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Clinical Characteristics and Antimicrobial Susceptibility Pattern of Hospitalized Patients with Community Acquired Urinary Tract Infections at a Regional Hospital in Taiwan

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Abstract

Background—Community-acquired urinary tract infection (UTI) is the most common bacterial infection encountered at hospitals. Effective empirical antibiotic therapy relies on updated epidemiological data.

Aim—We described the epidemiology of patients with urosepsis presenting to a community hospital in Taiwan in order to assess the appropriateness of empirical therapy.

Methods—Retrospective cohort study of hospitalized adult patients with UTI from January 1 to December 31 in 2010. The clinical and microbiological characteristics were analyzed using descriptive statistics. Logistic regression analysis was performed to determine predictors of antibiotic resistance.

Findings—A total of 420 consecutive patients with 599 isolates were identified. Most patients were ≥ 65 years old and women (75.4%), and 114 patients (27.1%) had bacteremia. *Escherichia coli* (69%) was the most common organism. Cefazolin was effective against *E. coli*, *K. pneumoniae*, and *P. mirabilis* in greater than 80% of the cases. In male patients, urinary catheter and renal stone were independent predictors for cefazolin resistance; while diabetes mellitus and malignancy were predictors among female patients.

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Conflict of Interest

Other authors disclose no conflicts of interest.

Conclusion—Patients admitted with UTI should be screened to identify risk factors for bacteremia and antimicrobial resistance. The treatment guideline in Taiwan needs to be revised in the current era of increasing antimicrobial resistance.

Keywords

Epidemiology; Antimicrobial resistance; Guidelines; Urinary tract infection; Community Hospitals

Introduction

Community-acquired urinary tract infection (UTI) is the most common bacterial infection among patients presenting to hospitals. The spectrum of disease related to UTIs varies, ranging from simple cystitis to bacteremia with septic shock. Studies show that bacteremia occurs frequently in patients with UTIs; approximately 15-42% of hospitalized patients with urosepsis develop bacteremia [1, 2]. When bacteremia develops during urosepsis, it can be associated with poor clinical outcomes [1], including prolonged hospitalization and high mortality [3].

The optimal empirical therapy for UTIs requires a thorough understanding of the local epidemiology and antimicrobial susceptibility of likely uropathogens in the patient's clinical setting. *E. coli* and *Klebsiella spp.* remain the most common pathogens associated with UTIs; species outside of the *Enterobacteriaceae* family, including *Pseudomonads*, enterococci and *Staphylococcus saprophyticus*, may also cause UTIs in hosts with specific risk factors [1, 3, 4]. In addition, the emergence of antibiotic resistance among these uropathogens has become an increasing problem that has complicated selection of antibiotics in recent years worldwide [5]. Prior studies have suggested that Taiwan is experiencing a significant increase in the incidence of multidrug-resistant uropathogens [4]. However, much of the prior data have come from tertiary care medical centers, and the true epidemiology and microbiology of urosepsis from regional hospitals is lacking.

Therapeutic guidelines are commonly used by clinicians to formulate initial therapy for patients for a variety of infections. However, guidelines are infrequently updated and may not reflect the epidemiology and local antibiotic resistance patterns [6, 7]. For instance, the Taiwanese guidelines for the treatment of UTIs were published in 2000 by the Infectious Diseases Society of Taiwan [7]. These guidelines have not been updated but are still being used by hospitals across the country, including ours, a regional hospital in the northwestern part of Taiwan.

We believe the current epidemiology of urosepsis in the community setting of Taiwan is poorly understood. We further hypothesize that some of the first-line antibiotics recommended by the Taiwanese UTI guidelines are now inappropriate (especially, first-generation cephalosporins). Therefore, we conducted a study to describe the clinical characteristics of patients with UTIs, to understand the microbiology and antibiotic resistance patterns of UTIs in the community setting and to assess the appropriateness of using the Taiwanese treatment guidelines for empirical therapy of patients with community-onset UTIs.

