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Serratia marcescens bacteremia at a medical center in southern Taiwan: high prevalence of cefotaxime resistance

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Antimicrobial resistance of isolates and risk factors for mortality were retrospectively investigated in 71 adult patients with *Serratia marcescens* bacteremia. During the 4-year study period, 78 clinically significant episodes of *S. marcescens* bacteremia occurred in 71 patients. The mean age of the patients was 65 years (range, 25-86 years) with a male predominance (45 patients, 63%). Most of the bacteremic episodes were nosocomial (78%), and 34% were polymicrobial. The overall mortality rate within 2 weeks after the onset of bacteremia was 41%. The presence of malignancy and critical illness at initial presentation were independent risk factors for mortality. By disk susceptibility test, 72 isolates were resistant to cefotaxime (92%) but susceptible to ceftazidime (99%). All isolates were susceptible to meropenem. Among the 47 patients with monomicrobial *S. marcescens* bacteremia, the mortality rate within 5 days of onset in patients receiving appropriate empirical antimicrobial therapy was lower than that in patients receiving inappropriate therapy although this difference was not significant (14% vs 28%, p=0.27). Among the patients with cefotaxime-resistant but ceftazidime-susceptible *S. marcescens* bacteremia treated with ceftazidime, 6 of 7 patients (86%) survived for more than 2 weeks, suggesting the potential effectiveness of ceftazidime in the treatment of cefotaxime-resistant *Serratia* infections. Further clinical studies are required to delineate the clinical role of ceftazidime therapy for infections caused by *S. marcescens* with this resistant phenotype.

Key words: Bacteremia, cefotaxime, drug resistance, *Serratia marcescens*

Serratia marcescens, a member of the family *Enterobacteriaceae*, is a frequent causative agent of nosocomial infections [1,2], and has been recognized as the cause of many hospital epidemics [2-14]. Several episodes of bacteremia traced to infusion pumps have been reported [7-11,14]. In addition to bacteremia, *S. marcescens* can cause a wide spectrum of infectious diseases, including urinary, respiratory, and biliary tract infections, wound infections, intravenous catheter-related infections, septic arthritis, osteomyelitis, infective endocarditis and peritonitis [1,15].

Like other *Enterobacteriaceae*, *Serratia* spp. constitutively possess chromosomally encoded, inducible AmpC β-lactamases, and may acquire plasmid-mediated extended-spectrum β-lactamases (ESBLs). Therefore, they have the ability to develop resistance to many β-lactam antibiotics [16-20]. Patients with *S. marcescens* infections often receive empirical antimicrobial agents before information about antimicrobial susceptibility becomes available. The empirical antimicrobial agents used often include extended-spectrum β-lactam drugs, such as third- and fourth-generation cephalosporins, and carbapenems. Several studies have demonstrated that multidrug-resistant strains of *S. marcescens* can cause serious nosocomial infections [3-5,12-14,21,22], but the impact of the use of different classes of antimicrobial agents on clinical outcome remains unclear. The present study evaluated the risk factors for mortality and the antimicrobial resistance of isolates, and the impact of appropriate antimicrobial therapy on the clinical outcome of patients with *S. marcescens* bacteremia.

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Materials and Methods

The blood culture records at the clinical microbiology laboratory of Cheng Kung University Hospital, a 1000-

bed teaching hospital with 100 beds for intensive care in southern Taiwan, were reviewed to identify cases of *S. marcescens* bacteremia during the period from August 1999 to August 2003. Medical charts of adult patients (at least 18 years old) were reviewed. The demographic and clinical data of patients were collected, including initial presentations, underlying diseases, possible predisposing factors such as implanted device, chemotherapy, and prior antimicrobial therapy, onset of bacteremia, portal of entry, antimicrobial susceptibility and therapy, and clinical outcome.

Microbiology and antimicrobial susceptibility

Blood cultures were incubated in the BACTEC 9240 instrument (Becton Dickinson Diagnostic Systems, Sparks, MD, USA) for 5 days at 35°C. Positive samples were stained with Gram stain and subcultured onto standard solid media [23]. *S. marcescens* were identified by biochemical tests and confirmed with the Vitek system (Biomerieux, France) with the GNI card for in vitro identification of *Enterobacteriaceae.* Antimicrobial susceptibilities were determined by the disk-diffusion method following the criteria proposed by the National Committee for Clinical Laboratory Standards [24].

