the second most common pathogen in Kobe but represented fewer than 7% of the bacteria in Taipei. Other GNBs such as *K. pneumoniae* and *P. aeruginosa* were also common to both cities. *Proteus mirabilis* was identified in Taipei cultures more often than in the Kobe group. Conversely, *S. aureus* was more commonly detected in the Kobe group. The differences between the two cities may reflect variations in patient types and distributions. For instance, *E. faecalis* and *S. aureus* may be more typically found in complicated UTIs.[13] In Japan, patients may attend local clinics for referrals and pay more if they go directly to university hospitals because of the need for referral letters. However, the difference in medical fees between clinics and university hospitals is low in Taiwan, so even patients with simple UTIs may directly attend a teaching hospital. We consider this to be one possible reason for the >10% difference in the *E. coli* ratio and the elevated *E. faecalis* occurrence rate in the Kobe group. Additionally, *P. mirabilis* has often been detected in catheter-associated UTIs.[14] Previous studies reported catheter use rates for hospitalized patients of 25% in Taiwan[15] and only 13.7% in Japan.[16] This may explain why the ratio of *P. mirabilis* was higher in the Taiwanese group.

We also noted that *E. coli* and *K. pneumoniae* in the Taiwanese group had lower CAZ and GEN susceptibilities than those seen in Kobe. The rates of *E. coli* resistance to CPFX and LVFX were 30% to 50% in both cities, and we observed a trend toward increasing resistance from 2015 to 2017. Both *K. pneumoniae* and *P. aeruginosa* showed higher resistance to CPFX and LVFX in Taiwan than in Japan, which may reflect the choice of antibiotics by physicians. For example, first generation cephalosporins, fluoroquinolones, and GEN are commonly used to treat UTIs in Taiwan,[17] while third generation cephalosporins and fluoroquinolones are initially given in Japan.[18] However, further prospective investigation is needed to fully understand the international epidemiology of antibiotic resistance.

The ESBL production rate of *E. coli* showed no significant difference between the two hospitals. In contrast, ESBL production rates in *K. pneumonia* were higher in the Taipei group. In the 2010 to 2013 Study for Monitoring Antimicrobial Resistance Trends, ESBL-producing GNB was frequently detected in China and Southeastern Asia, and the ESBL-producing rate of *E. coli* and *K. pneumonia* may be up to 60% in certain Asian countries.[19] ESBL production is strongly associated with decreasing *E. coli* and *K. pneumonia* susceptibility to fluoroquinolones.[20] Our study showed that the ESBL production rate of *K. pneumonia* was higher in the Taipei group, so resistance to CPFX and LVFX was also higher.

We previously identified *E. coli* as the most common UTI pathogen in Indonesia in a comparison with Kobe.[7] Moreover, the ESBL production rates of *E. coli* and *K. pneumoniae* were high in Indonesia, and susceptibility to LVFX was poor, which is also similar to the current findings. Ampicillin, cephalosporins, and fluoroquinolones are choices for treating UTIs in Indonesia.[21] Previous studies revealed cephalosporin exposure as an independent risk factor for ESBL-producing *E. coli*.[22] This is because when under high cephalosporin stress, *E. coli* can acquire multiple ESBL genes and increase their transcriptional expression.[23] The broad use of cephalosporins and fluoroquinolones therefore influences the microbiologic environment and antibiotic susceptibility. We therefore propose that updated guidelines for choosing UTI antibiotics and treatment durations should take regional differences into account.

Our study has several limitations. First, urine culture data were collected retrospectively from two hospitals, and the number of isolated cultures was not the same. Moreover, urine culture samples derived from both outpatients and inpatients, but the distribution of intensive care unit patients, hospitalized patients, and walk-in patients was unknown. Second, the complexity of UTIs and the catheterized status of UTI patients were not identified. Third, we lacked data about the socioeconomic status and presence of underlying diseases in UTI patients in both groups, as well as information about antibiotic types, doses, and treatment durations, which may influence bacterial resistance. Prospective studies using identical treatment protocols would better reflect the true microbiological conditions. Moreover, future work should obtain details of patient status and comorbidities to decrease patient bias.

In conclusion, our study showed that UTI-causative bacteria varied between Kobe and Taipei. Additionally, antibiotic susceptibilities for common UTI pathogens differed, which appeared to reflect ESBL production. The increasing resistance to fluoroquinolones should be monitored because active surveillance of resistance patterns in UTI pathogenesis is necessary for effective treatment.

Declaration of conflicting interest

The author(s) declare that there is no conflict of interest.

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