Methods

We conducted a retrospective cohort study of consecutive hospitalized adults identified by a discharge diagnosis of UTI (International Classification of Diseases-9: 590.X, 595.X, 597.X, 601.X, 599.0) from January 1, 2010 to December 31, 2010 at Landseed Hospital, a regional hospital with 580 beds in northern Taiwan. This study was approved by the Institutional Review Board. Clinical and laboratory data were collected and verified by study personnel. We excluded patients with the following characteristics: < 18 years old, those without at least one documented symptom of UTI (dysuria, frequent urination, urgent urination, perineal pain, flank pain, or costo-vertebral tenderness), lack of blood or urinary microbiologic data within 48 hours of admission, those with concurrent infection at another site, history of hospitalization or antimicrobial therapy within the previous 14 days, and patients transferred to another hospital. All microbiological isolates from urine and blood were collected, inclusive of duplicates. Bacterial cultures were processed using BACTEC 9240 (Becton Dickinson, Sparks, MD, USA) and identification, and antimicrobial susceptibility including identification of extended spectrum β -lactamase (ESBL) phenotype were performed using Phoenix (Becton Dickinson, Sparks, MD, USA) according to Clinical and Laboratory Standards Institute criteria [8].

We defined systemic inflammatory response syndrome (SIRS) as having two or more of the following: (1) fever (oral temperature $>38^{\circ}\text{C}$) or hypothermia ($<36^{\circ}\text{C}$); (2) tachypnea (>20 breaths/min); (3) tachycardia (heart rate >90 beats/min); (4) leukocytosis ($>12 \text{ K}/\mu\text{L}$), leucopenia ($<4 \text{ K}/\mu\text{L}$), or $>10\%$ bands [9]. Cardiovascular disease was defined as disorders of the heart and blood vessels but not as hypertension. Immunosuppression was defined as receipt of cytotoxic agents, corticosteroids at a dosage equivalent to or higher than 0.5 mg/kg of prednisolone daily, or other immunosuppressive agents within 2 weeks before UTI onset. Concordant antimicrobial therapy was defined as the pathogen was susceptible to at least one of the administered antimicrobial agents in the first 24 hours of admission.

Statistical analysis was performed using SAS 9.3 (Cary, NC, USA). The chi-square test and Student's t test were used for hypothesis testing as appropriate. Two tailed p-values of 0.05 or less were regarded as significant. For logistic regression analysis, all variables with $p < 0.2$ on univariable analysis were entered into the multivariable model. Odds ratios (OR) and 95% confidence interval (CI) were calculated for risk estimates.

Results

Demographic and Clinical Outcomes of Patients

A total of 420 consecutive patients with community-acquired UTIs were enrolled. Demographic and clinical characteristics of these patients are summarized in table 1. The majority of patients were females (75.4%) and of older age; median age was 67.5 (range, 18-101). Up to 73% of patients had at least 1 underlying medical comorbidity and the most common were hypertension (46.7%), diabetes mellitus (36.2%), and cardiovascular disease (20.7%). Fever and tachycardia were common on admission and 68% had symptoms consistent with systemic inflammatory response syndrome on admission.

Clinical outcomes of patients with UTIs are also summarized in table 1. Twenty-two (5.2%) patients were admitted into the intensive care unit (ICU). The mean lengths of ICU and hospital stay were 0.3 ± 1.8 and 6.1 ± 3.9 days, respectively. The mean number of antibiotic days was 11.9 (range 2 - 45). About three-quarters of patients received concordant empirical antimicrobial therapy. Only 2 patients died in the study and the mortality rate was 0.5%.

Development of bacteremia was of particular interest. One hundred and fourteen patients (27.1%) had urosepsis with concurrent bacteremia. Moreover, we found the presence of liver disease to be an independent predictor of bacteremia among patients with urosepsis. Of note, patients who developed bacteremia were more likely to require vasopressors ($p < 0.001$) and ICU admission ($p = 0.024$), and had longer hospital days (median 7.3 vs 5.8) ($p = 0.009$).