The date of onset of bacteremia was defined as the date of collection of the first positive blood culture. When the same organism with the same susceptibility was isolated from a subsequent blood culture within 14 days after the first positive blood culture, it was regarded as the same episode. Nosocomial infections were defined as infections occurring more than 48 h after hospital admission, or those occurring less than 48 h after admission among patients hospitalized within 2 weeks prior to admission [25]. A localized infection was regarded as the portal of entry of bacteremia if it was microbiologically and clinically documented.

The severity of acute illness was assessed by the Pittsburgh bacteremic score, a previously validated scoring system that is based on mental status, vital signs, requirement for mechanical ventilation, and recent cardiac arrest [26,27]. Relapsing bacteremia was defined as the isolation of *S. marcescens* from bloodstream after the completion of at least 10 days of appropriate therapy, and recurrent bacteremia as the isolation of *S. marcescens* during appropriate therapy, which had been given for at least 5 days. Polymicrobial bacteremia was defined as a bacteremic episode associated with the isolation of any additional micro-organism, other than *S. marcescens*, from the same blood culture specimen.

Use of glucocorticoid was defined as the receipt of 10 mg prednisone per day or equivalent dosage for more than 2 weeks, or the presence of clinical pictures of Cushing's syndrome, low serum cortisol levels (less than 10 μg/dL) in acute illness, and compatible medical history. Sepsis-induced hypotension in a patient with a systemic blood pressure lower than 90 mm Hg not responsive to an intravenous fluid challenge was classified as septic shock. Coagulopathy was defined by the presence of abnormal bleeding or characteristic alterations in blood coagulation tests, including a decline in fibrinogen levels to 150 mg/dL, an increase in fibrin split products to 10 mg/dL, thrombocytopenia with a platelet count lower than 100,000/mm^3, or a prolonged prothrombin time or activated partial thromboplastin time.

Prior antibiotic use was defined as the receipt of systemic antibiotics for at least 48 h within 2 weeks prior to the onset of bacteremia. Antibiotics administered more than 48 h after the onset of bacteremia within 5 days were referred to as empirical therapy [28]. Initial regimens were classified as "appropriate" or "inappropriate", if they were in vitro active or inactive, respectively, against the etiologic *Serratia* isolate. No receipt of antimicrobial agent was regarded as "inappropriate therapy". Definite antimicrobial therapy was defined as the prescription of antibiotics after the microbiologic report was available, usually at 5 days after the onset of bacteremia. Clinical outcome was evaluated at 5 and 14 days after the onset of bacteremia, and at discharge.

Statistical analysis

The data were analyzed using a commercially available software package (Statistical Package for the Social Sciences [SPSS], version 11.0; SPSS Inc., Chicago, IL, USA). For categorical data, proportions were compared with chi-squared test or Fisher's exact test. Univariate and multivariate analyses to determine the independent risk factors for mortality were performed using logistic regression models. Multivariate analysis was performed by stepwise logistic regression, and variables were eligible for entry into the multiple logistic models if p values were ≤0.1. The odds ratio (OR) and 95% confidence interval (CI) were calculated at the same time. Survival curves were constructed by the Kaplan-Meier method, and the log-rank test was used to compare the time to mortality between patients who received appropriate and inappropriate empirical antimicrobial agent treatment. All tests of significance were 2-tailed;

a *p* value of 0.05 or less was considered to be statistically significant.

Results

During the 4-year study period, 78 clinically significant episodes of *S. marcescens* bacteremia occurred in 71 patients. Two patients (2.6%) had recurrent bacteremia, and 5 (6.4%) had relapsing bacteremia. Only the first bacteremic episode was included, and thus 71 episodes in 71 patients were included for further analysis. Among the 71 episodes, 55 (78%) were nosocomial, and 28 (39%) occurred in the intensive care units. The mean age of patients was 65.2 ± 15.3 years (range, 25-86 years), with a male predominance (45, 63%).

Underlying diseases and portal of entry

Table 1 summarizes the demographic characteristics and underlying conditions of the 71 patients with *S. marcescens* bacteremia. The most common underlying condition was malignancy (37%), followed by steroid use (35%). Before the onset of *S. marcescens* bacteremia, 68 patients (96%) had received antimicrobial therapy. At the time of onset of bacteremia, the majority of patients had a central venous catheter (49, 69%), an indwelling urinary catheter (36, 51%), or were receiving mechanical ventilation (29, 41%). An indwelling central venous catheter was present at the time of onset in 49 patients. The central venous catheter was removed within 24 h in 23 patients, and only 1 patient (4%) died within 2 weeks of onset. In contrast, 6 (23%) of 26 patients without removal of the central venous catheter at more than 24 h after onset died within 2 weeks (p=0.06). Of 23 patients with catheter removal within 24 h, *S. marcescens* grew in the catheter tip in 14 (20%), and the intravascular catheter was regarded as the most likely portal of entry in these patients. However, of the 39 patients (55%) with 2 sites recognized as possible portals of entry, lower respiratory tract (16, 23%) was the most common one.