Distribution of Organisms

Of 420 patients, 599 isolates were collected including duplicates from one patient. Gram-negative bacteria accounted for 92% while Gram-positive bacteria accounted for 6% of total uropathogens. The frequency and antimicrobial susceptibility pattern of detected uropathogens were summarized in table 2. *E. coli* (69%) was the most commonly isolated organism, followed by *K. pneumoniae* (7%), *Pseudomonas aeruginosa* (5%), *Proteus mirabilis* (4%), *Enterobacter* (3%) and *Citrobacter species* (2%).

Of all 416 *E. coli* isolates, 19 (4.6%) had ESBL phenotype. Among the antimicrobials tested, imipenem and amikacin were universally effective (100% of the isolates were susceptible). Of the empirical agents recommended by the Taiwanese Infectious Diseases society, only cefazolin retained effectiveness against 81% of *E. coli* isolates; the remaining recommended drugs were effective in less than 50% of the *E. coli* isolates, including trimethoprim-sulfamethoxazole (TMP-SMX) (effective in 49%), ampicillin (30% effective) and ampicillin/sulbactam (44% effective). Of *K. pneumoniae* isolates, 4.9% had ESBL phenotype. More than 80% of these organisms were susceptible to all antibiotics tested. *Pseudomonas aeruginosa* isolates were highly susceptible (>90%) to ceftazidime, amikacin, imipenem, and gentamicin, but not to levofloxacin (only 58% were susceptible).

Enterococcus species, the most common Gram-positive bacteria in our study, were susceptible to ampicillin in 83% of isolates. No vancomycin-resistant *Enterococcus* was found. Following *Enterococcus*, group B *Streptococci* were the next most common Gram-positive organisms; they were universally susceptible to penicillin, levofloxacin, and vancomycin. There were 4 isolates of *Staphylococcus aureus*; 50% of which were methicillin-resistant.

Resistance to First Generation Cephalosporins

Cefazolin is commonly used regimens for empirical therapy of urosepsis in Taiwan. The overall resistance to cefazolin was 33.8% of tested isolates. Using all study isolates and patients, we determined factors that predicted *in vitro* resistance to cefazolin empirical therapy (table 3). For male patients, urinary catheterization (OR 4.50; 95% CI 1.28 - 15.86), and renal stone (OR 2.86; 95% CI 1.02 - 8.01) were independent predictors for non-susceptibility to cefazolin. For females, having diabetes mellitus (OR 2.32; 95% CI 1.32 -

4.07) and malignancy (OR 3.87; 95% CI 1.61 - 9.34) were predictors of cefazolin non-susceptibility.

Discussion

We conducted a large cohort study at a regional hospital in Taiwan describing the clinical, epidemiological and microbiological characteristics of 420 consecutive patients admitted with UTI. Nearly three-quarters of patients were female, with at least underlying disease, and presenting SIRS on admission. *E. coli* was the most frequent uropathogen. We also determined risk factors of resistance to cefazolin. Not surprisingly, these risk factors were different for males and females. Although the overall mortality was low, we found that development of bacteremia during urosepsis increased the incidence of shock (by 395%), duration of hospitalization (by 26%), and ICU admission (by 169%).

Despite a low mortality rate, the incidence of bacteremia during urosepsis was high, (~27%) [2, 4]. This observation suggests that UTIs are the commonest etiology of community-acquired bacteremia [10]. Appropriate treatment of bacteremia during sepsis could further reduce case-mortality. Thus, predictors for bacteremia can identify patients for aggressive therapy and monitoring. Prior studies found that fever >38.6°C, tachycardia, and diabetes were useful predictors for bacteremia during urosepsis [11]. We found liver disease as a new risk factor for bacteremia. We suspect that liver disease, especially cirrhosis, leads to functionally impaired humoral and cell-mediated immunity which may lead to higher risk of infection [12].