Table 1. Demographic and clinical characteristics of 71 patients with *Serratia marcescens* bacteremia

Characteristic	Case no. (%)
Gender	
Male	45 (63)
Female	26 (37)
Underlying diseases	
Malignancy	26 (37)
Steroid use	25 (35)
Diabetes mellitus	24 (34)
Chronic obstructive pulmonary disease	5 (7)
End stage renal disease	5 (7)
Liver cirrhosis	5 (7)
No obvious underlying disease	31 (44)
Acute illness severity	
Pittsburgh score <4	29 (42)
Pittsburgh score ≥4	42 (59)
Portal of entry	
Lower respiratory tract	16 (23)
Intravascular catheter	14 (20)
Urinary tract	5 (7)
Wound	4 (6)
Comorbid or predisposing conditions	
Indwelling central venous catheter	49 (69)
Long hospital stay (≥30 days) before illness	48 (68)
Indwelling urinary catheter	36 (51)
Ventilator support	29 (41)
Prior surgery within 1 month	25 (35)
Stay in intensive care units at onset of sepsis	28 (39)
Prior chemotherapy within 1 month	12 (17)

Microbiology and susceptibility data

Among 71 episodes of *S. marcescens* bacteremia, 24 (34%) were polymicrobial. The coexisting organisms were mainly Gram-negative bacilli, including *Pseudomonas aeruginosa* (6 episodes), *Actinetobacter baumannii* (4), *Enterobacter cloacae* (4), *Klebsiella pneumoniae* (2), ESBL-producing *E. coli* (1), *Stenotrophomonas maltophilia* (1) *Proteus mirabilis* (1), *Ralstonia pickettii* (1) and *E. coli* (1). Only 2 episodes had concomitant isolation of Gram-positive bacteria. Eleven episodes (15%) had more than 2 organisms isolated from bloodstream.

The in vitro susceptibilities of the 78 bacteremic isolates to 12 commonly used antimicrobial agents are shown in Table 2. Seventy seven isolates (99%) were susceptible to ceftazidime, but only 7 isolates (8%) were susceptible to cefotaxime. More isolates were susceptible to levofloxacin than to ciprofloxacin. Meropenem, a carbapenem, was the most active drug in vitro.

Clinical outcome and risk factors for mortality

Thirty patients (42%) died after the detection of *S. marcescens* bacteremia and before discharge, 23 (32%) within 5 days, and 29 (41%) within 2 weeks of onset of positive culture. To examine the risk factors for mortality, the clinical outcome at 2 weeks after the onset of *Serratia* bacteremia was analyzed (Table 3). Only the presence of malignancy was associated with 2-week mortality. Other factors, including elderly status, polymicrobial bacteremia, severity score, presence of septic shock, acute renal

Table 2. Antimicrobial susceptibility of 78 *Serratia marcescens* isolates from bloodstream by disk-diffusion method

Antimicrobial agent	Number of susceptible isolates	Susceptibility rate (%)
Meropenem	78	100
Ceftazidime	77	99
Cefepime	71	91
Aztreonam	65	83
Amikacin	62	79
Piperacillin-tazobactam	55	71
Levofloxacin	25	32
Ciprofloxacin	15	19
Trimethoprim-sulfamethoxazole (co-trimoxazole)	14	18
Cefotaxime	7	9
Cefmetazole	2	3
Cefuroxime	0	0

failure, disseminated intravascular coagulopathy, and inappropriate empirical therapy, were not significantly associated with a fatal outcome at 2 weeks. In the multivariate analysis, malignancy (OR, 3.31; 95% CI, 1.15-9.51; p=0.03) and a critical illness at initial presentation (i.e., a Pittsburgh bacteremic score of ≥4 points) [OR, 1.24; 95% CI, 1.02-1.51; p=0.03] were independent factors for mortality.

To avoid the confounding effect of coexisting pathogens in patients with polymicrobial bacteremia, 47 patients with monomicrobial *Serratia* bacteremia were evaluated to determine the impact of appropriate antimicrobial therapy on clinical outcome and the therapeutic efficacy of different classes of antimicrobial agents (Table 4). Of the 18 patients who received inappropriate empirical therapy, 5 (28%) died, and 4 (14%) of 29 patients who received appropriate empirical therapy died. However, using the Kaplan-Meier method with log-rank test, the crude case fatality rates at 14 days and 30 days were not significantly different (p=0.45 vs p=0.45, respectively). Among patients with cefotaxime-resistant but ceftazidime-susceptible *S. marcescens* bacteremia, none of 10 patients treated empirically with ceftazidime died, and 1 of 7 patients definitively treated with ceftazidime died. The detailed demographic and clinical information of the 6 patients who died after treatment with appropriate agents is summarized in Table 5. All 6 patients who died within 2 weeks after the onset of bacteremia had a critical illness at initial presentation, and 3 of them had underlying malignancy.

Table 3. Risk factors of fatality at 14 days among 71 patients with *Serratia marcescens* bacteremia

Variable	Fatal case no./ total case no.	Fatality rate (%)	p
Age (years)			0.21
≤65	14/27	52	
>65	15/44	34	
Place of acquisition			1.00
Hospital	6/16	38	
Community	23/55	42	
Polymicrobial bacteremia			0.06
Yes	15/24	62	
No	14/47	29	
Diabetes mellitus			0.07
Yes	6/24	25	
No	23/47	49	
Malignancy[a]			0.04
Yes	15/26	58	
No	14/45	31	
Acute illness severity[a]			0.08
Pittsburgh score ≥4	21/42	50	
Pittsburgh score <4	8/29	28	
Acute renal failure			0.21
Yes	7/12	58	
No	22/58	38	
Disseminated intravascular coagulopathy			0.21
Yes	13/25	52	
No	16/46	35	
Septic shock			0.63
Yes	16/36	44	
No	13/35	37	
Appropriate empirical antibiotics			0.15
Yes	9/30	30	
No	20/41	49	

[a]p<0.05 in multiple logistic regression analysis.

Discussion

The overall mortality rate of *S. marcescens* bacteremia in this study was 42%. This is similar to rates reported in previous studies, which ranged from 25-58% [1,5, 12,14,21,22,29]. At least 2 previous studies reported independent risk factors associated with mortality,

Table 4. Impact of appropriateness of antimicrobial therapy on clinical outcome of 47 patients with monomicrobial *Serratia marcescens* bacteremia

Variable	Fatal case no./total case no.	Fatality rate (%)
Empirical therapy (fatality within 5 days)	9/47	19
Inappropriate agents	5/18	28
Appropriate agents	4/29	14
Carbapenem	2/10	20
Ceftazidime	0/10	0
Cefepime	1/3	33
Others[a]	1/6	17
Definite therapy (fatality between 5-14 days)	5/38	13
Inappropriate agents	3/10	30
Appropriate agents	2/28	7
Carbapenem	1/9	11
Ceftazidime	1/7	14
Others[b]	0/12	0

[a]Cefotaxime, aztreonam, piperacillin-tazobactam, amikacin, cefepime + amikacin.

[b]Cefepime, cefotaxime, aztreonam, piperacillin-tazobactam, amikacin, piperacillin + gentamicin, ceftazidime + gentamicin.

including cancer patients with septic shock, pneumonia, and hemorrhage [3], old or young age, rapidly fatal or ultimately fatal disease, and intensive care unit acquisition [3,30]. In the present study, malignancy or a critical illness at initial presentation were associated with mortality within 2 weeks. The Pittsburgh bacteremic score used to evaluate illness severity has been previously validated [31,32], and was found to be a significant predictor of clinical outcome of individuals with Gram-negative bacteremia in this study.

Theoretically the early administration of appropriate antimicrobial agents will improve the clinical outcome of severe bacterial infections. In the present study, patients with appropriate empirical therapy tended to have a lower early fatality rate (14%) than that of patients (28%) with inappropriate therapy, although this difference was not significant. In contrast, in a Korean study involving 249 patients with monomicrobial bacteremia caused by third-generation cephalosporin-resistant *Citrobacter freundii*, *S. marcescens* or *Enterobacter* species, the attributable mortality rate (13%) among patients given appropriate treatment was similar to that (15%) among patients given inappropriate treatment [33]. Variations in the definitions of duration and appropriateness of therapy, antimicrobial regimens, underlying medical conditions, the severity of septicemia at the initiation of therapy, and clinical endpoints could confound interstudy comparisons of the net effect of appropriate therapy for patients with Gram-negative bacteremia. More clinical studies with a large number of patients with subclassification into homogenous groups at baseline are necessary in order to elucidate the impact of appropriateness of antimicrobial therapy.