Our study also showed that fulfilling SIRS criteria was not predictive of bacteremia in urosepsis. Other studies support this observation, showing that SIRS has poor sensitivity for bacteremia, of only 7 to 69% [13].

E. coli, *K. pneumoniae* and *Proteus mirabilis* were the most common uropathogens in our study.. These organisms are frequently resistant to cephalothin, trimethoprim-sulfamethoxazole (TMP-SMX), and ampicillin [4]. In our study, the resistance rates of *E. coli* and *P. mirabilis* to TMP-SMX, ampicillin, and ampicillin/sulbactam were more than 50%, which was higher than previous reports [4]. The higher observed antibiotic resistance in our study may be due to outdated data in prior studies (>10 years old); thus, the epidemiology of UTIs has evolved and antimicrobial resistance has worsened in Taiwan.

Surprisingly, cefazolin showed >80% *in vitro* effectiveness against the organisms that comprised 80% of the uropathogens in our study (*E. coli*, *K. pneumoniae*, and *P. mirabilis*) [14]. It is not completely clear why cefazolin retained such wide *in vitro* effectiveness when TMP-SMX, quinolones and other first generation cephalosporins are the three most commonly prescribed antibiotics for urosepsis in Taiwan [15]. Further studies about antibiotic utilization, clinical characteristics and microbiological features of urosepsis should be conducted to better understand the difference in the emergence of these antibiotic resistances.

Trimethoprim-sulfamethoxazole (TMP-SMX), ampicillin, and ampicillin/sulbactam are part of the first line regimen in the Taiwanese treatment guidelines published in 2000. We found

that these antibiotics were not appropriate empiric antibiotics due to lack of coverage against uropathogens in this study. Only imipenem and amikacin were effective against at least 80% of all Gram-negative organisms identified.

We believe cefazolin is still an appropriate empirical antibiotic for urosepsis in our hospital. The rationale for this conclusion is as follows. The infectious diseases society of American previously stated that an antibiotic may reasonably remain an appropriate empirical agent if less than 20% of the likely pathogens show in vitro resistance.^{11, 13} In our study, cefazolin had more than 80% effectiveness against *E. coli*, *K. pneumoniae*, and *P. mirabilis*, and these three organisms comprised 80% of detected uropathogens.. A separate study conducted in southern Taiwan also showed low rate of resistance to cefazolin and still supported cefazolin as appropriate empirical antibiotic for UTI [10]. Importantly, we were able to determine when cefazolin would likely fail; cefazolin should be avoided in male patients with a urinary catheter or nephrolithiasis and in female patients with diabetes and malignancy.

Our data led us to conclude that the 2000 Taiwanese guidelines for treatment of UTIs should be updated and revised based on new epidemiology data. As indicated in our study, TMP-SMX and ampicillin may no longer be appropriate for empirical therapy. Risk factors for resistance to first-generation cephalosporins should be included. Furthermore, we urge that the new guidelines recommend individual hospitals to understand its local epidemiology of pathogens so that management may be optimized according to the local susceptibility patterns.

There were limitations of this study. The study was a retrospective design based on an inpatient population. We also excluded patients without microbiological data and those with concurrent infections at another site. This methodology may have caused underestimate of true urosepsis. Moreover, the current health insurance in Taiwan pays hospitals for all inpatient care of UTIs and inadvertently incentivizes hospitals to admit patients even with mild symptoms. This admission bias may have reduced the power to detect predictors of poor outcomes in urosepsis. Despite these limitations, our study had excellent internal and external validity. Furthermore, we analyzed detailed clinical, epidemiological and microbiological data from a large cohort of consecutive patients from the community setting, an area that is truly poorly understood in Taiwan.

Urinary tract infections are common infections and healthcare providers can improve their outcomes. Liver disease is a new risk factor for bacteremic complications and clinicians should target patients with this risk factor for aggressive therapy and monitoring. Furthermore, better treatment outcomes can be achieved through matching antibiotic recommendations with current microbiological data of urosepsis in Taiwan. Finally, cefazolin appears to remain a suitable empirical agent but there are instances where cefazolin resistance is predictable. We believe an improvement in the management of UTI can be achieved in Taiwan. Let us begin by revising the treatment guidelines based on new epidemiology studies. It's been thirteen years since its last revision – that's a millennium in the era of increasing antimicrobial resistance.

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Implications

- Common uropathogens in Taiwan (such as *E. coli*, *Klebsiella* spp. and *Proteus mirabilis*) are now resistant to many recommended first line antibiotics.
- National treatment guidelines should be updated to reflect changes in epidemiology of microbiology.
- Clinicians and hospitals should be aware of local antibiotic resistance patterns for optimal treatment selection.

Table 1**Demographic and Clinical Characteristics of Patients with Bacteremic and Non-Bacteremic Urosepsis**

	All 420 (100%)	Bacteremic 114 (27.1%)	Non-Bacteremic 306 (72.9%)	p value
Demographic characteristics				
Gender (female)	317 (75.4)	89 (78.1)	228 (74.5)	0.524
Urinary catheter	33 (7.8)	8 (7.0)	25 (8.2)	0.839
At least 1 underlying disease	308 (73.3)	96 (84.2)	212 (69.3)	0.002 *
Diabetes mellitus	152 (36.2)	48 (42.1)	104 (34.0)	0.138
Renal stone	68 (16.2)	23 (20.2)	45 (14.7)	0.182
Benign prostate hypertrophy	45 (10.7)	13 (11.4)	32 (10.5)	0.859
Malignancy	36 (8.6)	11 (9.7)	25 (8.2)	0.695
Hepatic disease	9 (2.1)	6 (5.3)	3 (1.0)	0.014 *
Immunosuppression	2 (0.5)	0 (0.0)	2 (0.7)	1.000
Clinical characteristics on admission				
Body temperature >38°C or <36°C	236 (56.2)	72 (63.2)	164 (53.6)	0.097
Tachycardia (heart rate >90 beat/minute)	273 (65.0)	78 (68.4)	195 (63.7)	0.421
Tachypnea (respiratory rate >20 beat/minute)	91 (21.7)	30 (26.3)	61 (19.9)	0.183
WBC >12 or <4 K/ μ L, or >10% band	217 (51.7)	61 (53.5)	156 (51.0)	0.662
SIRS	286 (68.1)	86 (75.4)	200 (65.4)	0.059
Creatinine >1.5 mg/dL	101 (24.1)	32 (28.1)	69 (22.6)	0.250
C-reactive protein >0.5 mg/L	321 (76.4)	91 (95.8)	230 (91.6)	0.246
Pyuria	36 (86.0)	100 (89.3)	261 (85.9)	0.417
Hematuria	208 (49.5)	64 (57.1)	144 (47.4)	0.097
Clinical Outcomes				
Renal failure	23 (5.5)	7 (6.14)	16 (5.23)	0.810
Vasopressor required	20 (4.8)	13 (11.4)	7 (2.3)	<0.001 *
Hospital days, mean$\pm$SD	6.1 $\pm$ 3.9	7.3 $\pm$ 5.5	5.8 $\pm$ 3.2	0.009 *
Intensive care unit admission	22 (5.2)	11 (9.7)	11 (3.6)	0.024 *
Intensive care unit days, mean$\pm$SD	0.3 $\pm$ 1.8	0.6 $\pm$ 3.2	0.2 $\pm$ 1.0	0.225
Concordant empirical therapy	316 (75.2)	88 (77.2)	228 (74.5)	0.613
Antibiotic days, mean$\pm$SD	11.9 $\pm$ 5.2	12.5 $\pm$ 6.2	11.7 $\pm$ 4.4	0.237
Death	2 (0.5)	1 (0.9)	1 (0.3)	0.470

Data are presented as n (%) unless otherwise stated; SD = standard deviation.