A nationwide surveillance study of antimicrobial resistance in 2000 in Taiwan found a discrepancy in the susceptibility of *S. marcescens* isolates to cefotaxime

Table 5. Clinical characteristics of 6 fatal cases of *Serratia marcescens* bacteremia treated with appropriate antimicrobial agents

Patient no./ age (years)/ gender	Onset day of bacteremia after admission	Underlying condition	Pitt's score	Cause of death	Antimicrobial therapy	Expired day after onset
1/83/male	0	Nil	9	Sepsis	Meropenem	0
2/86/male	34	Alzheimer's disease, hollow organ perforation postoperation	8	Sepsis	Imipenem-cilastatin	1
3/50/male	28	Hepatoma, chronic renal failure	8	Sepsis	Cefepime	1
4/42/female	18	Breast cancer, post-chemotherapy neutropenia	8	Sepsis	Piperacillin-tazobactam	1
5/74/male	20	Lung cancer	9	Fungemia	Imipenem-cilastatin	6
6/66/female	27	Lower leg skin graft necrosis, diabetic nephropathy, coronary artery disease	6	Sepsis	Ceftazidime	6

(resistant rate: 48%) and ceftazidime (5%) [34]. Similarly, this study found a high rate of cefotaxime resistance, but nearly all isolates were susceptible to ceftazidime. Moreover, such a resistant phenotype was described among 68 putative AmpC cephalosporinase-derepressed mutants of *S. marcescens* [35]. In the present study, the majority of patients with *S. marcescens* bacteremia treated with ceftazidime survived for more than 2 weeks. Thus, data from this study does not strongly suggest against the use of ceftazidime in treating clinical *Serratia* isolates with such a resistant phenotype. Likewise, it remains debatable whether isolates resistant to cefotaxime should be regarded as being resistant to other third-generation cephalosporins, as suggested by Choi et al [30].

The susceptibility rate of *S. marcescens* isolates to fluoroquinolone in this study was lower than expected. The susceptibility rates to ciprofloxacin and levofloxacin of 19% and 32%, respectively, suggest a progression in the resistant rate of ciprofloxacin (50%) since the reporting of the Taiwan Surveillance of Antimicrobial Resistance study in 2000 [34]. Sheng et al reported that the susceptibility rate of *S. marcescens* to ciprofloxacin decreased from 100% in 1985-1986 to 80% in 1996-1997 [36]. The continuous increase in fluoroquinolone resistance among clinically important Gram-negative bacilli poses a serious problem because of the widespread use of fluoroquinolones to treat both community-acquired and nosocomial infection.

The mechanism of cefotaxime resistance in *Enterobacteriaceae* is likely to result from the presence of β-lactamases, ESBL, AmpC β-lactamases or metallo-β-lactamases. The most common enzymes associated with resistance to third-generation cephalosporins in certain Gram-negative bacilli, including *S. marcescens*, are chromosomally encoded, inducible AmpC β-lactamases. However, ESBLs were increasingly found among clinical *S. marcescens* isolates in the past decade. CTX-M-3, TEM-47 and SHV-5 were discovered in 19% of 347 *S. marcescens* isolates in Poland from 1996 to 2000 [35]. In Taiwan, Wu et al reported that 21 (62%) of 34 *S. marcescens* isolates non-susceptible to cefotaxime exhibited an ESBL-resistant phenotype and all possessed CTX-M-3 [20], suggestive of the wide spread of such a β-lactamase, at least among *S. marcescens*. The presence of ESBL will further limit the choice of appropriate antimicrobial therapy for cefotaxime-resistant *S. marcescens* bacteremia. Ongoing monitoring of phenotypic and genetic trends of β-lactamase types in bacteremic isolates is needed.

Although meropenem was the antibiotic with the greatest in vitro activity against *S. marcescens*, there was no significant difference in 5-day mortality in patients empirically treated with a carbapenem or other agent which was active in vitro in the present study. The lack of association between carbapenem use and improved outcome may have been related to the limited number of cases as well as the severity of underlying disease or critical illness at initial presentation. However, because of the emergence of ESBL in *S. marcescens*, treatment with a carbapenem can be regarded as the last resort for severe infections caused by third-generation cephalosporin-resistant *Serratia* isolates. Unfortunately, carbapenem resistance mediated by a metallo-β-lactamase has been described in clinical *S. marcescens* isolates [37,38]. Thus, increased attention to clinical use of carbapenems to avoid unnecessary pressure for the selection of resistant organisms is needed.

In conclusion, *S. marcescens* bacteremia often occurred during hospitalization in patients with severe underlying diseases, and heralded a poor prognosis in patients with malignancy or a critical illness at initial presentation. A higher prevalence of cefotaxime resistance than ceftazidime resistance was found. Further study is needed to establish the therapeutic role of ceftazidime for cefotaxime-resistant *S. marcescens* infections.

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