WBC = white blood cell; SIRS = systemic inflammatory response syndrome

* $p < 0.05$

Table 2

Distribution of Uropathogens and Susceptibility Pattern

Susceptibility rate (%)												No. (%)
Gram-negative organism	TMP-SMX	Amp	Amp/sb	Cfx	Ctz	Ctx	Etp	Imp	Levo	Gent	Amk	552 (92)
<i>E. coli</i>	49	30	44	81	74	89	81	100	85	77	100	416 (69)
<i>K. pneumoniae</i>	80	0	78	80	85	83	88	100	83	95	100	41 (7)
<i>P. aeruginosa</i>	0	NT	NT	NT	NT	97	NT	94	58	94	97	31 (5)
<i>P. mirabilis</i>	44	32	44	88	92	100	92	96	64	44	88	25 (4)
<i>Enterobacter species</i>	94	0	13	0	63	81	75	100	100	88	100	16 (3)
<i>Citrobacter species</i>	71	0	36	36	57	79	93	100	93	86	93	14 (2)
<i>Morganella morganii</i>	33	0	33	0	67	67	67	100	67	33	100	3 (1)
<i>Providencia rettgeri</i>	67	0	0	0	100	100	100	100	100	100	100	3 (1)
<i>Salmonella group D</i>	100	100	NT	NT	100	NT	NT	NT	100	NT	NT	3 (1)
Gram-positive organism	P	Amp	Oxa	Vanc	Teico	HGent	Levo	TMP-SMX	36 (6)			
<i>Enterococcus species</i>	NT	83	NT	100	100	42	NT	NT	12 (2)			
<i>Streptococcus group B</i>	100	NT	NT	100	NT	NT	100	NT	7 (1)			
<i>Staphylococcus aureus</i>	0	0	50	100	100	NT	50	75	4 (1)			
<i>viridans Streptococci</i>	100	NT	NT	100	NT	NT	67	NT	3 (1)			
Others	11 (2)											
<i>Candida species</i>	10 (2)											
Total	599 (100)											

NT = not tested; TMP-SMX = trimethoprim-sulfamethoxazole; Amp = ampicillin; Amp/sb = ampicillin/sulbactam; Cfx = cefazolin; Ctz = ceftiofur; Ctx = ceftriaxone; Etp = ertapenem; Imp = imipenem; Levo = levofloxacin; Gent = gentamicin; Amk = amikacin; P = penicillin; Oxa = oxacillin; Vanc = vancomycin; HGent = high-dose gentamicin; Teico = teicoplanin.

Table 3

Demographic Characteristics of Patients with Cefazolin-Susceptible and Cefazolin-Resistant Organisms

	Cfz-S 278 (66.2)	Cfz-R 142 (33.8)	Univariable <i>p</i> value
Age ≥ 65 years old	137 (49.3)	84 (59.2)	0.063
Gender (female)	234 (84.2)	83 (58.5)	<0.001 *
Urinary catheter	15 (5.4)	18 (12.7)	0.012 *
At least 1 underlying disease	185 (66.6)	123 (86.6)	<0.001 *
Hypertension	128 (46.0)	68 (47.9)	0.757
Diabetes mellitus	87 (31.3)	65 (45.8)	0.004 *
Cardiovascular disease	51 (18.4)	36 (25.4)	0.099
Old stroke	42 (15.1)	26 (18.3)	0.404
Renal stone	35 (12.6)	33 (23.2)	0.008 *
Renal insufficiency	32 (11.5)	21 (14.8)	0.354
Bed-ridden status	29 (10.4)	20 (14.1)	0.266
Benign prostate hypertrophy	23 (8.3)	22 (15.5)	0.030 *
Pulmonary disease	23 (8.3)	13 (9.2)	0.854
Malignancy	15 (5.4)	21 (14.8)	0.002 *
Hepatic disease	5 (1.8)	4 (2.8)	0.494
Immunosuppression	1 (0.4)	1 (0.7)	1.000

Data are presented as n (%) unless otherwise stated; Cfz-S = cefazolin-susceptible; Cfz-R = cefazolin-resistant.

*
p < 0.05